

# Acetic Acid in Ethanol-Induced in Regulating Cardiovascular Function

Subjects: Physiology

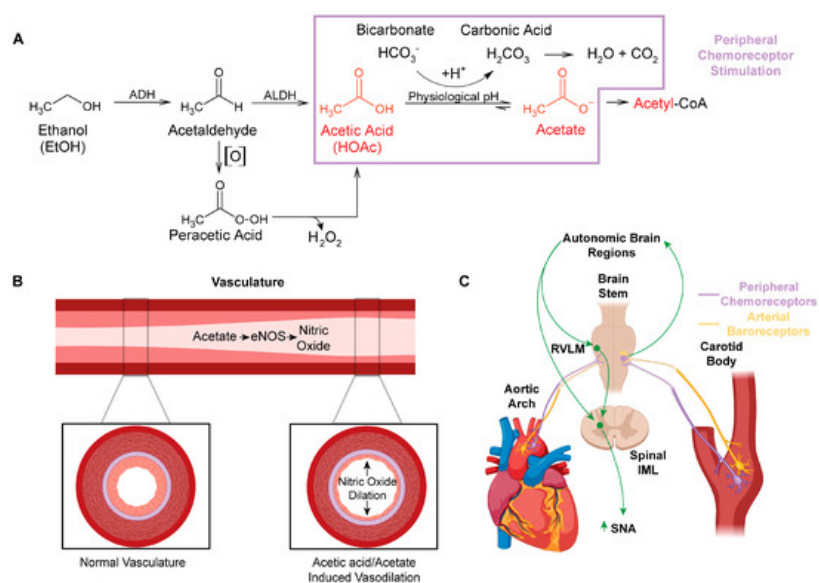
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Acetic acid is a bioactive short-chain fatty acid produced in large quantities from ethanol metabolism. How acetic acid/acetate generates oxidative stress, alters the function of pre-sympathetic neurons, and can potentially influence cardiovascular function in both humans and rodents after ethanol consumption are described.

Keywords: ethanol ; acetic acid ; acetate ; nitric oxide ; sympathetic nerve activity ; cardiovascular function

## 1. Introduction

Ethanol metabolism produces systemic maladaptive changes through oxidative stress. Ethanol metabolism in vivo generates reactive oxygen and nitrogen species, predominantly through oxidative pathways involving NADPH/NADP<sup>+</sup>, NAD<sup>+</sup>/NADH, and/or H<sub>2</sub>O<sub>2</sub> [1]. Ethanol is oxidized to acetaldehyde, which becomes acetate at physiological pH (Figure 1A) [2]. Acetate is then shuttled into the citric acid cycle, where additional oxidative stress is likely generated through electron transport chain electron leak [3]. Chronic oxidative stress from ethanol metabolism leads to liver [4][5][6][7][8], brain [9][10][11][12][13], and cardiovascular pathologies [14][15][16][17][18][19][20].

