

ACETALDEHYDE EFFECTS IN THE BRAIN

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ABSTRACT

The effects of alcohol have been widely studied during the past century as alcohol abuse is a major health problem in Western society. In the last years, a growing body of evidence indicates that acetaldehyde, the first oxidation product of ethanol, is one of the mediators of peripheral and central effects of ethanol. Indeed, acetaldehyde has been recently taken into account as the mediator of the rewarding properties of alcohol. The role of acetaldehyde in ethanol-related properties has been proved by enzymatic manipulation studies in which the inactivation of acetaldehyde potentially synthesized in the brain produces the same results as blocking the formation of acetaldehyde by inhibiting brain catalase activity. Moreover, electrophysiological and pharmacological analyses showed that acetaldehyde is able to stimulate dopamine release in the nucleus accumbens through enhancement of firing rate, spikes/burst, and burst firing of ventral tegmental neurons. Thus, the aim of this review is to summarize latest results on the role of acetaldehyde as the mediator of ethanol-central effects.

Key words: Acetaldehyde, Alcoholism, Ethanol-related effects, Dopaminergic pathway.

Received November 30, 2014; Accepted May 02, 2015

Introduction

Alcohol use disorder is considered a chronic relapsing and remitting disease defined by the development of tolerance, abstinence, drug consumption for alleviating abstinence, exaggerated consumption beyond original intention, failure to reduce drug consumption, use of a considerable amount of time to obtaining or recovering from the substance's effects, and maintenance of drug consumption, despite facing adverse consequences^(1,2). In particular ethanol (EtOH) produces a wide range of neurocognitive effects such as impairment in judgment, learning, memory, perception and psychomotor agitation^(3,4,5).

There is a growing body of evidence indicating that acetaldehyde (ACD), the first oxidation product of ethanol, is one of the mediators of the peripheral and central effects of ethanol⁽⁶⁻¹⁴⁾. ACD is usually considered a highly aversive substance: in the past the indirect use of ACD was taken into account for discouraging drinking in alcoholic patients. In fact, several drugs able to inhibit the activity of aldehyde dehydrogenase (ALDH) such as disulfiram and calcium carbimide, were widely used in the treatment of withdrawn alcoholics to produce an aversion for alcohol⁽¹⁴⁾. Nevertheless, it was reported that patients under treatment with ALDH inhibitor declared pleasant relaxing effects, after taking small doses of ethanol, highlighting

that ACD might exert positive emotional as well as motivational effects. More recently, many reports pointed out the role of centrally formed ACD^(16,17), which can facilitate locomotor activity, may produce anxiolytic effect in rats⁽⁷⁾ and can contribute to the overall psychotropic action of alcohol consumption⁽¹⁸⁾.

Thus, many researches support the theory that the motivational properties of ethanol might depend upon the action of its metabolites in the central nervous system (CNS), and by ACD in particular^(8, 19-22). Given these premises the issue addressed in this review is an overview of the latest data on the role of ACD as the mediator of the central effects of ethanol, focusing on its capacity to affect the neurocircuitries and neuropeptides involved in addictive behaviour⁽²³⁾.

Materials and methods

The author's search targeted evidence-based guidelines, evidence-based summaries, systematic reviews and recent experimental research on acetaldehyde formation in the brain and its role as the mediator of ethanol-central effects. The keywords used were "ACD" or "ACD in the brain" or "dopaminergic pathway" or "EtOH-central effects" or "ACD and VTA" or "ACD and EtOH-related addictive behaviour". Through this simple strategy we identified more than 10000 using two primary sources for identify relevant information: PubMed and SCOPUS (last accessed via PubMed and SCOPUS on February 16, 2015).

ACD Formation In The Brain

ACD formation by the oxidative metabolism of ethanol takes place in different organs and involves multiple enzymes, including alcohol dehydrogenase (ADH), catalase and cytochrome P4502E1 (CYP2E1)⁽²⁴⁾. In detail, ACD is obtained from peripheral metabolism of EtOH by the activity of ADH-1, the most important enzyme that metabolizes ethanol in the liver^(25,26). In the brain, ADH is idle⁽²⁷⁾, and ACD formation from EtOH occurs by the catalase system, whose presence in the central nervous system has been demonstrated through the study of ethanol metabolism in neuronal cultures and brain homogenates⁽²⁷⁾, and by the CYP2E1⁽²⁸⁾. Finally, in the liver ACD is converted rapidly into acetic acid by ALDH.

