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Ethanol Metabolism and Effects: Nitric Oxide and its Interaction

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Abstract

Ethanol (EtOH) in alcoholic beverages is consumed by a large number of individuals and its elimination is primarily by oxidation. The role of nitric oxide (NO) in ethanol's effects is important since NO is one of the most prominent biological factors in mammals. NO is constantly formed endogenously from L-arginine. Dose and length of EtOH exposure, and cell type are the main factors affecting EtOH effects on NO production. Either acute or chronic EtOH ingestion affects inducible NO synthase (iNOS) activity. However it seems that EtOH suppresses induced-NO production by inhibition of iNOS in different cells. On the other hand, it is clear that acute low doses of EtOH increase both the release of NO and endothelial NOS (eNOS) expression, and augment endothelium-mediated vasodilatation, whereas higher doses impair endothelial functions. EtOH selectively affects neuronal NOS (nNOS) activity in different brain cells, which may relate to various behavioral interactions. Therefore, there is an excellent chance for EtOH and NO to react with each other. Effects of EtOH on NO production and NOS activity may be important to ethanol modification of cell or organ function. Nitrosated compounds (alkyl nitrites) are often found as the interaction products, which might be one of the minor pathways of EtOH metabolism. NO also inhibits EtOH metabolizing enzymes. Furthermore, NO is involved in EtOH induced liver damage and has a role in fetal development during ethanol exposure in pregnancy. The mechanisms underlying these effects are only partially understood. Hence, the current discussion of the interaction of ethanol and NO is presented.

Keywords

Ethanol; Nitric oxide; Nitric oxide synthase; Interaction; Metabolism

1. Introduction

NO is an inorganic gas with good solubility in water [1]. It is synthesized by the enzyme NOS in which L-arginine is the substrate and NO as well as L-citrulline are products [2,3]. There are three NOS isoforms: neuronal NOS (nNOS, NOS-1), inducible NOS (iNOS, NOS-2), and endothelial NOS (eNOS, NOS-3) [2]. All mammalian NOS are hemoproteins, require NADPH and O₂ for the production of NO, and use FAD, FMN, and BH₄ as cofactors [2,4,5].

NO is an odd electron species with a half-life of only a few seconds in biological systems. It degrades rapidly to nitrite (NO₂⁻) then nitrate (NO₃⁻) [1,6,7]. Putative intermediate metabolites include an array of low and high molecular weight compounds-nitrosoglutathione, nitrosoalbumin, and S-nitrosohaemoglobin [8,9,10]. This is not only a mechanism for scavenging NO but also serves to transport NO. NO is associated with vital biological events, such as control of blood pressure, modulation of neurotransmission, memory formation, and antimicrobial activity [11]. The chemical reactivity of biological NO is relatively limited though possessing an unpaired electron [12]. In the presence of O₂, NO reacts with O₂⁻ to form

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peroxynitrite (ONOO^-), a potent oxidizing agent and other NO radicals [13]. Those radicals in turn can lead to cytotoxicity. NO rapidly oxidizes sulfhydryl groups and thioethers in peptides, proteins, and lipids [14,15]. In addition, NO nitrates and hydroxylates aromatic compounds, including guanosine (DNA damage) [16,17,18], tyrosine (nitrotyrosine) [19,20], tryptophan [21], and tocopherol [22]. These deleterious effects of NO radicals may disturb cell signaling processes and result in pathological conditions [23,24,25].

EtOH is primarily metabolized in the liver by the multiple isoenzymes of alcohol dehydrogenase (ADH) [26] and microsomal ethanol-oxidizing system (MEOS) [27] and by other ethanol-metabolizing enzymes such as catalase [28]. About 90% to 95% of ethanol is eliminated by oxidation. The rest is excreted by the kidneys, the lungs and the skin [29]. We recently found that EtOH reacts with peroxynitrite and ethyl nitrite is formed [30]. In addition to the oxidative pathways and excretion, ethanol is also detoxified via conjugation with activated glucuronic acid [31,32] to form ethyl glucuronide (EtG), sulfate conjugation through the action of sulfotransferase to produce ethyl sulfate (EtS) [32,33], esterification with fatty acids to generate fatty acid ethyl esters (FAEEs) [34,35]; ethanolysis of endogenous phosphate esters to generate ethyl phosphate (EtP) [33].

