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DNA damage and neurotoxicity of chronic alcohol abuse

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Abstract

Chronic alcohol abuse results in a variety of pathological effects including damage to the brain. The causes of alcohol-induced brain pathology are presently unclear. Several mechanisms of pathogenicity of chronic alcoholism have been proposed, including accumulation of DNA damage in the absence of repair, resulting in genomic instability and death of neurons. Genomic instability is a unified genetic mechanism leading to a variety of neurodegenerative disorders. Ethanol also likely interacts with various metabolic pathways, including one-carbon metabolism (OCM). OCM is critical for the synthesis of DNA precursors, essential for DNA repair, and as a methyl donor for various methylation events, including DNA methylation. Both DNA repair and DNA methylation are critical for maintaining genomic stability. In this review, we outline the role of DNA damage and DNA repair dysfunction in chronic alcohol-induced neurodegeneration.

Keywords

alcohol; DNA damage; neuron; cell death

Introduction

Chronic alcohol consumption is associated with an increase in the incidence of a variety of diseases, including central nervous system (CNS) degeneration.[1] The brain is one of the major targets of alcohol actions. In adult human chronic alcoholics, brain damage is characterized by cerebral and cerebellar atrophy, and impaired neuronal function within the hippocampus and frontal cortex.[2,3] Besides specific alcohol-related disorders, such as Wernicke–Korsakoff syndrome, hepatic encephalopathy and pellagra, heavy alcohol consumers exhibit cognitive and motor impairments, cholinergic deficits and dementia. It is estimated that 50–75% of long-term alcoholics show cognitive impairment and structural damage to the brain, making chronic alcoholism the second leading cause of dementia behind Alzheimer's disease.[4–6] These changes may be caused by loss of neurons, shrinkage of neuronal cell bodies, or reduction in the number and extent of dendrites. Careful neuropathological analyses have provided evidence for loss of neurons in certain regions of the brain of alcoholics.[2,7] A direct toxic effect of ethanol on the brain has been suggested as the primary cause of alcohol-related neuronal loss.[8] The effects of alcohol on the brain are well documented. However, the mechanisms are poorly understood. Several mechanisms have been proposed to explain ethanol-related brain damage. The *N*-methyl-D-aspartate (NMDA)-glutamate receptor could contribute to alcohol-induced brain damage. Ethanol, when administered acutely, potently inhibits NMDA receptors, while chronic exposure causes adaptive upregulation in the sensitivity of NMDA receptors and can result in an

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increased vulnerability for glutamate-induced cytotoxic response (excitotoxicity).[9] Increased calcium influx through NMDA receptors, in turn, is tightly coupled to uptake into mitochondria and causes the production of reactive oxygen species (ROS). Alcohol metabolism is also associated with ROS production[10,11] (Figure 1). Ethanol oxidation by cytochrome P450 2E1 (CYP2E1) and catalase is particularly relevant to ethanol metabolism in the brain.[12] It is well known that ROS cause damage to DNA.[13] Acetaldehyde, the primary metabolite of ethanol, can also damage DNA.[14,15]

Chronic ethanol exposure has been shown to be more harmful than acute exposure.[16,17] Chronic alcoholism is mutagenic and carcinogenic in humans and is also associated with brain dysfunction.[1,6,10,13,18–20] However, the mechanisms by which long-term chronic excessive alcohol consumption leads to a variety of pathologies are unclear.

