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# Brain ethanol metabolism and mitochondria

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## Abstract

Alcohol abuse and dependence in humans causes an extreme shift in metabolism for which the human brain is not evolutionarily prepared. Oxidation of ethanol and acetaldehyde are not regulated, making ethanol a dominating metabolic substrate that prevents the activity of enzymes from oxidizing their usual endogenous substrates. The enzymes required to oxidize ethanol across the variety of affected tissues all produce acetaldehyde which is then converted to acetate by aldehyde dehydrogenases (ALDHs). ALDHs are NAD+-dependent enzymes, and mitochondrial ALDH2 is likely the primary contributor to ethanol-derived acetaldehyde clearance in cells. Metabolism of alcohol has several adverse effects on mitochondria including increased free radical levels, hyperacetylation of mitochondrial proteins, and excessive mitochondrial fragmentation. This review discusses the role of astrocytic and neuronal mitochondria in ethanol metabolism that contributes to the acute and chronic changes in mitochondrial function and morphology, that might promote tolerance, dependence and withdrawal. We also propose potential modes of therapeutic intervention to reduce the toxicity of chronic alcohol consumption.

### Keywords

ethanol; brain; mitochondria

## INTRODUCTION

Prolonged and excessive alcohol consumption leads to wide-ranging and diverse effects of ethanol on the central nervous system and contributes to the development of brain pathology. The toxic effects of ethanol and its downstream metabolites are associated

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CONFLICT OF INTEREST STATEMENT

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with cancer, cardiovascular problems, and neurodegenerative diseases such as Alzheimer's and Parkinson's disease [1–4]. Ethanol readily passes through biological membranes and distributes throughout the body into all organs including brain [5]. Since during the evolution of human species there was little alcohol in consumed food, mechanisms for regulation of ethanol metabolism did not evolve, leaving both adult and developing humans vulnerable to ethanol toxicity [5]. Ethanol dependence is now a significant problem leading to pathologic consequences, causing significant medical, social, and economic burdens [3, 4]. Both acute and chronic alcohol exposure produce molecular and cellular neuroadaptations that modulate the activity of discrete brain regions and cell types [3, 6, 7].

After consumption, the elimination of alcohol from blood occurs at a constant rate of about 0.016 g/dl/h for men and slightly higher 0.018 g/dl/h for women [8]. The removal of ethanol by the human body, consumed during social drinking (about 0.9 g/kg of body weight), takes 5 to 7 hours and throughout this time ethanol oxidation is the largest carbon source for energy metabolism [9, 10]. Further intake of ethanol extends the time of increased alcohol levels in blood, but the rate of its elimination does not change. Thus, in individuals consuming alcohol several times a day the blood ethanol levels remain significantly high most of the time, considerably affecting brain energy metabolism, and triggering epigenetic changes associated with development of alcohol use disorder, or addiction.

## Enzymes involved in alcohol and acetaldehyde metabolism

Since ethanol readily passes through biological membranes, the concentration in brain tissue approximates that of blood [5]. Oxidation of ethanol in brain is carried out by three enzymes, alcohol dehydrogenase (ADH), catalase, and cytochrome P540 2E1 (CYP2E1) (for review see [9]). However, ethanol metabolism by CYP2E1 and catalase makes only minor contributions [11]. All three enzymes produce acetaldehyde (Figure 1). Conversion of ethanol to acetaldehyde by ADH also reduces $NAD^+$ to NADH. Catalase generates acetaldehyde from ethanol in the presence of hydrogen peroxide, and CYP2E1 requires oxygen and NADPH to convert ethanol to acetaldehyde plus $NADP^+$ and acetate.

Acetaldehyde can react nonenzymatically with other cellular components leading to cytotoxic effects with pathologic consequences for cell function and survival [12]. The concentration of acetaldehyde is kept low by the activity of aldehyde dehydrogenase (ALDH) that is widely distributed in the brain tissue [13, 14]. ALDH oxidizes acetaldehyde to acetate and during this process $NAD^+$ is reduced to NADH. The oxidation of acetaldehyde is extremely efficient keeping the circulating levels of acetaldehyde more than thousand-fold less than ethanol levels in the blood [15, 16]. Furthermore, acetaldehyde does not penetrate the blood vessels into the brain due to the presence of ALDH in the blood-brain barrier [17, 18].

Most of the consumed alcohol is oxidized in liver by alcohol dehydrogenases and then by aldehyde dehydrogenase enzymes. However, the elevated blood alcohol levels during liver-facilitated oxidation will also keep the brain ethanol levels elevated ensuring an effect on brain metabolism and functions. It should be noted that ethanol *per se* has specific binding sites on several proteins, including neurotransmitter receptors, channel proteins and enzymes that may act directly or indirectly to produce biological effects [3].