EtOH is widely distributed in body water in vivo. It has a broad range of pharmacological and toxicological actions, some of which overlap with those thought to be modulated or mediated by NO. For instance, EtOH alters NOS expression and activity in the brain [36,37]. Therefore, this review will be focused on the effects of ethanol on production of NO, NOS activities, and interactions of NO with alcohol metabolism enzymes as well as ethanol.

2. Effect of EtOH on NO levels

Acute or chronic EtOH consumption increases blood NO in both intact animals [38,39,40, 41] and humans [42,43]. For example, EtOH (80 g as a 40% solution) was ingested within 30 min after an over-night fast by human subjects. Total serum $\text{NO}_3^- + \text{NO}_2^-$ (NOx) concentrations were doubled at 12h. A similar pattern of NOx levels was observed in patients with chronic hepatitis. By contrast, in patients with cirrhosis, either viral or alcoholic, no significant increase was found after EtOH administration. "However, basal levels in cirrhotics were significantly elevated (82.2 ± 13.8 vs. $43.1 \pm 7.2 \mu\text{mol/l}$, $p < 0.01$) compared to healthy controls" [43]. The increase of NO production might protect liver microcirculation from a deleterious EtOH effect.

However, there are also disparate reports. EtOH (3–30 mM/kg, i.v.) dose dependently reduced the levels of exhaled NO in rabbits [44]. The same inhibition was also found in humans [45]. When EtOH (0.25 and 1 g kg⁻¹, 20% in orange juice) was ingested, NO production in exhaled air was inhibited, likely by inhibition of airway formation of nitric oxide [45].

3. Effect of EtOH on NOS

EtOH exhibits a different effect on iNOS, eNOS, and nNOS in a variety of cells or tissues. Acute EtOH ingestion enhances neutrophil NO production via activation of iNOS, leading to neutrophil apoptosis [46]. "Human neutrophils harvested from healthy subjects after an alcohol drinking binge showed enhanced apoptosis (before, 0.5 ± 0.25 vs. after, $26.1 \pm 2.6\%$ apoptotic neutrophils/field)". NOS inhibitor attenuated and NOS donor stimulated the apoptosis, which seems to be mediated through the generation of NO [46]. However acute EtOH inhibits the lipopolysaccharide (LPS)-induced NO response in Kupffer, hepatic endothelial cells [47], and macrophages [48,49]. Similarly acute EtOH exposure enhanced cytokine-induced iNOS expression at a pretranslational site in astroglial cells [50]. Acute EtOH also depressed polyinosinic:polycytidylic acid (poly I:C) induced NO response in microglia [51]. Both acute (24 h, 150 mM) and chronic (10 days, 30 mM) EtOH exposure suppressed iNOS induction by

co-administration of phorbol 12-myristate 13-acetate (PMA) and LPS in brain glial cells [52]. The inhibitory effects of EtOH on iNOS mRNA is not due to the metabolism of EtOH to acetaldehyde and acetate [53] but due to inhibiting nuclear transcription factor-kappaB (NF-kappaB) [48] and inhibiting signal transducer and activator of transcription-1 (STAT-1) activation [49]. Furthermore, different doses of EtOH affected iNOS expression in glial cells. For example, acute (6–24 h) exposure of activated human A172 astrocytoma cells to 50 mM ethanol enhanced iNOS activity recovered from the cytosol, whereas 200 mM ethanol decreased it [54].

On the other hand, chronic EtOH ingestion increases expression of T cell surface major histocompatibility costimulatory molecules B7.1 (CD80) and B7.2 (CD86) via NO in mouse splenocytes [55] and induced iNOS and cyclooxygenase -2 (COX-2) expressions in astrocytes [56]. Chronic EtOH exposure also increased iNOS activity in rat liver [40]. Rats were pair-fed EtOH containing liquid diets for 24 days. EtOH increased NO by 52% in liver and iNOS activity in the liver cytosol was increased by 5-fold [40].

The effects of EtOH on the endothelium are complicated. For example, the endothelium responds to increases in flow by releasing vasodilator mediators, most notably endothelium derived relaxing factor, identified as NO [57]. There are favorable effects on endothelial function with low-dose EtOH exposure but the induction of endothelial dysfunction with higher doses [58,59,60,61].

