Ethanol-derived acetaldehyde: pleasure and pain of alcohol mechanism of action

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INTRODUCTION

A recurring emergent theory in the alcohol field is that the reinforcing properties of alcohol are not produced by the ethanol (EtOH) molecule itself, but may depend upon the action of EtOH metabolites/products within the central nervous system (CNS) (Deitrich, 2004; Quertemont et al., 2005c; Correa et al., 2012).

This stance proposes EtOH as a pro-drug, and metabolism of EtOH to acetaldehyde (ACD) within the CNS could mediate most, if not all, of the CNS effects of EtOH (Quertemont et al., 2005a). The reinforcing properties of alcohol are most likely generated through a complex series of peripheral and central effects of both alcohol and its metabolites. Therefore a better understanding for how the metabolites/products of alcohol contribute to the reinforcing properties of alcohol is important for the development of efficacious pharmacotherapies for alcohol abuse and alcoholism.

BRIEF HISTORY OF ACD AND ALCOHOLISM

Acetaldehyde (ACD), the first metabolite of ethanol (EtOH), has been implicated in several actions of alcohol, including its reinforcing effects. Previously considered an aversive compound, ACD was useful in alcoholic’s pharmacological treatment aimed at discouraging alcohol drinking. However, it has recently been shown that EtOH-derived ACD is necessary for EtOH-induced place preference and self-administration, thereby suggesting a possible involvement of ACD in EtOH motivational properties. In addition, EtOH-stimulating properties on DA neurons are prevented by pharmacological blockade of local catalase H$_2$O$_2$ system, the main metabolic step for biotransformation of EtOH into ACD within the central nervous system. It was further shown that pretreatment with thiol compounds, like L-Cysteine or D-Penicillamine, reduced EtOH and ACD-induced motivational effects, in fact preventing self-administration of both EtOH and ACD, thus suggesting a possible role for ACD as a biomarker useful in evaluating potential innovative treatments of alcohol abuse. These findings suggest a key role of ACD in the EtOH reinforcing effects. In the present paper we review the role of EtOH-derived ACD in the reinforcing effects of EtOH and the possibility that ACD may serve as a therapeutically targetable biomarker in the search for novel treatments in alcohol abuse and alcoholism.

Keywords: ethanol, acetaldehyde, ethanol metabolism, catalase, biomarkers, pharmacological

Published: 17 July 2013
Published: 17 July 2013
published: 17 July 2013
doi: 10.3389/fnbeh.2013.00087
The most strident theories suggested that ACD was responsible for all the effects associated with alcohol and that alcoholism would be more appropriately termed acetaldehydeism (Walsh et al., 1970; Raskin, 1975).

**ETOH METABOLISM**

ETOH is first metabolized into ACD through several enzymatic and nonenzymatic mechanisms, the main enzymatic pathways being alcohol dehydrogenase (ADH), cytochrome P450 (CYP2E1) and catalase H2O2 system. In the periphery, ACD is formed from ETOH through the action of ADH primarily in the liver. In the brain, ADH is inactive (Zimatkin et al., 1998), and formation of ACD from ETOH is achieved primarily through the action of another enzyme, catalase H2O2 system (Sippel, 1974; Zimatkin, 1991).

A prerequisite for the involvement of ACD in ETOH behavioral effects is the occurrence of pharmacologically significant levels of ACD in the brain after alcohol consumption.

The levels of ACD in the CNS have profound effects in mediating the reinforcing actions of ETOH. ACD derived from the peripheral metabolism of ETOH penetrates from blood to brain with difficulty because of the metabolic barrier presented by ALDH across the Blood-Brain Barrier (BBB) (Eriksson and Sippel, 1977; Deitrich, 1987; Zimatkin, 1991; Hunt, 1996; Quertemont and Tambour, 2004). In addition, in the liver ALDH rapidly converts ACD into acetate and very low levels of ACD are detected in blood after the administration of moderate doses of ETOH (Quertemont and Tambour, 2004). Further research indicated that high levels of peripherally administered ACD results in detection of ACD in the brain within minutes (Ward et al., 1997). Therefore, peripheral ACD may over saturate the peripheral ALDH, allowing some percentage of ACD to enter the brain (Quertemont et al., 2005b). However, this mechanism does not provide an absolute protection of the brain because high blood concentrations allow ACD to cross the BBB. Additional local metabolic pathways (e.g., CYP2E1) can also result in the formation of ACD from ETOH within the brain (Zakhari, 2006) and pharmacologically significant amounts of ACD can be generated in situ thereby producing effects that are difficult to ascribe to peripheral mechanisms.