In this review we will discuss acute brain ethanol oxidation, its impact on enzymes oxidizing ethanol, on mitochondrial functions, and protein posttranslational modifications.

## Initial step in brain alcohol oxidation

There are six main classes of the ADH enzyme, and their expression levels are tissue specific [19]. Originally, it was suggested that only the subtype ADH3 was expressed in the brain [20–22]. However, its contribution to alcohol oxidation was questioned due to very high Km values (about 15 mM) for ethanol [23]. Another group demonstrated the presence of mRNA for ADH1 and ADH4 in rat brain cells [24]. Interestingly, the ADH activity was localized only in specific neurons of cerebral cortex, pyramidal and granule cells of hippocampus, hypothalamus, and cerebellum (granule cells and Purkinje cells), whereas no significant ADH activity was found in whole brain homogenate [24–27]. This suggests that only specific neurons within the brain can significantly contribute to initial ethanol oxidation *via* ADH activity.

Catalase probably also contributes to conversion of ethanol to acetaldehyde in brain [28]. The finding that inhibitors of catalase were effective in inhibiting the production of acetaldehyde from ethanol in rat brain tissue supports this role [13]. Furthermore, inhibitors of the CYP2E1 or ADH had no significant effect on production of acetaldehyde in experiments using brain homogenate. However, the role of catalase in systemic alcohol metabolism has not been clarified *in vivo* [29], and the oxidation of ethanol by catalase is also limited by the availability of hydrogen peroxide that is required for the ethanol metabolism.

It should be noted that the endogenous function of ethanol-metabolizing enzymes is not linked directly to ethanol oxidation but rather ADH participates in brain retinol and serotonin metabolism [30, 31], and catalase has an important role in cellular antioxidant defense systems as it detoxifies hydrogen peroxide. Furthermore, ADH3 was suggested to contribute to the defense of the brain against degenerative processes since it is considered a glutathione-dependent formaldehyde dehydrogenase [32], and ADH3 partially regulates nitrosothiol homeostasis by catalyzing the reduction of the endogenous nitrosylating agent S-nitrosoglutathione [33]. The mechanisms that might regulate ADH are not known. However, recently ADP-ribosylation was suggested to be a posttranslational modification affecting the enzymatic activity of ADH [34].

Cytochrome P450 enzymes oxidize ethanol in liver, and have also been implicated in ethanol metabolism in the brain, particularly the isoenzyme CYP2E1 [35]. This isoform of cytochrome P450 was found in both neurons and astrocytes within cerebellum, cerebral cortex, thalamus and hippocampus [35–37]. The biological function of CYP2E1 is to metabolize xenobiotics and endogenous compounds including acetate, fatty acids, and bile acids [38, 39]. Therefore, ethanol intake will lead to competitive inhibition of CYP2E1 activity and reduce the protective oxidation of xenobiotics that can have serious consequences. However, since this enzyme is expressed mostly in liver the ethanol-induced pathologic effect is observed preferentially in this organ [40].

The experiments with catalase, CYP2E1, ADH and ALDH inhibitors in combination with transgenic animal models with a deficiency in ethanol-metabolizing enzymes (catalase and CYP2E1) suggest that the key ethanol-oxidizing enzyme in brain is catalase, which is responsible for about 80% of the ethanol-metabolizing activity, and CYP2E1 which metabolizes about 20% of ethanol [13]. Follow-up studies confirmed that the majority of alcohol oxidation in brain occurs *via* catalase [41, 42].

## Detoxification of acetaldehyde derived from ethanol oxidation

Although, ethanol metabolism and its regulation in brain remains somewhat controversial, the enzymes that process the acetaldehyde derived from ethanol in brain cells have been long known [43, 44]. Aldehyde dehydrogenases (ALDHs) represent a large family of $NAD^+$-dependent dehydrogenases responsible for metabolism of endogenous and exogenous aldehydes produced under many different pathophysiological states or exposure to toxic agents including alcohol. ALDH1 is also essential for formation of retinoic acid from retinal, the oxidation product of retinol (Vitamin A) [45]. Exposure to toxins is usually associated with increased oxidative stress leading to lipid peroxidation and elevated levels of lipid peroxides such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) that are detoxified by ALDH [46]. These aldehydes are highly reactive and lead to modification of cellular macromolecules including DNA and proteins [47, 48].