In vitro, acute exposure to EtOH increases NO production and eNOS expression in endothelial cells derived from systemic vessels [62,63]. For example, treating human umbilical vein endothelial cells with EtOH (20–60mM) for 2 hr produced a dose-dependent increase in eNOS activity [62]. Similarly, treating bovine aortic endothelial cells with 0.1% (w/v) EtOH for 3–6 hr increased NO production as well as eNOS protein and mRNA expression [63]. Furthermore eNOS activity is regulated not only at the level of expression [64,65,66,67,68], but also post-translationally by mechanisms including protein-protein interactions [69,70,71,72,73,74] and phosphorylation [75,76,77,78]. Indeed acute low-dose EtOH (10–50 mmol/liter) directly activates Ca^{2+} -activated K^{+} channels in cultured human umbilical vein endothelial cells, leading to an increase of endothelial proliferation and production of NO. However, higher dose EtOH (100 and 150 mmol/liter) significantly reduced NO synthesis [79].

In vivo, animal studies have shown that acute low doses of EtOH increase the release of NO and augment endothelium-mediated vasodilatation, whereas higher doses impair endothelial functions [80,81,82,83,84].

“In contrast, chronic administration of EtOH to rats has generally been associated with tolerance to the acute effects of EtOH on endothelium-mediated vasodilatation (low dose EtOH increased vasodilatation via NO release) and may even result in the augmentation of such responses” [58,85]. Porcine pulmonary artery endothelial cells were treated with EtOH (0.04–0.16%, w/v) for 3 days. NO release was increased by molecular mechanisms involving phosphatidylinositol 3 kinase (PI3 K)-mediated increases in eNOS expression and increases in protein-protein interactions between eNOS and heat shock protein (hsp90) [86]. Chronic EtOH enhances the NO-dependent vasorelaxant responses to adenosine receptor activation in spontaneously hypertensive rats [87].

In mouse cardiac myocytes, EtOH induced delayed cellular protection dependent on iNOS [88]. EtOH altered both endothelium-dependent and independent vascular contractile responses in rat aorta [89]. Study of acute EtOH treatment on iNOS knockout senescent mice showed that cardiac function of ageing iNOS^{-/-} mice was comparable with that of normal young mice. EtOH increased cardiac contractility of senescent mice through inhibition of iNOS

activity, indicating that perhaps moderate EtOH consumption is beneficial to heart function, especially in the older individual [90]. Thus, EtOH indeed has complex direct vascular effects, which include basal vasoconstriction as well as potentiation of both endothelium-dependent (NO related) and -independent vasodilatation.

The effects of EtOH on brain NOS activity have also been studied. Acute EtOH usually inhibits nNOS activity. For example, acute EtOH (25–200 mM) inhibited nNOS activity in cultures of rat cortical neurons by decreasing NMDA- and cytokine-stimulated NO synthesis [91]. The same inhibition of NMDA-NOS activity was observed in hippocampus slices and BH4 was also involved [92]. In another study, inhibition of nNOS by acute EtOH exposure was correlated with decreased number of muscarinic acetylcholine receptors in neuroblastoma SH-SY5Y cells [93].

On the other hand, chronic EtOH appears to increase nNOS expression, which could modify the amount of NO produced by cells in different brain areas. For example, chronic EtOH exposure has been shown to increase NO levels in neuronal cultures by enhancing NMDA- and cytokine-stimulated NO synthesis but not receptor density [91,94]. However, nNOS activity was increased in the rat cerebellum due to sensitivity of cerebellar neurons to oxidative insult in a chronic EtOH study [95]. Chronic EtOH alone had no effect on nNOS activity in PC12 cells. But nNOS expression was amplified in the presence of nerve growth factor [96].

NO is also important in repeated restraint stress (RRS). In animals treated by RRS, administration of EtOH lowered RRS- induced corticosterone release through inhibition of iNOS activity [97]. It has been found that NO regulated EtOH action on hypothalamic beta-endorphin (beta-EP) neurons. EtOH treatment for 3 hr increased the release of beta-EP but reduced NO levels in the media of hypothalamic cells in primary cultures. In contrast, EtOH exposure for 48 hr reduced the release of beta-EP but increased the release of NO from these cells, due to altered the expression of nNOS mRNA [98]. In addition, prenatal EtOH exposure blunted ACTH released in response to interleukin-1 beta (IL-1 beta), while inhibition of NO formation reversed this decrease [99]. Moreover EtOH inhibits luteinizing hormone-releasing hormone (LHRH) release from incubated medial basal hypothalamic explants via reducing NO production [100]. More NO was found in the rat striatum during chronic EtOH feeding [101].