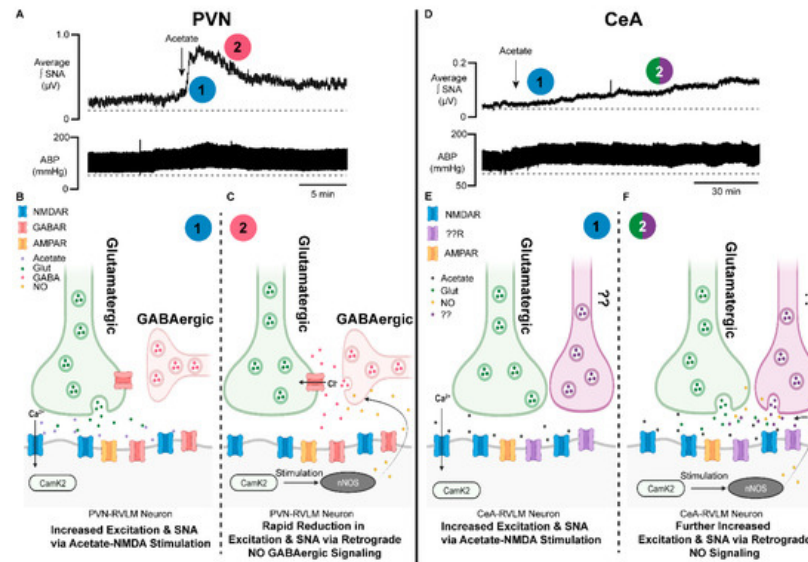


**Figure 1.** Impact of acetic acid/acetate on peripheral vasculature and the regulation of cardiovascular function. **(A)** Major metabolic pathway for ethanol metabolism (box in purple highlights potential chemoreceptor-stimulating pathways). Auto-oxidation (denoted [O]) of acetaldehyde, which can be increased by the presence of Fe<sup>3+</sup> to form peracetic acid (peroxyacetic acid). Peracetic acid decomposes to acetic acid, generating hydrogen peroxide. **(B)** Acetate stimulates eNOS in the peripheral vasculature, which increases production of the powerful vasodilator, nitric oxide. **(C)** Schematic of the location of peripheral arterial baroreceptors and chemoreceptors, their innervation to the brainstem, and their relationship with neural control of autonomic function. Abbreviations: alcohol dehydrogenase (ADH), cytochrome P450 (CYP 450), aldehyde dehydrogenase (ALDH), endothelial nitric oxide synthase (eNOS), nitric oxide (NO), rostral ventrolateral medulla (RVLM), intermediolateral column (IML), sympathetic nerve activity (SNA).

For many years, moderate ethanol consumption was thought to provide some benefit to cardiovascular health [21][22]. This was endorsed by the American Heart Association (AHA) [23]. However, this was at odds with the literature on alcohol use disorder suggesting that chronic use of ethanol leads to the development of hypertension and cardiovascular disease [24]

[25][26]. By 2023, after several research articles suggested that ethanol offers no cardiovascular benefit [27][28], the AHA reversed course, warning that even one ethanol-containing drink a day can increase cardiovascular disease risk [29].

A major gap in the ethanol research field is the limited investigation of the role of acetic acid/acetate in the pathologies associated with ethanol use. Acetic acid/acetate has been assumed to be a relatively benign compound [41], as acetate is a feedstock for the generation of ATP through the citric acid cycle [30] and for the generation of acetyl-CoA and acetylation reactions [31][32]. However, acetic acid is linked to several distinct disease states, including Alzheimer's disease [33][34], neurodegenerative disease [33][35], obesity [36], and gut–brain dysbiosis [33][35][36]. How acetic acid/acetate may influence the regulation of cardiovascular function are highlighted through several mechanisms, including the generation of reactive oxygen and nitrogen species (Figure 1 and Figure 2).



**Figure 2.** Brain-generated sympathoexcitatory responses to microinjections of acetate differ by autonomic region: implications for nitric oxide. (A) Representative sympathetic nerve recording and arterial blood pressure in response to PVN microinjected acetate. Note the rapid increase in sympathetic nerve activity (1, blue) and time of onset, followed by a rapid reduction in excitation (2, red). (B) Proposed schematic of the synaptic mechanisms contributing to the acetate-induced sympathoexcitatory response in PVN–RVLM neuronal circuitry. Note that (1, blue) corresponds to the response in (A). (C) Proposed schematic of NO retrograde synaptic signaling in PVN–RVLM neurons. Acetate activation of the NMDAR stimulates NO production, which increases presynaptic GABA release on glutamatergic synapses, reducing sympathoexcitation. Note that (2, red) corresponds to the response in (A). (D) Representative sympathetic nerve recording and arterial blood pressure in response to CeA–microinjected acetate. Note the steady increase in sympathetic nerve activity (1, blue) and the steady increase in excitation (2, green/purple). (E) Proposed schematic of the synaptic mechanisms contributing to the acetate-induced sympathoexcitatory response in CeA–RVLM neuronal circuitry. Note that (1, blue) corresponds to the response in (D). (F) Proposed schematic of NO retrograde synaptic signaling in CeA–RVLM neurons. Acetate activation of the NMDAR stimulates NO production, which increases the release of presynaptic glutamate and other neurotransmitters, increasing sympathoexcitation. Alternative inputs may also be propagating increased SNA. Note that (2, green/purple) corresponds to the response in (D). Abbreviations: paraventricular nucleus of the hypothalamus (PVN), rostral ventrolateral medulla (RVLM), neuronal nitric oxide synthase (nNOS), calcium calmodulin kinase 2 (CAMK2), nitric oxide (NO), calcium ( $\text{Ca}^{2+}$ ), chloride ( $\text{Cl}^-$ ), N-methyl-D-aspartate receptor (NMDAR), gamma aminobutyric acid receptor (GABAR), sympathetic nerve activity (SNA), glutamate (Glut), gamma aminobutyric acid (GABA),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA).