There are at least 19 ALDH isozymes that have different kinetic parameters including distinct $K_m$ values and catalytic activities [49, 50]. Human cytosolic ALDH1A1 isozyme exhibits a high $K_m$ value, about 180 mM for acetaldehyde. However, acetaldehyde can hardly be the natural substrate for human cytosolic ALDH1, because the physiological concentrations of acetaldehyde are typically around 2 mM [51, 52]. However, the higher affinity mitochondrial ALDH2 has a $K_m$ for acetaldehyde 0.2 mM, a 900-fold lower value when compared to cytosolic ALDH1 [53]. Therefore, the action of the mitochondrial ALDH2 is widely believed to be the major contributor to the clearance of ethanol-derived acetaldehyde in cells [54–56]. This suggests compartmentation of ethanol disposal since most of the ethanol in the brain is oxidized to acetaldehyde by catalase, an enzyme that is localized in microsomes and peroxisomes. To prevent the acetaldehyde accumulation, the acetaldehyde produced needs to be taken up into the mitochondrial matrix for oxidation to acetate by ALDH2. This compartmentation also suggests that after ethanol consumption there are elevated levels of acetaldehyde in microsomes and peroxisomes that show high catalase activity, and in the cytosol compared to mitochondria [13], rendering the cytosolic and nuclear macromolecules vulnerable as the primary targets of acetaldehyde toxicity.

The catalytic activity of ALDH isozymes is modified by several post-translational modifications (for review see [57]). Alcohol consumption induces oxidative modifications of cysteine residue ($Cys^{302}$) at the active site of ALDH1 and ALDH2 [58], leading to inhibition of their activity [59–61]. Other studies show that *S*-nitrosylated ALDH2 found in alcohol-exposed animals also has lower activity [59, 62]. Similarly, phosphorylation of ALDH2 by JNK kinase at $Ser^{463}$ residue results in lower activity of this enzyme [63], thereby decreasing cellular defense capacity against aldehyde toxicity. Suppression of ALDH2 activity triggers an increase in reactive lipid peroxide levels and the subsequent

accumulation of these toxic molecules will damage cellular macromolecules including microsomal and mitochondrial proteins, causing mitochondrial dysfunction and eventually cell death [48, 64–66].

In contrast to JNK-dependent phosphorylation, protein kinase Cε (PKCε)-mediated phosphorylation of ALDH2 at $Thr^{185}$, $Thr^{412}$ or $Ser^{279}$ leads to stimulation of ALDH2 activity and has protective effects against ischemia-induced pathology in heart [67–69]. Furthermore, phosphorylation by inositol-3-kinase also leads to stimulation of ALDH2 [70].

Since ALDH2 is a mitochondrial protein, the inhibition of this enzyme can have detrimental effects, leading to the intramitochondrial accumulation of toxic aldehydes that consequently trigger mitochondrial dysfunction and compromise cell survival.

## Acetylation, mitochondria and brain ethanol metabolism

Acetylation is one of the most common post-translational modifications of proteins, and changes in the acetylation levels are linked mainly to regulation of cellular metabolism [71, 72]. In particular, acetylation has significant impact on the function of mitochondrial enzymes. The end product of ethanol metabolism is acetate generated by ALDH from acetaldehyde. Acetate is an energy substrate that can be converted to acetyl-CoA by Acetyl-CoA synthetase in the presence of coenzyme A (CoA) and ATP. Acetyl-CoA in mitochondria can enter the TCA cycle where it condenses with oxaloacetate to form citrate which is oxidized in the cycle for energy. Alternatively, mitochondrial acetyl-CoA can serve as a substrate for the acetyl transferase enzyme (KAT) to acetylate lysine residues on target proteins (Figure 2). Therefore, it is not surprising that many cytosolic and mitochondrial proteins including cytosolic ALDH1A1 and mitochondrial ALDH2 are hyper-acetylated in alcohol-exposed animals [73]. Hyperacetylation of ALDH2 leads to increased activity, and therefore facilitates the detoxification of acetaldehyde or other toxins [74–76].

## Effect of ethanol on cellular bioenergetics

Ethanol oxidation has a significant impact on cellular bioenergetic metabolism since it leads to an unregulated increase in intramitochondrial and cytosolic NADH [77]. Furthermore, the downstream acetyl-CoA generated from ethanol-derived acetate can lead to hyperacetylation of intracellular proteins including mitochondrial proteins [9, 78]. There are two sources of acetate that supply acetate to brain cells after ethanol intake. One is the acetate released from liver into the blood and then transported into brain and astrocytes via the high capacity, low affinity monocarboxylate transporter (MCT1) with reported $K_m$ values between 1.6–9.3 mM, which is expressed mostly in astrocytes [79, 80]. The neuronal, higher affinity, lower capacity monocarboxylate transporter (MCT2; $K_m$ value 2.6 mM) also transports acetate (Figure 2); however, at high concentrations this system would be saturated allowing for more uptake into astrocytes [80]. The other source of acetate is intramitochondrial production. In mitochondria, acetate is formed by mitochondrial ALDH2 from acetaldehyde (see above). Both cytosolic and mitochondrial acetate serve as a substrate for Acetyl-CoA synthetase 1 and 2 (AceCS1 and AceCS2) leading to production of acetyl-CoA [72, 80–82]. Interestingly, acetate from both sources will end up mostly in astrocytes since MCT1, which has a high capacity for uptake [83] is expressed preferentially in astrocytes and ALDH2 is expressed