In addition, studies in the rat have shown that NOS inhibition (a) potentiates the sleep time induced by EtOH [102], (b) alleviates the symptoms of EtOH withdrawal [103], and (c) enhances the anxiolytic effect of EtOH [104], and (d) prevented the development of alcohol tolerance [105,106], and (e) attenuation of alcohol consumption in alcohol-preferring rats [107], in Sprague–Dawley rats selected for high alcohol intake [108], and in rats that underwent chronic alcohol intoxication prior self-administration experiments [109]. In contrast, activation of the NO pathway opposes the effects of acute EtOH administration in rats [110], raising the possibility that NO could act as a feedback inhibitory loop following exposure to EtOH. Actually it was recently found that genetic deletion of nNOS increased alcohol consumption in mice [111]. Therefore NO modulates EtOH behaviors in rodents.

4. Interaction of NO with alcohol metabolizing enzymes

NO has interaction with alcohol metabolizing enzymes. For example, glyceryl trinitrate (GTN) was reported to inhibit erythrocyte aldehyde dehydrogenase (ALDH) [112]. GTN is widely used in the treatment of angina pectoris and cardiac failure by release of NO or NO related substance. However, the rapid onset of GTN tolerance limits its clinical utility. Research suggests that a principal cause of tolerance is inhibition of ALDH which is responsible for the production of physiologically active concentrations of NO or NO related substance from GTN by virtue of its esteratic activity [113,114,115,116,117]. The mechanism of ALDH inhibition is that NO oxidizes sulfhydryl groups of proximal cysteine residues [118,119].

NO or its derivatives also interact with the sulfhydryl groups of glutathione and other proteins to form nitroso thiols [120,121]. Attachment of the NO group to sulfhydryl residues of active site thiols in enzymes (S nitrosylation) such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [122], PKC [123], glutathione peroxidase [124], or ecto-5-nucleotidase [125] is likely to be responsible for inhibition of their catalytic activity. NO was also proposed to play a role in endogenous ADP autoribosylation of GAPDH [126,127,128,129] and in NAD attachment to this enzyme [130]. Also, there have been studies concerning the effects of NO on alcohol dehydrogenase (ADH). NO donor, 3-morpholino sydnonimine (SIN-1) inhibited yeast ADH [129], and it has been found that peroxynitrite inhibited yeast ADH [131]. Furthermore, the simultaneous generation of O and ·NO under physiological conditions can inactivate yeast ADH in the same way as additions of peroxynitrite [132]. The inhibition of ADH by peroxynitrite or other NO generating compounds was associated with release of zinc and oxidation of thiol residues of the enzyme, and inhibition was also observed with other powerful oxidants such as hypochlorite and to a lesser extent H₂O₂ [131,132,133].

5. Interaction of EtOH with NO

NO is constantly formed endogenously. Since NO readily reacts with reactive molecules to change their behavior, NO-derived substances may have significant activities. Nitrosation is the reaction of NO at the center of nitrogen, sulfur, carbon, and oxygen containing compounds in biological systems. Among them, nitrosamines [134,135], nitrosothiols [120,136,137,138], and nitrotyrosine [19,20,139,140,141] are extensively studied. Nitrosamines are shown to have potent carcinogenic activities [135]; nitrosothiols have the ability as an endogenous NO donor or NO carrier [136,137,138]; and nitrotyrosine serves as a footprint of peroxynitrite formation [142,143].

It is well known that EtOH is distributed in body water. Hence, there is an excellent chance for EtOH and NO to react with each other. NO reacts with alcohol to yield alkyl nitrites [144, 145,146], which are also conveniently applied to alcohol determination in the aqueous solution [147,148] and biological samples [149]. The mechanism is that EtOH in vitro is nitrosated by NO or NO donors (e.g., N₂O₃ and nitrosyl halides) to yield an O-nitroso compound or ethyl nitrite [150,151]. Interestingly when EtOH was perfused into rat gastric chamber system, luminal nitrite and nitrate levels decreased remarkably. This is proposed as the depletion of NO by formation of ethyl nitrite from EtOH and NO [152]. Furthermore, ethyl nitrite was found in the breath of volunteer subjects when 60 ml of 40% (v/v) EtOH and tobacco were consumed concurrently [153]. Ethyl nitrite has also been identified in exhaust emissions from alcohol/gasoline blends [154]. We found that ethyl nitrite is generated of EtOH reacting with peroxynitrite in vitro [30]. We detected ethyl nitrite both in mouse tissues and human breath by GC-MS [30]. Therefore, ethyl nitrite is one of EtOH metabolites.