A plausible source of ACD in the brain is the in situ synthesis from some of the ETOH that escapes peripheral metabolism. ACD can be formed in the brain through the peroxidatic activity of catalase H2O2 system and by oxidation via other oxidizing enzymes such as CYP2E1.

Indeed, production of ACD during ETOH oxidation in situ was found and confirmed in several laboratories (Aragon et al., 1992; Gill et al., 1992; Hamby-Mason et al., 1997; Zimatkin et al., 1998; Person et al., 2000). Although ADH is not expressed in the brain (Zimatkin and Buben, 2006; Deitrich, 2011), ACD can nevertheless be generated by the action of catalase H2O2 system and to a minor extent by CYP2E1, both enzymes present in the brain (Aragon and Amit, 1992; Zimatkin et al., 2006; Deitrich, 2011). In vitro studies indicate that catalase H2O2 system generates 60 to 70% of brain ACD while CYP2E1 some 15 to 20% (Zimatkin et al., 2006).

In a study in mice, Correa et al. found that when catalase H2O2 system-mediated metabolism of ETOH into ACD is blocked (Correa et al., 2008) there is a suppressive effect of the anxiolytic actions of ETOH (Correa et al., 2008), suggesting that centrally formed ACD contributes to the anxiolytic effects of ETOH. Additionally, it has been reported that when catalase H2O2 system activity is pharmacologically reduced, via 3-aminotriazole (3-AT), rats reduce their intake and preference for ETOH (Koehling and Amit, 1994), a decreased voluntary ETOH intake in UChB rats is observed (Tampier et al., 1993) and ETOH-induced conditioned place preference (CPP) in mice (Font et al., 2008) is blocked. Furthermore the presence of 3-AT induced a concentration-dependent reduction of the amount of ACD generated after incubation. Homogenates of perfused brains of rats treated with AT or cyanamide (another H2O2-dependent catalase blocker) also showed a dose-dependent reduction of ACD (Aragon and Amit, 1992).

Recently, Karahanian et al. (2011) developed lentiviral vectors that coded for an shRNA designed to inhibit the synthesis of catalase H2O2 system. The single stereotaxic administration of an anticatalase-lentiviral vector into the ventral tegmental area (VTA), which reduced catalase H2O2 system levels by 70 to 80% (Quintanilla et al., 2012; Tampier et al., 2013), virtually abolished the voluntary ETOH consumption (up to 95%) by UChB rats. The lentiviral anticatalase shRNA administration also abolished the increases in dopamine release in nucleus accumbens (Acb) induced by the acute administration of ETOH. These effects strongly support a role of catalase H2O2 system and thus ACD in the central metabolism and in the motivational properties of ETOH.

**REINFORCING PROPERTIES OF ACD**

ACD itself possesses reinforcing properties, which suggests that some of the behavioral pharmacological effects attributed to ETOH may be a result of the formation of ACD, supporting the involvement of ACD in ETOH addiction (Brown et al., 1979). On this account, the positive reinforcing properties generally attributed to ETOH may in fact be mediated centrally by its metabolite. ACD, per se, would then be responsible for many biological effects which are not clearly distinguishable from those of ETOH (Quertemont et al., 2005c; Font et al., 2006a,b; Peana et al., 2008, 2009, 2010b; Correa et al., 2012).

ACD induces CPP in rats after intracerebroventricular administration (Smith et al., 1984), is self-administered directly into the cerebral ventricles (Brown et al., 1979) and into the (VTA) (McBride et al., 2002) whereas Rodd-Henricks et al., (2002) reported ACD self-administration into VTA in alcohol-preferring rats.