in astrocytic mitochondria [84]. Thus, one could expect that a significant hyperacetylation of astrocytic proteins will be detected after ethanol consumption [85]. Furthermore, due to localization of AceCS1 in cytosol and nucleus with its attachment to the chromatin, AceCS1 will be able to directly regulate histone acetylation [86, 82]. The mitochondrial AceCS2 enzyme apart from generating Acetyl-CoA for the TCA cycle, will also support the acetylation of mitochondrial proteins [87, 88] by supplying acetyl-CoA to mitochondrial acetyl transferase GCN5L1 [89]. Additionally, both AceCS isoforms are found in neurons and astrocytes, and are subjected to post-translational regulation *via* acetylation under control of $NAD^+$-dependent deacetylases, Sirtuins (SIRTs). AceCS1 is deacetylated by cytosolic SIRT1 and AcesCS2 is deacetylated by mitochondrial SIRT3 [90].

Ethanol metabolism-driven increases in redox pressure reflected in an elevated NADH/$NAD^+$ ratio will increase superoxide production by respiratory complexes [91] and reduce the activity of mitochondrial $NAD^+$-dependent deacetylase SIRT3 due to low $NAD^+$ levels [92–95]. Thus, the hyperacetylation of mitochondrial proteins will be further accelerated due to SIRT3 inhibition. As a result, the activity of the pyruvate dehydrogenase complex, Electron Transport Chain respiratory complex I, and TCA cycle enzymes including citrate synthase, isocitrate dehydrogenase 2, α-ketoglutarate dehydrogenase and malate dehydrogenase will be reduced [92, 96, 97].

One can envisage that due to differential capacity of MCT1 and MCT2 for acetate uptake, moderate drinking will cause acetylation changes preferentially in astrocytes. However, heavy drinkers or repeated intake of ethanol will lead to profound changes in neuronal protein acetylation, alterations in their mitochondrial and cellular metabolism with subsequent epigenetic effects leading to alcohol use disorder and addiction.

## Ethanol metabolism-driven mitochondrial free radical generation

It is generally accepted that ethanol metabolism increases free radical production that contributes to its pathophysiological effects [98, 99]. However, the initial cause of higher reactive oxygen species (ROS) generation due to ethanol consumption is not completely understood. Mitochondria are a main source of free radicals in the cell and possess an active antioxidant system comprised of enzymes that detoxify free radicals [100]. Superoxide, mostly generated by the mitochondrial respiratory complexes [101, 102], is converted to hydrogen peroxide by mitochondrial superoxide dismutase 2 (SOD2) [100, 103]. In the next step, hydrogen peroxide is then detoxified by glutathione peroxidase to water. The mitochondrial ROS levels are determined by the rates of superoxide production and of its detoxification. Ethanol consumption results in hyperacetylation of mitochondrial proteins that has an inhibitory effect on the activity of some of the detoxification enzymes [92, 96, 97]. The hyperacetylation of SOD2 leads to increased levels of ROS due to reduced rate of superoxide detoxification by this enzyme [104, 105]. The ethanol-induced high ROS levels further impair the mitochondrial antioxidant mechanisms by decreasing the mitochondrial glutathione content [106, 107]. The significance of mitochondria-generated ROS as a main source of free radicals after ethanol administration was confirmed by the protective effects of the mitochondria-targeted antioxidant, lipophilic ubiquinone (MitoQ), which ameliorated alcohol-induced oxidative stress, reversed the ethanol-induced inhibition of

ALDH2 activity and increased acetaldehyde clearance [108]. Furthermore, ROS generated during EtOH metabolism in mitochondria will inhibit the activity of aconitase, an enzyme which is downstream of citrate leading to intramitochondrial accumulation and transport of citrate from the mitochondrial matrix into the cytosol. The increase in cytosolic citrate will stimulate generation of cytosolic acetyl-CoA by ATP citrate lyase (ACLY) and further contribute to hyperacetylation of cytosolic proteins and histones [109]. ACLY is mostly localized to neurons [110] and is stabilized by acetylation due to blocking of acetylated ACLY ubiquitylation and degradation [111]. Thus, ethanol-induced changes in mitochondrial TCA cycle metabolism can indirectly modulate histone acetylation and alter gene expression *via* ACLY activity.