Actually ethyl nitrite itself is a NO donor [155] and may have a longer half life than does NO itself and thus may serve as a transport molecule for NO and prolong its effective life time. Thus the interaction between EtOH and NO is reversible, making ethyl nitrite not only be NO donor but also an intermediate or metabolite of EtOH in vivo.

6. Clinical relevance

1). Alcoholic liver disease (ALD)

Alcoholic liver disease (ALD) ranks among the major causes of morbidity and mortality among alcoholics in the world [156]. The role of NO in ALD is not clear. It has been shown that arginine can significantly prevent ethanol-induced liver injury, whereas L-NAME, a nonselective NOS inhibitor, increased the severity of ALD in rats [157]. Further iNOS from Kupffer cell was shown to be required for ALD, because alcohol toxicity was significantly attenuated in iNOS

knockout mice [158]. A similar protection was found if wild-type mice were treated with a selective iNOS inhibitor (1400W). NO produced from eNOS may be protective as well, and application of NOS inhibitor L-NAME, enhanced liver damage [158]. What regulates this balance or distribution of NO production in ALD is not known, however, peroxynitrite anion (ONOO^-) from reaction of NO with superoxide is blamed for those damages. ALD is prominently seen by chronic ethanol exposure, which induces CYP2E1 and activates other enzymes such as xanthine oxidase and NADPH oxidase [159,160,161], and generates more peroxynitrite. Obviously there are reduced levels of oxidation scavengers such as glutathione and other antioxidants [159,160,161] and the activity of certain protective enzymes such as isocitrate dehydrogenase [162] and peroxiredoxin [163] under chronic conditions. Alcohol-related increases of NO [40,162] may lead to inhibition of ALDH2 and other mitochondrial proteins. Indeed, the activity of 3-ketoacyl-CoA thiolase involved in mitochondrial β -oxidation of fatty acids was significantly inhibited in alcohol-exposed rat livers, consistent with hepatic fat accumulation, as determined by biochemical and histological analyses. "Measurement of activity and immunoblot results showed that ALDH2 and ATP synthase were also inhibited through oxidative modification of their cysteine or tyrosine residues in alcoholic fatty livers of rats" [164]. Supplementation with *S*-adenosylmethionine (SAM), a precursor for glutathione (GSH), has been shown to prevent the alcohol-associated increased sensitivity of mitochondrial respiration to inhibition NO through the attenuation of iNOS induction [165, 166]. Therefore NO acts as a two-edged sword in ALD.

2). Fetal alcohol syndrome (FAS)

EtOH exposure in pregnancy may result in fetal alcohol syndrome (FAS). The mechanism is still unknown. Placental villous tissue perfused with ethanol was examined and found that there were higher levels of eNOS expressed, lower NO release, and increased levels of superoxide dismutase (SOD), indicating that NO is involved [167]. Villous tissues from normal placentas were further perfused and 100 mM ethanol was added to the perfusate. It was found that ethanol exposure significantly increased nitrotyrosine levels in the trophoblasts. Nitrotyrosine and 8-hydroxyguanosine (8-OHDG) levels were also increased in stroma [167].

Cerebellar granule neuron (CGN) cultures at 1 day in vitro (1-DIV) or 4 days in vitro (4-DIV) were exposed to agents that either activated or inhibited NO-cGMP-PKG pathway, either in the presence or in the absence of alcohol. NMDA, which activates nNOS by raising intracellular calcium levels via the NMDA receptor, DETA-NONOate and 8-Br-cGMP (cGMP analogue) all reduce background cell death in 4-DIV alcohol-free CGN cultures, and this neurotrophic effect is mediated by the NO-cGMP-PKG pathway. Treatment with NAME and LY83583 rendered the cultures more vulnerable to alcohol-induced cell death. Second, the neurotrophic effect of agents that activate the NO-cGMP-PKG pathway is not impaired by the presence of alcohol. Third, developmental stage-dependent acquisition of alcohol resistance, which occurs as the CGN cultures mature from 1-DIV to 4-DIV, is mediated by the NO-cGMP-PKG pathway [168].