The sulfur-containing amino acid homocysteine (Hcy) has been suggested to be toxic in alcoholism.[6,21] Chronic alcoholic patients often have sustained hyperhomocysteinemia, a marker of one-carbon metabolism (OCM) impairment and a role for alcohol in disrupting OCM is strongly supported by the literature.[10,21] OCM impairment directly impacts the brain in the conditions of ethanol exposure, as evidenced by increased Hcy concentrations in the cerebellum of rats[22] and increased risk of alcohol withdrawal seizures with the increase of Hcy plasma concentrations.[23] Also, plasma Hcy concentrations show the most significant correlation to hippocampal volume reduction in patients with alcoholism.[3] Such effects of OCM impairment can be explained by the critical importance of OCM for the synthesis of DNA nucleotides (dNTPs), precursors for DNA biosynthesis and repair, and for methylation reactions.[24,25] DNA repair and methylation of DNA play essential roles in maintaining genomic stability. Given that ethanol (or its metabolites) is genotoxic[14,17] and OCM is critical for maintaining genomic stability,[26] alcohol-induced OCM impairment may play a significant role in alcohol pathogenicity. In addition, Hcy itself may act as a convulsant through its agonism at NMDA receptors.[27]

Here, we link chronic alcohol-induced neurotoxicity to DNA damage, which suggests far-reaching implications for the understanding of the pathogenesis of alcoholism in humans.

Potentially toxic metabolites of ethanol

As shown in Figure 1, ethanol is metabolized mainly through oxidation catalyzed by alcohol dehydrogenase (ADH), cyto-chrome P450 2E1 (CYP2E1) and catalase enzymes.[28–30] Due to the low capacity and the relatively high affinity (K_m = 0.05–0.1 g/L) of ADH, the enzyme gets saturated after only a few drinks. Once formed, acetaldehyde is oxidized by the mitochondrial isoform of aldehyde dehydrogenase (ALDH), ALDH2, to acetate, in an irreversible reaction. ALDH2 has a very low K_m value, which makes the elimination of toxic acetaldehyde highly efficient. The rates of ethanol metabolism by ADH and ALDH2 are critical in determining its toxicity because the alcohol metabolite acetaldehyde is highly toxic.[29,31] ADH and ALDH2 use the co-factor nicotinamide adenine dinucleotide (NAD+), which converts to NADH and significantly changes the ratio NADH/NAD+, resulting in an altered cellular redox and overall energy metabolism states.[32] ALDH2 is one of 19 members of the ALDH gene family in humans that play a crucial role in the oxidation and detoxification of numerous reactive aldehydes including 4-hydroxy-2-nonenal (4-HNE), a well-known, highly toxic by-product of lipid peroxidation, and nitroglycerin.[32–34] Consistent with the critical importance of ALDH2 for detoxification of acetaldehyde, a risk of alcohol-induced toxicity in individuals with mutant ALDH2 is remarkably increased. Approximately 500 million Asians are heterozygous for the ALDH2 gene and, therefore, possess one normal and one mutant copy of the ALDH2 gene, termed ALDH2*2. The mutant copy encodes an inactive isozyme.[35,36]

Although ADH activity is not present in the brain, there is evidence of brain ethanol metabolism through ethanol oxidation into acetaldehyde by catalase[37,38] and CYP2E1[39] (Figure 1). It is estimated that catalase accounts for 60–70% of ethanol-generated acetaldehyde in the brain, while CYP2E1 accounts for 10–20%.[39,40] Acetaldehyde is then readily oxidized into acetate by ALDH.[38] A number of studies based on the analysis of brain homogenates[39,41] and at least one study based on the *in vivo* microdialysis[42] provide evidence for the presence of acetaldehyde in the brain following ethanol intake. The levels of acetaldehyde were significantly increased under conditions of ALDH2 deficiency in ALDH2-knockout mice and were consistent with the dose of ethanol.[42] ALDH2 transgenic overexpression alleviated chronic alcohol-induced cell death in the cerebral cortex of mice.[43] Since ALDH2 is essential for detoxification of acetaldehyde, ALDH2 deficiency can directly contribute to excess acetaldehyde accumulation, while its overexpression can reduce acetaldehyde concentrations (and toxicity). Other indications of acetaldehyde presence in the brain include a reduction in acetaldehyde accumulation under conditions of pharmacological[38] or genetic (via injection of anti-catalase shRNA construct into the CNS)[44] inhibition of catalase. Thus, acetaldehyde can be produced in the brain by metabolic transformation of ethanol, and neurotoxic effects of ethanol may be associated with its toxicity.