## Effects of ethanol on mitochondrial dynamics

Mitochondrial response to stress is reflected not only in modification of their function but also in their structure and morphology. To efficiently respond to cellular metabolic demands, mitochondria possess the unique capability as an organelle that can go through cycles of fission and fusion [112–114]. This process of dynamic change in the mitochondrial morphology is controlled by several proteins, the activities of which are regulated by post-translational modifications (Figure 3) [115]. Fission and fragmentation of mitochondria are triggered by various stress conditions including elevated free radical levels [115, 116]. Excessive mitochondrial fission is associated with both acute brain injury and neurodegenerative diseases [117–120]. The main fission controlling enzyme, dynamin-related protein (Drp1), is activated by several post-translational modifications [115, 121–123]. The *S*-nitrosylation, phosphorylation at Ser616, SUMOylation, and acetylation increase the translocation of Drp1 to the mitochondria and activate the fission process [115]. *In vitro* studies showed that ethanol treatment increased mitochondrial fission and this process was inhibited by the mitochondria-targeted antioxidant MitoQ [124]. Similarly, ethanol treatment of neuroblastoma cells caused an increase in ROS levels and phosphorylation of Drp1 by activation of calmodulin-dependent protein kinase 2 (Camk2) which led to increased mitochondrial fragmentation [125]. Pretreatment of cells with antioxidants or using KN-93 a Camk2 inhibitor attenuated Drp1 phosphorylation and subsequent mitochondrial fission [125]. In addition, acetylation of Drp1 at lysine 642 (K642) was associated with Drp1 phosphorylation at Ser616, and its translocation to mitochondria followed by mitochondrial fission [122]. Acetaldehyde's toxicity to neuronal cell lines is accompanied by excessive mitophagy and a drastic reduction in mitochondrial mass [126]. Mitophagy was attenuated by treatment with N-acetyl-L-cysteine, highlighting the oxidative stress induced by ethanol [126].

The opposite process to fragmentation is a mechanism that carries out fusion of the small organelles into larger mitochondrion [115, 127, 128]. The process of fusion is controlled by the intramitochondrial optic atrophy 1 protein (OPA1) enzyme, responsible for inner membrane fusion and mitofusin1 and 2 (Mfn1, Mfn2) that regulate the fusion of the mitochondrial outer membrane [127]. Similar to the enzymes regulating the fission process, the activity of fusion-controlling proteins is also modulated by post-translational modifications. Hyperacetylation of OPA1 reduces its activity, thus inhibiting the fusion and subsequently leading to increased mitochondrial fragmentation [129]. Hyperacetylation of

Mfn1 will also cause inhibition of fusion, as reflected in high levels of small mitochondrial organelles [130].

Apart from stress or pathologic conditions, mitochondria fragmentation is also initiated by energy requirements in distal part of the cells where smaller mitochondria organelles are required to move to provide energy [131]. A recent study demonstrated that changes in spine morphology and the trafficking of mitochondria to synapses is a critical step in the adverse effects of exposure to ethanol. Mitochondrial trafficking was also determined as necessary for acquisition of alcohol-induced place preference [132]. Thus, changes in mitochondrial dynamics in response to ethanol are similar to those observed in memory formation, where they fuel the synapse to support translation [131].

Alcohol metabolism has several adverse effects on mitochondria including an increase in free radical levels, hyperacetylation of mitochondrial proteins, and excessive fragmentation with pathologic dysregulation of oxidative energy metabolism. Since activation of Sirtuins can reverse these adverse effects, a therapeutic approach that will increase cellular and mitochondrial $NAD^+$ levels and activate Sirtuins could be beneficial in preventing posttranslational changes leading to addiction or associated with ethanol-induced damage. This notion is supported by the data showing that animal exposure to running wheels prevents ethanol rewarding effects *via* activation of SIRT1 and SIRT2 [133].

## CONCLUSION

Ethanol metabolism represents a complex process that includes several downstream pathways and has tissue-type specific characteristics. Generally, the normal functions of the enzymes that oxidize alcohol are not to process ethanol, but rather they are part of specific metabolic pathways in cells that are not directly related to ethanol oxidation. Since there was no evolutionary pressure for developing ethanol-specific oxidizing enzymes in humans, there are no intrinsic control mechanisms that could reduce the toxic and adverse effects of increased ethanol consumption.

Although most of the ethanol oxidation is carried out in the liver, the increased blood levels of acetate and elevated blood ethanol concentrations have significant impact on brain metabolism and the functions of specific neuronal subpopulations leading to alcohol use disorder and alcohol addiction. There are several adverse effects induced by ethanol metabolism in brain cells. First, the function of enzymes participating in ethanol oxidation will be inhibited leading to perturbed metabolism of their endogenous substrates. Second, the intracellular redox change due to an increased ratio of NADH to $NAD^+$ will contribute to the increased generation of superoxide by the mitochondrial respiratory complexes and alter the metabolism of carbohydrates in cytosol and mitochondria in brain. Third, the rise in production of acetyl-CoA due to uptake of acetate from blood and the acetate intracellularly generated from ethanol oxidation will lead to hyperacetylation of cellular proteins, and modification of histones, which can lead to epigenetic consequences.