Further ACD induces positive motivational effects not only by central administration but also when administered peripherally. In fact, studies have shown that ACD induces CPP in rats after intraperitoneal administration (Quertemont and De Witte, 2001) and rats self-administer ACD intravenously (Myers et al., 1984; Takayama and Uyeno, 1985). Importantly, ACD induces CPP after intragastric administration (Peana et al., 2008), and is orally self-administered (Peana et al., 2010b) thereby mimicking the commonly employed route of administration of alcoholic.
beverages in humans. Further, ACD induces conditioned stimu-
lus preference (Quertemont and De Witte, 2001), and directly
enhances the activity of putative dopamine (DA) neurons in the
rat VTA in vivo (Foddaï et al., 2004). In addition, blockade of
alcohol dehydrogenase with 4-MP prevents EtOH-induced CPP,
oral EtOH self-administration and stimulation of the mesolim-
bic DA system (Foddaï et al., 2004; Melis et al., 2007; Peana et al.,
2008). As 4-MP administration mainly prevents peripheral ACD
formation, thereby reducing ACD available to penetrate the brain
(Iss et al., 2005), and provokes a consequent increase in blood
EtOH levels (Wallner et al., 1982), it is possible that the lack of
EtOH-induced CPP could be ascribed to high blood EtOH con-
centrations (Melis et al., 2007). However, reduction of pharmaco-
logically active ACD, by administration of the ACD-sequestering
agent D-penicillamine (DP), which does not increase blood
EtOH concentrations, also prevents spontaneous EtOH drinking
and strongly sustain the hypothesis that some of the behavioral
(Font et al., 2006b) and rewarding (Font et al., 2006a) effects of
EtOH are mediated by ACD.

**ACD ACTIONS IN THE VTA**

Most abused drugs, including EtOH, stimulate the release of DA
in several limbic regions (Di Chiara, 2002). Therefore, the rein-
forcing properties of ACD may be mediated by increasing the
release of DA in terminal areas.

Through utilization of the intracranial self-administration
(ICSA) paradigm, Rodd-Henricks et al. (2002) established that
rats will readily self-administer ACD directly into the poste-
rior ventral tegmental area (pVTA) at concentrations that were
1000-fold lower than that for EtOH (Rodd-Henricks et al., 2002;
Rodd et al., 2005, 2008). It appears that the pVTA is signifi-
cantly more sensitive to the reinforcing properties of ACD com-
pared to EtOH. Alcohol preferring rats display the highest lev-
els of ICSA for ACD doses that are approximately 2,000-fold
lower than the optimal dose of EtOH (Rodd-Henricks et al.,
2002; Rodd et al., 2005, 2008). Responding/infusion data from the
ICSA experiments exhibit an inverted “U-shaped” dose–response
curve for ACD, in which lower and higher doses do not pro-
duce reliable responding (Rodd-Henricks et al., 2002; Rodd et al.,
2005, 2008), suggesting that the reinforcing effects of ACD
within the pVTA appears to involve activation of DA neurons
(Rodd et al., 2005, 2008). In line with this, Melis et al. (2007)
found that ACD is essential for EtOH-increased microdialyse
da levels in the Nucleus Accumbens shell (AcbSh) and that this
effect is mimicked by intra-VTA ACD administration that pro-
duced an increase in DA release in the AcbSh to 150% that of
baseline.

ACD has excitatory actions on neurons of the VTA as clearly
demonstrated by the effects on DA release and on the firing fre-
cuency of individual VTA neurons. In experiments using in vivo
recording methods, ACD was injected intravenously, and a dose-
dependent increase in firing of dopaminergic VTA neurons was
reported (Foddaï et al., 2004). Thus, ACD parallels the effects
observed with EtOH, but at 50 times lower concentrations. The
effects of EtOH on VTA neuronal activity were blocked by sys-
temic pretreatment with the ADH inhibitor 4-MP, but this drug
had no effect on ACD induced excitation (Foddaï et al., 2004),
suggesting that the excitatory effects of EtOH on the VTA are
mediated by ACD. Sequestration of ACD in vivo by adminis-
tration of DP is sufficient to block the effects of intragastric-
ally administered EtOH or ACD (Enrico et al., 2009). These
key results indicate that ACD-induced activation of dopaminer-
gic VTA neurons mimics EtOH-induced excitation (Diana et al.,
2008), and is produced at much lower concentrations compared
to EtOH (Brodie et al., 1990; Brodie and Appel, 1998). Further-
more, EtOH applied in the presence of a catalase H2O2 system
inhibitor, 3-AT, failed to produce its characteristic excitation of
the VTA. Further, in exploring the mechanism of ACD exci-
tation of VTA neurons, Melis et al. (2007) examined the effect
of ACD on two ion currents, A-current and h-current. An A-
current represents a rapidly inactivating potassium current that
contributes to spike after hyperpolarization and is involved in
the regulation of firing frequency of dopaminergic VTA neu-
rons (Koyama and Appel, 2006). The authors noted a right-
ward voltage shift produced by ACD on I_A (Melis et al., 2007).
Also noted was a significant increase in h-current produced by
acutely applied ACD; this is reminiscent of the effect of EtOH,
which has been shown to acutely increase I_h of VTA neurons
(Brodie and Appel, 1998; Okamoto et al., 2006). The most parsi-
onious explanation suggests that EtOH is metabolized to ACD
by local catalase H2O2 system in the VTA, and the authors of
these studies suggest that, in general, EtOH actions on the VTA
are mediated by ACD (Deehan et al., 2013a,b).