Alcohol and DNA damage

Preservation of genetic information is of prime importance to all living systems. However, the integrity of the genome is continuously threatened by environmental agents (e.g. the ultraviolet [UV] component of sunlight, ionizing radiation and genotoxic chemicals) or intrinsic sources of DNA damage (metabolic by-products, spontaneous disintegration of DNA structure). DNA damage can lead to mutations, a primary step into cancer initiation. DNA damage may also result in cellular malfunction, senescence or death. Together, these changes may cause the progressive loss of tissue homeostasis and organismal decline. Oxidative stress, ionizing radiation, UV light and numerous chemicals induce a wide verity of DNA lesions.[45] To cope with this permanent challenge, cells are equipped with an efficient genome defense mechanism responsible for detecting and removing DNA lesions, as well as eliminating the irreparably damaged cells. Alcohol metabolism generates potentially genotoxic ROS and acetaldehyde, which have been shown to induce DNA damage, including oxidative modifications, acetaldehyde-derived DNA adducts and cross-links.[14,17,18,46–48] One of the most abundant ROS-induced DNA lesions is the oxidative DNA damage, 7,8-dihydro-8-oxo-2′-deoxyguanosine (oxo8dG),[49] which is repaired by the base excision repair (BER) pathway. The primary acetaldehyde-derived DNA adduct is *N*2-ethylidene-deoxyguanosine,[50] which may be converted *in vivo* to *N*2-ethyldeoxyguanosine (*N*2-ethyl-dG). *N*2-ethyl-dG has been found in the DNA of ethanol-treated mice[51] and human alcoholics,[52] suggesting that *N*2-ethyl-dG is a potential biomarker of acetaldehyde-induced DNA damage. This DNA adduct blocks translesion DNA synthesis (a DNA damage tolerance process that allows the DNA replication machinery to replicate past DNA lesions) catalyzed by a variety of DNA polymerases, and induces mutations.[53,54] DNA polymerase η can bypass *N*2-ethyl-dG in an error-free manner.[55] The DNA repair pathway for *N*2-ethyl-dG has not been identified. *N*2-ethyl-dG is not the only acetaldehyde-generated DNA damage. Acetaldehyde can also form DNA–DNA and DNA–protein cross-links.[46,47] The major mechanism responsible for efficient cross-link removal is the Fanconi anemia (FA) pathway. Cross-link repair also involves the coordinated activities of other DNA repair pathways, such as nucleotide excision repair (NER) and homologous recombination (HR).[56] Defects in a cluster of FA proteins leading to inactivation of associated DNA repair pathways are associated with hereditary disease FA that causes developmental defects, sterility, bone-marrow failure and a highly elevated risk of cancer.[15] Langevin *et al.*[15] recently provided strong evidence that metabolically produced acetaldehyde is indeed a