Since alcohol addiction and alcohol-triggered brain pathology is tightly associated with alterations of functions in specific neuronal subpopulations, most research in this field has

focused on adverse effects of ethanol consumption on these specific cells/brain regions. However, considering that the acetate generated from ethanol oxidation in liver enters brain and is taken up by astrocytes and converted to acetaldehyde by the enzyme ALDH2, which is selectively expressed in astrocytic mitochondria, more research should be focused on the role of astrocytes and their mitochondria in processes leading to addiction and alcohol use pathology.

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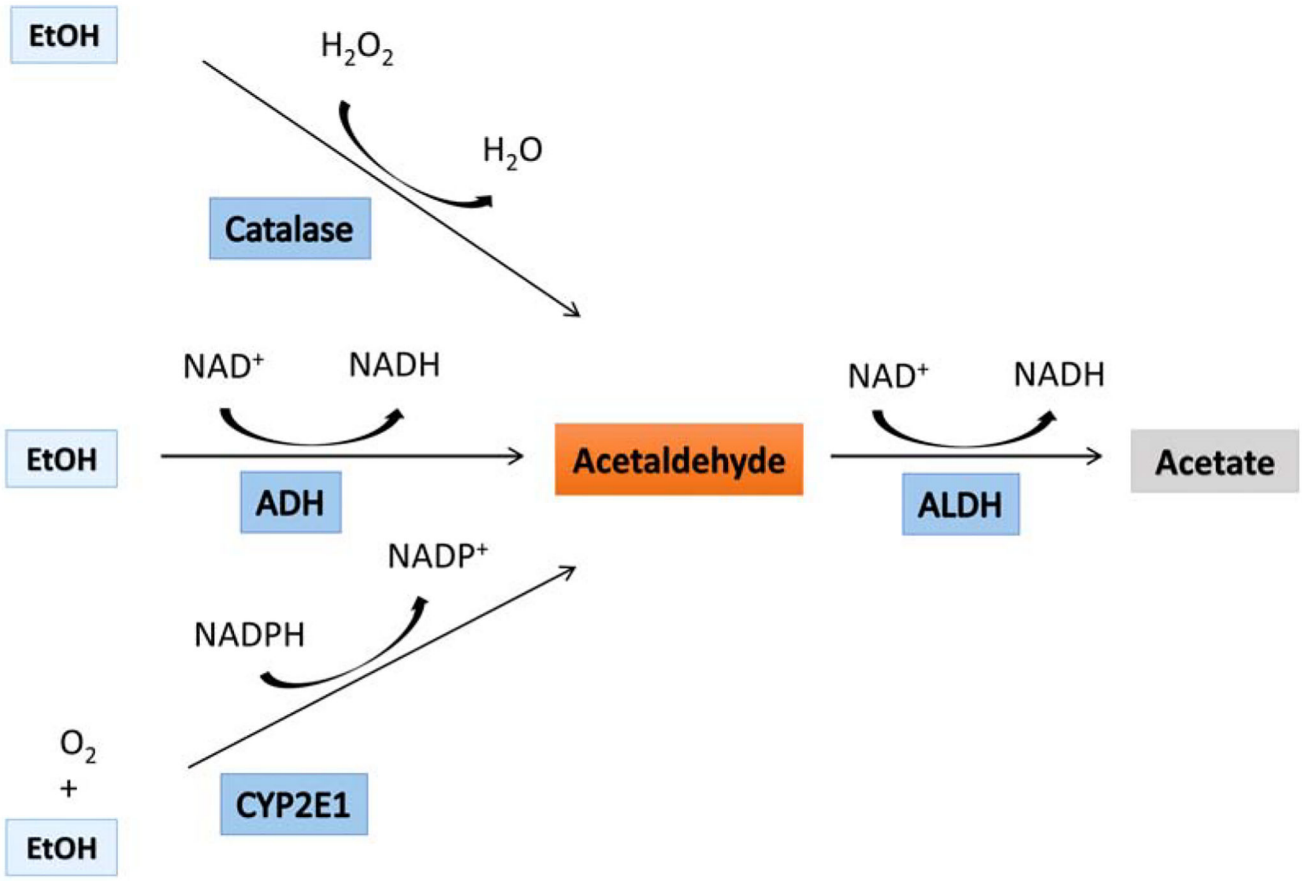


**Figure 1.**

Ethanol-oxidizing enzymes. There are three enzymes that can oxidize ethanol in cells. All three enzymes convert ethanol to acetaldehyde. Alcohol dehydrogenase (ADH) during ethanol oxidation is reducing $NAD^+$ to NADH. Catalase requires a presence of hydrogen peroxide to oxidize ethanol, and Cytochrome p450 2E1 (CYP2E1) uses oxygen and NADPH to convert ethanol to acetaldehyde, and $NADP^+$. Acetaldehyde is oxidized by aldehyde dehydrogenase (ALDH) to acetate with concomitant generation of NADH.