## 2. Acetaldehyde and Peracetic Acid: All Roads Lead to Acetic Acid/Acetate

Acetaldehyde has been one of the most highly researched ethanol metabolites and has been implicated in the generation of reactive oxygen species, protein adduct formation [37][38][39], the increased production of salsolinol [40][41][42][43][44][45][46], and neuronal toxicity [47][48][49][50]. In individuals with aldehyde dehydrogenase (ALDH) 2 deficiencies, the buildup of acetaldehyde is thought to cause flushing, nausea, and headache [51][52][53][54]. Disulfiram, an ALDH inhibitor and alcohol use deterrent, also increases the buildup of acetaldehyde, which is thought to be the mechanism of action for reducing alcohol consumption [55][56][57].

Interestingly, blood acetaldehyde concentrations are not easily measured and have been reported in the range of 10–40 nM when blood ethanol concentrations are 10–20 mM [58][59]. Part of the prevailing theory on why blood acetaldehyde

concentrations are so low is due to its rapid metabolism to acetic acid [1]. And while this may be true, there are other chemical factors and conversion routes for acetaldehyde that may be contributing to its low detection.

First, acetaldehyde is a volatile liquid that is soluble in aqueous solutions [60]. Its boiling point is 20.2 °C (68 °F) [60], much lower than the physiological temperature of 37 °C (98.6 °F). Thus, it is highly likely that any acetaldehyde that is not converted to acetic acid/acetate and remains in circulation passing to the lungs is exhaled in its gaseous state. Second, in a report published in 1929 by Bowen and Tietz, they noted that acetaldehyde shaken in the presence of oxygen (auto-oxidation) produced a peroxide, identified as peracetic acid [61]. These authors also noted that this type of reaction and similar reactions produced a “long chain mechanism” [61], which would be consistent with what is now a free radical-type mechanism. Indeed, follow-up work in 1950 by Bawn and Williamson further elucidated that aqueous solutions of acetaldehyde were also capable of auto-oxidation, producing the peracetic acid reported by Bowen and Tietz [61], and that these reactions could be increased and/or induced in the presence of metals, of note, iron III ( $\text{Fe}^{3+}$ ) [62]. Interestingly, hemoglobin, the iron-containing protein that is responsible for oxygen and carbon dioxide transport in the blood, has an iron oxidation state of  $\text{Fe}^{3+}$  when oxygen is bound [63]. This close proximity of oxygen and  $\text{Fe}^{3+}$  with any circulating acetaldehyde may convert acetaldehyde into peracetic acid, and account for the low to undetectable circulating levels following ethanol consumption [59].

Peracetic acid (peroxyacetic acid) is a peroxide of acetic acid. It is utilized as a broad-spectrum disinfectant, displaying bactericidal, virucidal, fungicidal, and sporicidal properties [64]. In cell toxicity studies, peracetic acid was more cytotoxic than sodium hypochlorite (bleach) [65]. Moreover, given that peracetic acid is an organic peroxide, it undergoes similar homolysis reactions as other peroxides do [66]. As such, the spontaneous or metal-catalyzed homolysis reactions of peroxides generate free radicals [66][67] and these free radicals are thought to induce cellular and tissue damage [68][69]. Hydrogen peroxide is a classic example of a peroxide used as a source of oxygen-derived free radicals in research studies [70]. Additionally, hydrogen peroxide also interacts with iron in the well-known Fenton reaction to generate additional sources of free radicals that can lead to tissue damage [71].

### 3. Peripheral Actions of Acetic Acid/Acetate: Impact on Nitric Oxide Synthase (NOS) and Nitric Oxide (NO)

Ethanol in humans has been found to influence heart rate, cardiac output, stroke volume, and sympathetic nerve activity [72][73][74][75][76][77][78]. It causes both vasoconstriction and vasodilation [14][79][80]. In rodent models, ethanol has been shown to increase the bioavailability of nitric oxide [80][81][82]. However, these studies did not account for ethanol metabolism or the production of acetic acid/acetate.