In a prenatal EtOH exposure model in guinea pigs, EtOH increased nNOS and iNOS expression in brain homogenates [169]. Furthermore, the nitric oxide-guanosine 3',5'-cyclic monophosphate-protein kinase G (NO-cGMP-PKG) pathway plays an essential role in the acquisition of EtOH resistance by neonatal neurons [168]

Postnatal mice were further employed to determine what role of nNOS plays in the presence of alcohol and found out that deficiency of nNOS decreases the ability of developing neurons to survive the toxic effects of alcohol [170]. Thus NO plays an important role in fetal development in the presence of ethanol.

7. Summary

Compelling data suggest that EtOH is crucially involved in the regulation of NO at several levels. EtOH indeed alters NO synthesis through NOS or other mechanisms. Dose and length of EtOH exposure are the main factors affecting EtOH' effects on NO production or NOS activity or NOS expression. Cell type also contributes to this effect. Either acute or chronic EtOH ingestion affects iNOS activity and NO production. However it seems that EtOH suppressed induced-NO production by inhibition of iNOS in different cells. iNOS^{-/-} knockout mice show decreased hepatotoxicity after exposure to EtOH. It is clear that acute low doses of EtOH increase both the release of NO and eNOS expression, and augment endothelium-mediated vasodilatation, whereas higher doses impair endothelial functions. As to nNOS, EtOH selectively affects NO production, which may relate to various behavioral interactions. Genetic deletion of nNOS increased alcohol consumption in mice. On the other hand, NO reacts with EtOH metabolism enzymes to modulate EtOH fate. Both ADH and ALDH can be inhibited by NO or peroxynitrite. More importantly, NO interacts with EtOH to generate alkyl nitrite (e. g. ethyl nitrite). This might be accomplished in vivo by interaction of EtOH with peroxynitrite. NO is involved in alcohol liver damage. NO from iNOS has detrimental effects and NO from eNOS has protective effects. Dietary supplementation has been shown to attenuate EtOH induced liver damage. NO might also play a role in FAS, which is still under investigation.

Abbreviations

ACTH	adrenocorticotrophic hormone
ADH	alcohol dehydrogenase
ADP	adenosine diphosphate
ALDH	aldehyde dehydrogenase
BH4	Tetrahydrobiopterin
COX-2	cyclooxygenase -2
EtOH	Ethanol
FAD	flavin adenine dinucleotide
FMN	flavin mononucleotide
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GTN	glyceryl trinitrate
hsp90	heat shock protein

IL-1 beta	interleukin-1 beta
LHRH	luteinizing hormone-releasing hormone
LPS	lipopolysaccharide
NAD	nicotinamide adenine dinucleotide
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NF-kappaB	nuclear transcription factor-kappaB
NMDA	N-methyl- D-aspartate
NO₂⁻	Nitrite
NO₃⁻	Nitrate
NO-cGMP-PKG	nitric oxide-guanosine 3',5'-cyclic monophosphate-protein kinase G
NO	nitric oxide
NOS	nitric oxide synthase
iNOS	inducible nitric oxide synthase
eNOS	endothelial nitric oxide synthase
nNOS	neuronal nitric oxide synthase
cNOS	constitutive nitric oxide synthase
iNOS^{-/-}	inducible nitric oxide synthase knockout
ONOO⁻	Peroxynitrite
PI3 K	phosphatidylinositol 3 kinase
PKC	protein kinase C

PMA

phorbol 12-myristate 13-acetate

poly I

C, polyinosinic:polycytidylic acid

RRS

repeated restrain stress

SIN-1

3-morpholino sydnonimine

STAT-1

signal transducer and activator of transcription-1

TNF- α

tumor necrosis factor-alpha

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Fig. 1.

Scheme of ethanol metabolism. Ethanol is mainly metabolized by the multiple isoenzymes of alcohol dehydrogenase (ADH) and microsomal ethanol-oxidizing system (MEOS), and by other ethanol-metabolizing enzymes such as catalase. The product is acetaldehyde. Free radicals are produced through MEOS. Ethanol reacts with peroxynitrite to form ethyl nitrite. There is also nonoxidation pathway in ethanol excretion. The phase II conjugates include ethyl glucuronide (EtG), ethyl phosphate (EtP), fatty acid ethyl esters (FAEEs), and ethyl sulfate (EtS).