DNA-damaging agent normally counteracted by the FA network. They demonstrated that simultaneous knockout of the *Aldh2* gene (which encodes Aldh2, the main detoxifying enzyme of acetaldehyde) and the *Fancd2* gene (a key player in the FA system) in double-mutant ($Aldh2^{-/-}$ $Fancd2^{-/-}$) mice make these mice unusually sensitive to ethanol exposure. Although many studies of alcohol-mediated DNA damage have been conducted in the liver and other proliferating tissues in association with carcinogenesis, evidence exists that alcohol can produce DNA damage in the brain. Brains of mice exposed to ethanol exhibited FA activation, suggesting formation of acetaldehyde-induced DNA damage in the brain, although DNA damage was not determined directly.[14] Importantly, acute alcohol intoxication induces reversible DNA lesions which do not exceed the capacities of the cellular repairing systems, while chronic alcohol exposure is associated with extensive DNA damage[17,18] associated with genomic instability. Genomic instability refers to a set of events capable of causing unscheduled alterations, either of a temporary or permanent nature, within the genome and encompasses diverse genetic changes. Genomic instability usually results from an aberrant cellular response to DNA damage. DNA damage response is an extremely important mechanism of preserving genomic stability which includes DNA repair machinery. Damage to the genome is not only caused by exogenous and endogenous chemical and physical agents but can also occur due to inherited or acquired defects in DNA repair,[57–59] conditions where the rate of DNA damage exceeds DNA repair capacity of the cell. As a result, fundamental changes to the genetic code and gene expression may cause serious defects in cellular function and tissue physiology. This can be a consequence of dysfunctional DNA repair, epigenetic changes leading to disturbed DNA damage response and accumulation of genetic aberrations in cells. These changes can be classified into the two major groups: instability occurring at the chromosomal and at the nucleotide levels. Instability at the nucleotide level occurs due to faulty DNA repair pathways such as BER and NER. The chromosomal instability represents alterations, which result in gains or losses of whole chromosomes as well as inversions, deletions, duplications and translocations of large chromosomal segments.[60] DNA repair processes play critical roles in repairing damaged DNA, and in ensuring accurate transmission of genetic material. Inherited defects of genes in these pathways lead to disorders, most of which significantly increase susceptibility to cancer and neurodegeneration.[26,61] Epigenetic modifications such as methylation and histone modification have also been shown to affect genomic stability.[60] Global hypomethylation and genomic instability are seen in many cancers.[62] The classic model for neurodegeneration due to dysfunctional DNA repair represents the idea that DNA damage accumulates in the absence of repair, resulting in the death of neurons.[5] According to this mechanism, which presently is generally accepted, endogenous DNA damage is constantly being produced in normal conditions but also repaired, resulting in a low-steady-state level of damage which is compatible with normal cellular function. However, under conditions of DNA repair deficiency, endogenous damage is not repaired and therefore accumulates over time, ultimately leading to neuronal death as a result of impaired transcription. Indeed, defects in DNA damage response/DNA repair observed in patients with a variety of hereditary DNA repair diseases are associated with neurological abnormalities.[61] Therefore, alcohol-induced DNA damage, if not repaired, may play a key role in alcohol-induced neurotoxicity.

Alcohol and OCM

Hyperhomocysteinemia, which is an indication of OCM dysfunction, is often observed in patients suffering from chronic alcoholism.[10,21] It has been known for many years that ethanol has an effect on folate metabolism. The etiology of folate deficiency in alcoholism can be caused by any or all of the following: poor absorption, decreased uptake and retention, and increased urinary excretion.[21] Furthermore, increased Hcy in patients suffering from alcohol dependence may be due to direct interactions of ethanol or its

metabolites with OCM.[63] Indeed, ethanol has been shown to directly affect OCM by inhibiting a key OCM enzyme, methionine synthase (MS), by 50% as early as six days of ethanol exposure.[64,65] These findings have been corroborated by other investigators using different animal models of ethanol injury.[21,66,67] Ethanol treatment has been demonstrated to reduce MS activity in the brain.[68] Based on *in vitro* experiments, it has been suggested that acetaldehyde, but not ethanol, causes inhibition of MS activity.[69] In spite of supraphysiological inhibitory levels of acetaldehyde in these experiments, the actual concentrations may be much lower than the reported values because acetaldehyde is highly volatile. Thus, it may be reasonable to assume that the *in vitro* assay could represent an acute treatment for a short time and the *in vitro* data may not reflect the true situation occurring *in vivo*. Given that MS is critical for OCM function, its down-regulation or direct inhibition may play a significant role in alcohol-induced OCM impairment.