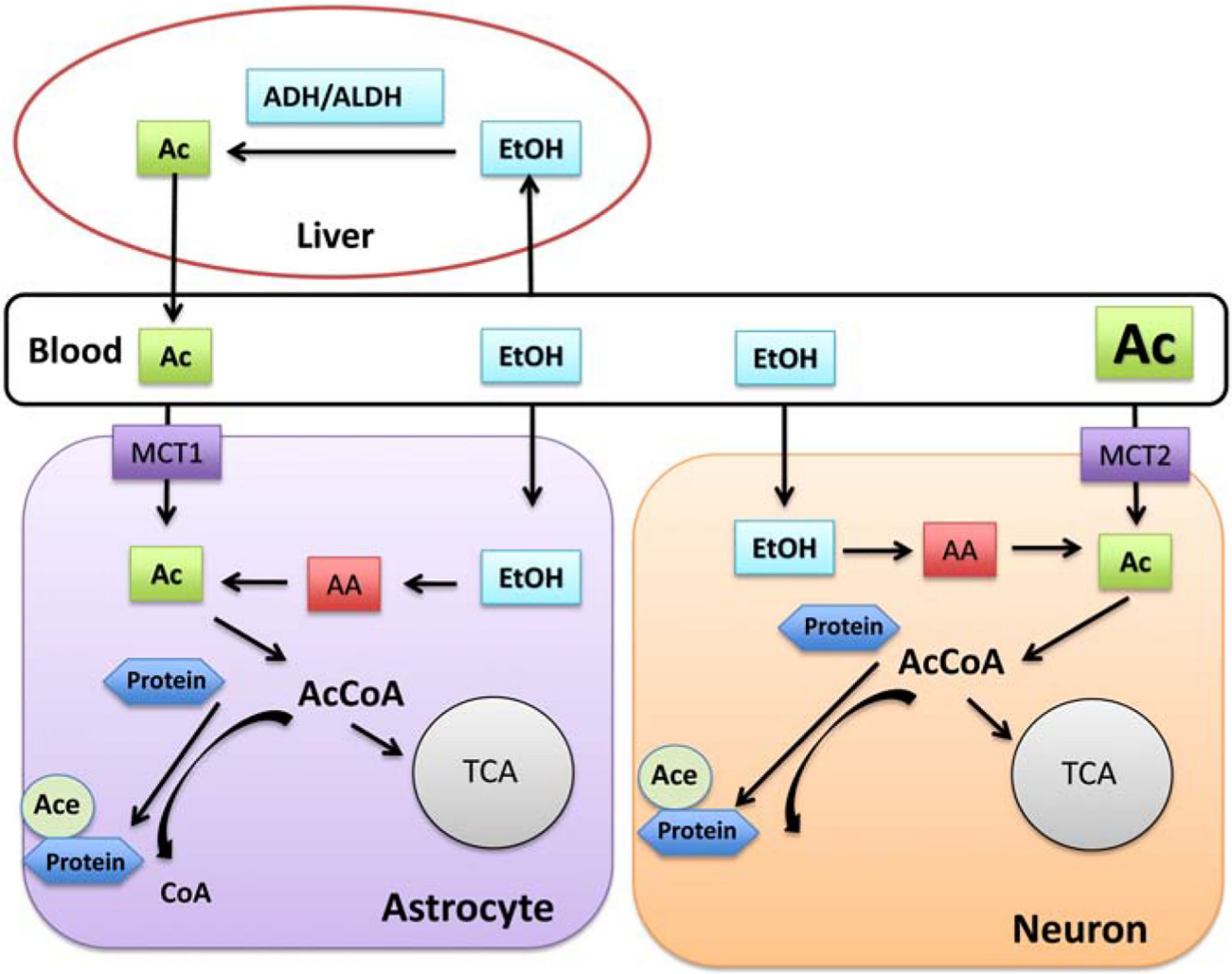


**Figure 2.**

Effects of ethanol oxidation on cellular metabolism in brain. Since ethanol can pass cellular membranes, it enters both liver and brain cells where it is converted to acetate. Acetate generated by liver *via* reactions of alcohol dehydrogenase (ALD) and acetaldehyde dehydrogenase (ALDH) enters the blood and it is transported into brain cells by monocarboxylase transporters (MCT1 and MCT2). The high capacity, low affinity MCT1 transporter is expressed on astrocytes and the low capacity, higher affinity transporter MCT2 is localized on neurons. Acetate after entering the cytoplasm is a substrate for acetyl-CoA synthetases that form Acetyl-CoA (AcCoA). In cells AcCoA is serving as a substrate for lipid and sterols metabolism and is required by acetyl transferases to acetylate histone and non-histone proteins. AcCoA formed in mitochondria can either enter mitochondrial TCA cycle or can be used for acetylation of mitochondrial proteins.