Overall, it seems most likely that ACD is a crucial component
of the overall effects of EtOH on dopaminergic neurons of the
VTA; the essential action of ACD could be parallel to EtOH, or it
could enhance EtOH-induced changes. Blockade of the formation
of ACD can reduce the response of dopaminergic VTA neurons
to EtOH, and could serve as a platform for the development of agents
that reduce the rewarding and reinforcing actions of EtOH.

**ACD AS A BIOMARKER**

The results reviewed above suggest that enzymatic manipu-
lations of EtOH metabolism would diminish its rewarding
properties, possibly discouraging drinking (Figure 1). There
could be several mechanisms by which reduction of ACD
levels could reduce alcohol intake. For example, advantage
can be obtained by exploiting the ACD-chelating properties
of thiol compounds (Nagasawa et al., 1980). Indeed, adminis-
tration of the ACD-sequestering agent DP, reduces voluntary
EtOH consumption, ACD motivational properties (Font et al.,
2005, 2006b) and free-choice EtOH drinking behavior in mice
(Font et al., 2006a), acting centrally to reduce EtOH-derived
acetaldehyde (Font et al., 2005; Serrano et al., 2007). Further,
L-cysteine, prevented EtOH and ACD-induced conditioned place
preference (Peana et al., 2009), reduced oral EtOH and ACD
self-administration (Peana et al., 2010a, 2012), and blunted both
EtOH and ACD-induced stimulation of DA release in the AcbSh
(Sirca et al., 2011).

In addition, modulation of catalase H2O2 system by enzy-
matic inhibition (Melis et al., 2007), or H2O2 scavenging may
reduce ACD formation in the CNS and the motivational prop-
erties of EtOH (Ledesma et al., 2012; Ledesma and Aragon,
2012, 2013). Since the enzyme catalase takes H2O2, as a co-substrate
to form compound I, the central production of ACD derived from the metabolism of EtOH in the brain (Cohen et al., 1980; Sinet et al., 1980), may be affected by pharmacological manipulation of this system. Accordingly, pretreatment with alpha lipoic acid, scavenger of H2O2, reduces the acquisition and reconditioning of this system. Accordingly, pretreatment with alpha lipoic acid (ALA) a radical scavenger for H2O2. ACD is subsequently oxidized into acetate by aldehyde dehydrogenase (ALDH) inhibited by disulfiram. An additional strategy is represented by sequestration agents of ACD, D-Penicillamine (DP) and L-Cysteine.

**CONCLUSIONS**

It is hypothesized that many neuropharmacological, neurochemical, neurotoxic, and behavioral effects of EtOH are mediated by the first metabolite of EtOH, ACD (Hunt, 1996; Deitrich, 2004; Quertemont and Tambour, 2004; Quertemont et al., 2005b,c; Zimatkin et al., 2006). In addition, the present observations suggest that the positive motivational properties following EtOH administration, and the EtOH-induced enhancement of DAergic transmission, require EtOH’s first metabolite, ACD.

The important distinction between the central and the peripheral effects of ACD lays the groundwork for considering that many of the central effects of EtOH could in fact be dependent on the actions of its first metabolite, ACD. Although peripherally accumulated ACD is a potential toxic and deterrent substance, high levels of this substance can reach the brain and generate positive effects that can promote later consumption.

At last, targeting ACD, instead of EtOH, may offer new potential biomarkers in the search for novel compounds to reduce excessive alcohol intake, abuse and ultimately alcoholism. In general, targeting drug metabolism may reveal new ways to treat addictive disorders not limited to alcohol abuse but possibly useful in other addictions such as tobacco (Pianezza et al., 1998), heroin and cocaine dependence (Kreek et al., 2005) and other chemical dependencies (reviewed in Bough et al. (2013) and references therein).

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Muggironi et al.

Ethanol-acetaldehyde interactions in the CNS

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July 2013 | Volume 7 | Article 87 | 5
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.