OCM reactions (Figure 2) can be viewed as two intertwined cycles, one producing dNTPs, the precursors for DNA biosynthesis and repair, and the other producing and utilizing *S*-adenosyl methionine (SAM), the universal donor in cellular methylation reactions.[24,25] 5,10-methylene-tetrahydrofolate (5,10-methylene-THF) is a critical OCM junction where one-carbon groups can either be used to produce dNTPs for DNA synthesis or serve for the methylation cycle via irreversible synthesis of 5-methyl-THF catalyzed by methylene THF reductase. Following SAM-dependent transmethylation and hydrolysis of the ensuing *S*-adenosyl homocysteine (SAH), the resulting Hcy can be re-methylated back to methionine by the folate-mediated MS reaction. OCM dysfunction causes alteration in the *de novo* synthesis of DNA precursors, purines and thymidylate, negatively affecting the intracellular dNTP pool and, consequently, DNA synthesis (and cell proliferation) and repair (and genomic stability).[70] The dNTP supply via the salvage pathway, whose purpose is to provide the cell with a low supply of dNTPs, cannot compensate DNA precursor pool imbalance from aberrant *de novo* dNTP synthesis. As a result, the dNTP synthesis pathway is the predominant mechanism for supplying dNTPs in the brain.[71,72] The DNA repair pathway for removal of an incorrect DNA base, such as one of the most abundant alcohol-induced DNA base lesions oxo8dG, is BER.[73] Acetaldehyde-derived cross-links are repaired by the FA-linked pathway, coordinated with classical NER, applicable to non-replicating cells such as neurons.[56,74] Both DNA excision repair pathways, BER and NER, involved in the repair of alcohol-generated DNA damage, operate through the removal of damaged bases and their substitution with correct ones by the pathway-specific polymerases. The availability of dNTPs from OCM is important for BER and NER because DNA polymerases involved in these pathways are not functional when nucleotides are depleted. This leads to compromised DNA repair and accumulation of DNA lesions.[75] Thus, OCM dysfunction is associated with compromised DNA excision repair pathways due to a decrease of synthesis of dNTPs and ensuing dNTP pool imbalance. Particularly, chronic alcohol administration has been reported to significantly reduce BER.[76] Dysfunctional DNA repair results in accumulation of DNA damage and death of neurons.[5]

OCM is essential for DNA methylation and its disturbance can result in global DNA hypomethylation.[77] DNA methylation is a major epigenetic mechanism central to regulation of chromatin structure, genomic stability, gene transcription, and ultimately cell function and development. Functionally, proper DNA methylation can restrain the inappropriate expression of genes, thereby shaping cellular fate and function. In higher organisms, a methyl moiety is preferentially targeted to the DNA base cytosine in the context of a CpG dinucleotide, with the exception being X-inactivation. DNA is highly methylated in CpG-rich sequences (>50%), which has been suggested to represent a defense mechanism for silencing parasitic DNA elements such as transposons and retrotransposons.[78] DNA methylation leads to a condensed structure and transcriptional repression. Aberrant methylation is associated with increased genomic instability[79] and carcinogenesis,[80] as well

as brain disorders such as ischemia.[81] At least three hereditary diseases with aberrant methylation, immunodeficiency/centromeric instability/facial anomalies (ICF), Rett and fragile X syndromes,[82] are characterized by mental impairment, indicating the importance of methylation for brain function. DNA methylation depends on OCM as a source of methyl groups and dNTP methyltransferases which methylate cytosine residues at CpG sites in DNA. For this reason, hypomethylation can be caused by OCM impairment or mutations/inactivation of methyltransferases. Indeed, DNA hypomethylation has been demonstrated experimentally as a result of dietary folate deficiency,[83] or mutations of enzymes, important for DNA methylation.[83,84] Given that alcohol interferes with OCM,[63,85,86] alcohol-induced aberrant DNA methylation[87] is likely mediated by OCM impairment. Interestingly, elevated Hcy (OCM impairment) is considered an independent risk factor for numerous neurodegenerative diseases.[26,78]