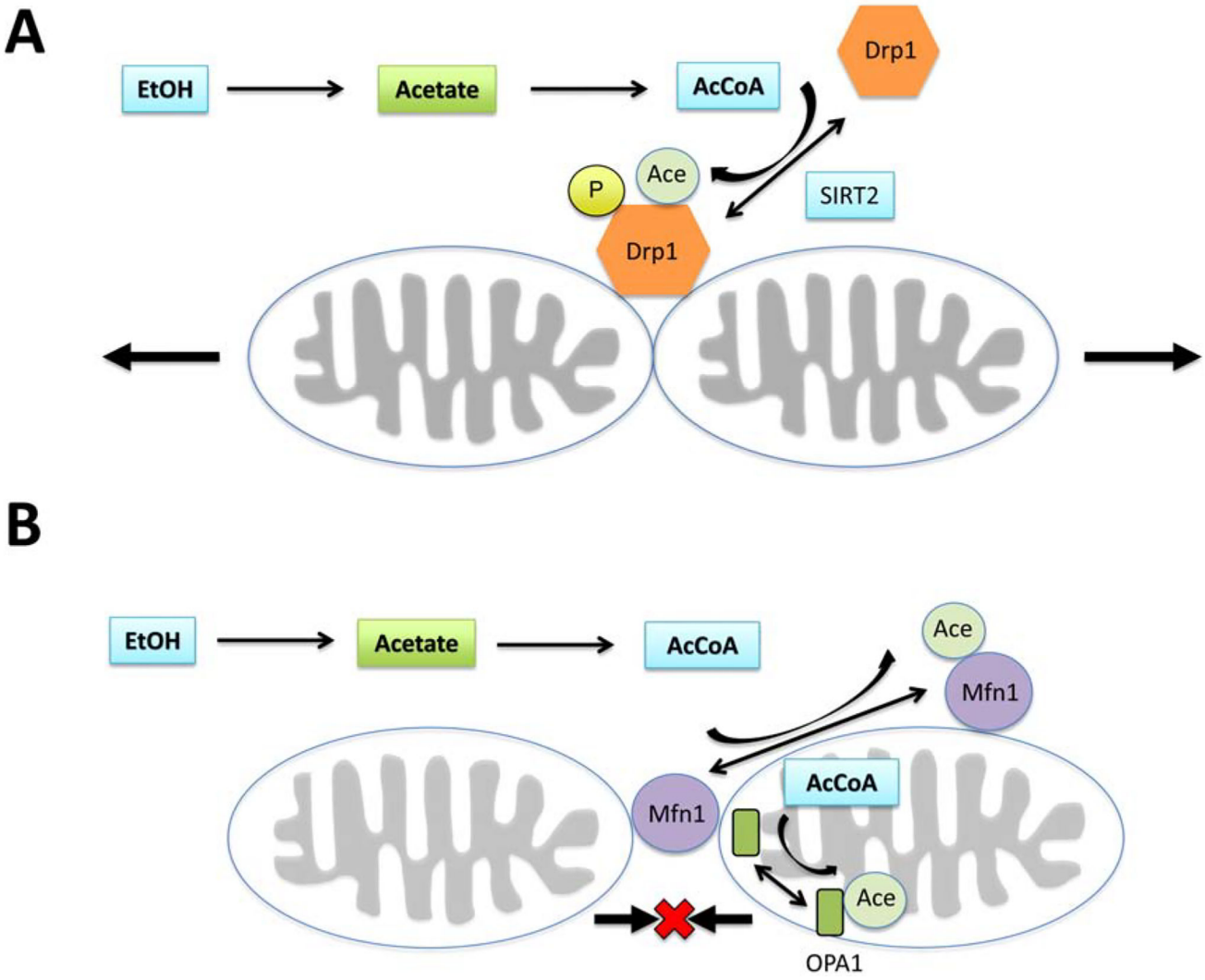


**Figure 3.**

Modulation of mitochondrial dynamics by ethanol oxidation. Activity of both fission and fusion-controlling proteins are altered by acetylation. (A) Elevated levels of AcCoA due to ethanol metabolism can lead to acetylation of Drp1 and its translocation to mitochondrial membrane and initiation of the fission process. Similarly, acetylation of Mfn1 and Opa1 will inhibit fusion, thus maintaining the mitochondria in fragmented state.