In studies investigating the effect of buffering agents in hemodialysis solutions, it is observed that acetate-based solutions create greater cardiovascular and hemodynamic instability than bicarbonate-based solutions do [83][84]. These instabilities include vasodilation, hypoxemia, increased cardiac output, and angina pectoris [85][86][87]. Methodical investigation identified that these acetate-based hemodialysis solutions increased levels of nitric oxide synthase (NOS) and nitric oxide (NO) [88][89], a powerful radical which stimulates vasodilation [90][91][92]. Several studies have also identified acetate-induced elevations in tumor necrosis factor alpha (TNF $\alpha$ ) and cyclic adenosine monophosphate (cAMP), both mediators of NOS [89]. This was seen in dialysis buffers containing as little as 4 mM acetate [89]. A likely mechanism through which ethanol produces vasodilation is through ethanol's metabolism to acetic acid/acetate, which stimulates production of NOS and NO (**Figure 1B**). This finding was also substantiated by Sakakibara S et al., who found that consumption of vinegar increased eNOS production with as little as 200  $\mu\text{M}$  acetate in both early-phase detection (20 min) as well as late-phase detection (4 h) [93]. Furthermore, they found increased forearm vasodilation in adults who had consumed acetic acid compared to a control. This time course of action for acetic acid/acetate suggests a profound impact on peripheral eNOS even with minimal concentrations of and exposure to acetate [93].

### 4. Direct Effects of Ethanol and Acetic Acid/Acetate on Cardiac Function

The potential of ethanol consumption to influence cardiac function has been well documented. In the acute setting, ethanol can increase cardiac output [94] and reduce plasma potassium [95], which may contribute to ethanol-induced arrhythmia or “holiday heart” [96]. The acute effects of ethanol on contractility appear to be mixed, with some studies suggesting either no change [94][97][98] or a decrease [99][100] in cardiac contractility. Chronic ethanol use also contributes to cardiomyopathy [101][102] and arrhythmias [20].

Similar to the effects of acute ethanol, acute acetate is also capable of altering cardiac function. Acute acetate administration has been found to increase cardiac output [103][104], precipitate hemodynamic instability [84][88][103], and

reduce myocardial contractility <sup>[105][106]</sup>. Interestingly, some of the direct cardiac effects of acetate were speculated to be tied to acetate-induced NO release <sup>[88]</sup>. Indeed, the direct cardiac effects of NO are bimodal, with lower concentrations of NO increasing the inotropic effects <sup>[107]</sup> and high concentrations of NO reducing cardiac myocyte contractility <sup>[108]</sup>. Whether the mixed effects of ethanol on cardiac function are a result of acetate and/or acetate-induced NO release remains to be determined. Furthermore, the effect of chronically elevated acetate from chronic ethanol use and metabolism on cardiac function has yet to be investigated. It is provocative to postulate that the major compound driving alcohol-induced cardiomyopathy <sup>[109][110]</sup> may be acetate rather than ethanol, and as such, future studies of chronic acetate seem warranted.

## **5. Ethanol Metabolism to Acetic Acid Alters Acid/Base Homeostasis and Likely Engages Peripheral Chemoreceptors**

Although ethanol itself is not acidic (pKa value ~16) <sup>[111]</sup>, ethanol acts as an exogenous source of acidic hydrogens. Once ethanol is fully oxidized to acetic acid (pKa value ~4.78) <sup>[112]</sup>, the labile acidic hydrogen becomes >95% dissociated at physiological pH <sup>[113]</sup>. pKa is a measure of hydrogen acidity, as a review of pKa (see *General Chemistry*, sixth edition, Julia Burdge). The higher the pKa value, the less acidic the hydrogen. At physiological pH, acetic acid likely reacts with the bicarbonate buffering system (i.e., the vinegar and baking soda reaction), forming acetate and carbonic acid (**Figure 1A**). Carbonic acid is then broken down into water and carbon dioxide. The acidic hydrogen on acetic acid and the excess carbon dioxide cause activation of (1) peripheral chemoreceptors located in the carotid sinus and aortic arches, and (2) neural control centers in the brain, which control sympathetic outflow and increase sympathetic nerve activity (SNA) (**Figure 1C**).

In the United States, humans are considered legally intoxicated at a blood alcohol concentration (BAC) of 0.08% or a blood serum concentration of ~17 mM ethanol <sup>[114]</sup>. The conversion of ethanol to acetic acid is nearly 1:1, with ~95% of ethanol converted to acetic acid <sup>[115]</sup>. Thus, for 17 mM of ethanol consumed, the predicted amount of acetic acid produced would be ~16–17 mM. To buffer or neutralize this concentration of protons, roughly 17 mM of bicarbonate would be consumed. The normal concentration of bicarbonate in the serum is ~23–28 mM <sup>[116][117]</sup>. This bicarbonate consumption creates a high acid load, generating compensatory mechanisms within the kidneys and lungs to maintain pH homeostasis <sup>[117][118][119]</sup>.