In summary, alcohol affects OCM function. OCM is critical for synthesis of DNA precursors and methylation reactions (including DNA methylation). OCM impairment may cause DNA precursor imbalance and ensuing disturbance of DNA synthesis, which is important for cell proliferation and DNA repair. Dysfunctional DNA repair leads to genomic instability, and is a unified genetic mechanism causing a variety of neurological and neurodegenerative disorders.[88–90] There has been compelling evidence accumulated that disorders such as Alzheimer's, Parkinson's and Huntington's diseases and Down's syndrome result from dysfunctional DNA repair and increased DNA damage.[90] Different brain regions are affected in these neurodegenerative diseases, as well as hereditary diseases with DNA repair deficiencies: cerebellar Purkinje neurons in ataxia telangiectasia, dopaminergic neurons in the substantia nigra in Parkinson's disease, neuronal loss in the striatum and cerebral cortex in Huntington's disease, and loss of neurons in the cerebral cortex in Alzheimer's disease.[90] It is unclear, however, why different brain regions are affected in these disorders. Analysis of the types of neurons lost from the frontal cortex of alcoholics revealed that this population of neurons is also more vulnerable in both Alzheimer's disease[91] and normal aging[92] in which DNA repair disturbance plays an important role.[26] Atrophy of the cerebellum is commonly associated with alcoholism. Torvik *et al*.[93] reported that 26.8% of alcoholics with Wernicke–Korsakoff syndrome had cerebellar atrophy with a loss of Purkinje cells that correlated with clinical ataxia/unsteadiness.[94] This is especially interesting given the ataxia and death of Purkinje neurons in patients with ataxia telangiectasia, a hereditary disease with impaired DNA damage response.[90] Understanding the causes and time-courses of DNA damage in the brain generally and in specific regions following chronic ethanol exposure will help to understand how DNA repair dysfunction and ensuing DNA damage may cause the damage of particular brain regions.

The phenotype of OCM impairment includes reduced tolerance to DNA-damaging agents, and genomic instability.[70,75,95,96] Genomic instability results in mutagenesis and carcinogenesis.[97] At the same time, it is associated with neuronal cell death and neurodegeneration.[88–90] Alcohol abuse is known to increase the risk for various types of cancer,[10,20,97–99] and contributes to neurodegeneration.[88–90] The contribution of genomic instability to both carcinogenesis and neurodegeneration is illustrated by the fact that DNA repair defects in various human syndromes are usually characterized by both cancer predisposition and neurological abnormalities.[90] Since OCM impairment is associated with DNA repair dysfunction and aberrant methylation, both linked to genomic instability, chronic alcohol-induced genomic instability and associated neuro-degeneration are likely mediated, at least in part, by alcohol's impact on OCM.

Conclusion

Throughout this paper, we have emphasized the role of genomic instability in the adverse effects of chronic alcohol abuse on the brain. Ethanol metabolism, including those in brain, elicits the formation of genotoxic ROS and acetaldehyde.[5,14,42] If not efficiently detoxified, these metabolites induce DNA damage, which is reversible in conditions of an acute alcohol exposure.[14,17,18,48] However, chronic alcohol abuse is characterized by extensive DNA damage and genomic instability,[14,17,18] which is a risk factor for different types of cancer[10,20,98,99] and neurodegeneration.[88–90] Alcoholism is known to increase the risk for cognitive impairment and dementia and is characterized by structural damage to the brain.[4–6] The present review describes the current knowledge concerning alcohol-induced genomic instability with alcohol-induced OCM impairment. Increased Hcy concentrations, a marker of OCM disturbance is common in alcoholics,[21,100] and at the same time is a risk factor for various neurodegenerative diseases.[101,102] OCM is vital for cellular homeostasis, providing cells with DNA precursors, essential for cell proliferation and DNA repair, as well as methyl groups for DNA methylation. Thus, OCM dysfunction can lead to a shortage of DNA precursors, resulting in impaired DNA repair, as well as aberrant DNA methylation. Both DNA repair dysfunction and aberrant DNA methylation cause genomic instabilty.[79,97] OCM impairment is among the factors that promote genomic instability.[67,95] Different factors can affect the sensitivity of brain to alcohol in this context. Two examples are age and gender. Accumulated DNA damage is thought to be an important factor underlying aging.[103] Defective DNA repair causes an accelerated aging-like phenotype of the brain.[104] Hcy concentrations (and OCM impairment) increase with age,[101] and age-related brain atrophy in healthy elderly people correlates with plasma Hcy concentrations.[105,106] Among the factors that influence vulnerability of the brain to alcohol is gender. Women show a greater susceptibility to alcohol-related diseases, including an increased risk for brain damage with significantly lower alcohol exposure compared with men.[107] The mechanism involving increased DNA damage and impaired DNA repair may contribute to the gender-related differences in vulnerability to alcohol. It is known, for example, that poly (ADP-ribose) polymerase-1 (PARP-1) deletion reduces ischemic brain injury in men but exacerbates injury in women.[108] Since PARP-1 is a factor that plays an important role in the DNA damage response and DNA damage-induced cell death signaling,[109] this difference suggests that the DNA damage response is different in men and women, and that the gender-related differences in vulnerability to alcohol may be caused by different responses to DNA damage. Further investigation of the cellular and molecular mechanisms involved in the genotoxicity of chronic alcohol, its interference with OCM, and the impact on DNA repair and DNA methylation will help to understand the mechanisms of ethanol-induced brain damage and will likely contribute to the development of treatments and/or therapeutic agents that could reduce or eliminate the deleterious effects of alcohol on the brain.