## **6. Integration of Arterial Baroreceptors, Chemoreceptors, and NO Signaling in Response to Acetic Acid Generated by Ethanol Metabolism**

The integration of the peripheral cardiovascular regulatory systems engaged by acetic acid likely explains the complex phenomenon of mixed vasodilation and vasoconstriction induced by ethanol. First, acetic acid increases NOS activity and NO production, which leads to vasodilation <sup>[85][88][89]</sup>. Arterial baroreceptors located in the carotid sinus and aortic arch <sup>[120]</sup> would relay the resultant drop in blood pressure to neural control centers, which regulate cardiovascular function <sup>[121]</sup> (**Figure 1C**). These neural control centers then increase SNA to constrict the vasculature in an attempt to maintain homeostasis <sup>[120]</sup>. Third, the acid load generated from the acetic acid and/or excess carbon dioxide would similarly be sensed by the peripheral chemoreceptors, also located in the carotid sinus and aortic arch. And, in the same type of neural feedback loop as the arterial baroreceptor activation, chemoreceptor activation would also increase SNA and constrict the peripheral vasculature <sup>[122][123][124][125]</sup>. Thus, the complex vasoconstriction and vasodilation effects of ethanol consumption <sup>[80]</sup> can be explained when looking at the effects being driven by acetic acid and not ethanol per se.

## **7. Acetic Acid-Induced Changes in Neural Control of Cardiovascular Regulation**

Acute oral consumption of ethanol consistently increases arterial blood pressure (ABP) and SNA in humans <sup>[72][76][77][78]</sup> and rodents <sup>[126][127][128]</sup>. Likewise, chronic ethanol use has been shown to increase norepinephrine, SNA, and ABP <sup>[98]</sup> <sup>[129][130][131][132][133]</sup>. In one acute human study, dexamethasone was found to blunt ethanol's sympathoexcitatory effect <sup>[77]</sup> through a reduction in corticotropin-releasing hormones (CRHs), suggesting that this response is at least partially mediated by central effects. In rodent studies, oral ethanol has been less consistent <sup>[79]</sup>, with some studies showing an increase in SNA and ABP <sup>[130][134]</sup> and other studies showing decreases in ABP <sup>[95][97]</sup>. As some other reviews have noted, the timing of measurements in rodents may be important <sup>[24]</sup>. In one rodent study, Crandall et al. observed that ABP was normal at peak blood ethanol concentrations but was significantly elevated 24 h post ethanol dosing <sup>[135]</sup>. Interestingly, we now know from pharmacokinetic studies that this time point corresponds to when serum acetate is still elevated, typically remaining elevated for 12–24 h post ethanol metabolism <sup>[136][137]</sup>. As such, reasonable evidence exists that suggests

acetate may be a lead compound in driving the ethanol-induced effects on cardiovascular function from a centrally mediated standpoint.

When attempting to elucidate the neuronal mechanisms of ethanol-induced changes in cardiovascular regulation, several brain regions that regulate autonomic function have been studied. The rostral ventrolateral medulla (RVLM) is a significant brain region involved in the integration of upstream brain regional sympathoexcitatory outputs <sup>[126][138][139][140][141][142][143][144][145]</sup>. The RVLM projects to the spinal intermediolateral column (IML), which is the first synapse in the central to peripheral sympathetic output pathway <sup>[145][146]</sup>. In direct application studies of the RVLM conducted by El-Mas and colleagues, ethanol microinjection dose-dependently increased RVLM norepinephrine and ABP in spontaneously hypertensive rats (SHRs) <sup>[128][147]</sup>. Additional follow-up studies by the same group suggested that this ethanol response was due to enhanced catabolism of ethanol to acetaldehyde <sup>[128]</sup>. They however indirectly speculated that acetate had little effect on increasing ABP levels <sup>[128]</sup>. Interestingly, when investigating catalase and ALDH enzyme activity in the RVLM between SHRs and non-hypertensive control (Wistar–Kyoto, WKY) rats, the SHRs had higher levels of catalase activity compared to the WKY rats, with no differences in ALDH activity, suggesting a potential genetic component in relation to differences in brain ethanol metabolism <sup>[128]</sup>. While this study described above did not detect differences in ALDH activity, a recent and exciting report has highlighted brain region differences in ALDH2 expression in mice <sup>[148]</sup>. This previous finding suggests that investigators must be cognizant of how brain regions and/or genetic differences in ethanol metabolism may influence behavior and/or cardiovascular function.

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