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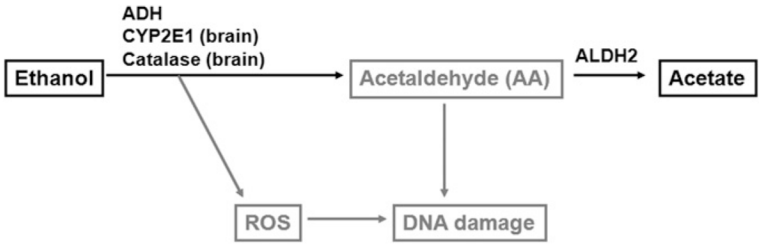

Figure 1.

How alcohol may impact DNA. Ethanol is metabolized to acetaldehyde (AA) by alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1) and catalase. AA is metabolized to acetate by aldehyde dehydrogenase 2 (ALDH2). Catalase and CYP2E1 are particularly relevant to ethanol metabolism in brain tissue. The CYP2E1-dependent pathway is a major contributor to ethanol-generated reactive oxygen species (ROS). ROS induce DNA damage

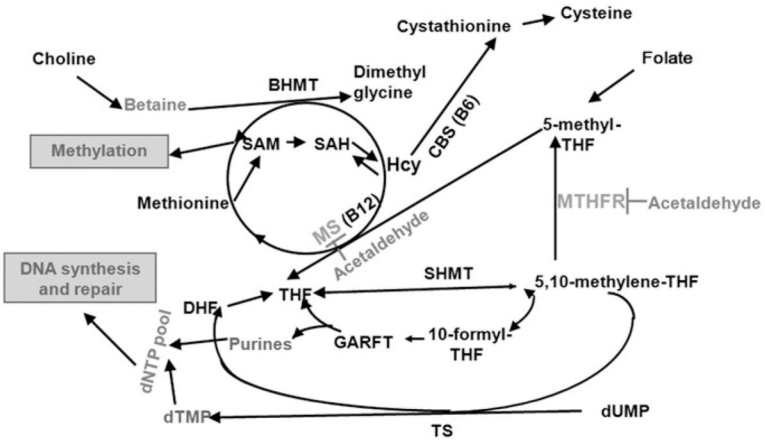

Figure 2.

One-carbon metabolism as a target for ethanol. BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine *β*-synthase; DHF, dihydrofolate; dNTP, deoxyribonucleotide triphosphate; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; GARFT, glycinamide ribonucleotide formyltransferase; Hcy, homocysteine; MS, methionine synthase; MTHFR, methylene THF reductase; SAH, *S*-adenosyl homocysteine; SHMT, serine hydroxy-methyltransferase; THF, tetrahydrofolate; TS, thymidylate synthase