The concentration of ACD in the brain is important for mediating the pharmacological effects of EtOH. ACD formed in the liver penetrates into the brain from the periphery with difficulty because of the presence of ALDH in the microvasculature of the brain⁽³⁰⁾. Therefore, the blood-brain barrier limits ACD diffusion into the brain, such that little ACD produced by peripheral ethanol metabolism penetrates into the brain under normal conditions⁽³¹⁾. Further research indicates that the saturation of peripheral ALDH, given by a high concentration of ACD, allows it to reach the brain⁽²⁰⁾. Studies showing central effects of peripherally administered ACD seem to validate this possibility^(22,32). Several groups have shown that brain ACD is produced during in situ ethanol oxidation⁽²⁹⁾. Brain catalase activity modulates ACD formation in the brain from ethanol metabolism and has been involved in the regulation of ethanol-induced behaviours⁽³³⁻³⁷⁾. Different studies have shown that inactivating ACD potentially synthesized in the brain with the sequestering agent D-penicillamine (DP) produces the same results as blocking the formation of ACD by inhibiting brain catalase activity^(8,38).

In addition to catalase system, CYP2E1, the major ethanol inducible CYP, expressed in the neuronal cells in rat and human brain (39,40), might play a role in the production of brain ACD by EtOH metabolism. This enzyme has been shown to be expressed in mammalian brain, although the levels of CYP2E1 reported in the brain vary considerably among laboratories. Most studies have indicated that CYP2E1 is expressed at extremely low levels in the brain⁽⁴¹⁾, whereas other reports have shown much higher expression of CYP2E1 in control rat brain⁽³⁹⁾.

Recently, in vitro studies conducted by Zimatkin et al., in 2006⁽²⁹⁾ have emphasized that CYP2E1 contributes to brain ethanol metabolism into ACD for about 20%, which respect to 80% of the catalase.

ACD And VTA Regulation

All substances of abuse are able to influence behaviour through their ability to stimulate dopamine (DA) release in the mesocorticolimbic system, composed of ventral striatum, extended amygdala, hippocampus, anterior cingulate, prefrontal cortex and insula, which are innervated by dopaminergic projections from the ventral tegmen-

tal area (VTA)⁽⁴²⁻⁴⁴⁾. EtOH, as well as other substances of abuse, has numerous specific actions on DA VTA neurons: electrophysiological studies have showed that acute EtOH increases VTA neuronal activity^(45,46) and augments DA release in nucleus accumbens (Nacc) shell⁽⁴⁷⁾. Increasing evidence focuses on ACD as one of the mediators of the rewarding and motivational properties of ethanol: indeed, ACD itself, and as a consequence of the metabolism of EtOH, has been reported to possess its own reinforcing effects. In particular, Foddai et al., 2004⁽⁴⁸⁾ have shown that acute intravenous ACD administration increases the firing rate, spikes/burst, and burst firing of VTA neurons. Moreover, micro-dialysis and electrophysiology studies have demonstrated that oral ACD administration increases dopamine levels in the NAcc shell and promotes VTA DA neuronal spontaneous activity⁽¹²⁾.

Beautifully performed electrophysiological and pharmacological experiments have showed that ACD exerts a modulatory activity on two different ion channels, A-type K⁺ and hyperpolarization-activated cation channels. In particular, it seems that inhibition of A-type K⁺ channels and activation of hyperpolarization-activated cation channels contribute to the enhancing effect of ACD on DA firing⁽⁴⁹⁾.

Other studies have investigated the role and the effects of ACD in the activation of the reward pathway, through the pharmacological modulation of peripheral metabolism and activity of ACD. In particular, the reduction in ACD in the presence of its tapping agent, penicillin-derived sulfhydryl amino acid DP, was able to interfere with EtOH action, strongly supporting the hypothesis that some of the behavioural and rewarding⁽²¹⁾ effects of ethanol are mediated by ACD. Rats pretreated with an ADH inhibitor, 4-methyl-pyrazole (4-MP), showed no increase in striatal dopamine levels following ethanol intragastric administration^(12,48).

In the last years many researchers have focused their attention on the role played by addictive drugs in the activation of extracellular signal regulated kinases (ERK), a biochemical index taken into account to better understand the ability of a drug to activate DA-neuronal activation^(50,51), and therefore proposed as a selective marker for addictive compounds⁽⁵²⁾. In this regard, Ibba et al., 2009⁽⁵³⁾ have reported that ethanol, similarly to other addictive drugs, activates ERK in Nacc and in the extended amygdala via a DA D1 receptor-

mediated mechanism, suggesting that this pathway plays a crucial role in the primary mechanism of ethanol rewarding and motivational effect. Recently Vinci et al., 2010⁽⁵⁴⁾, in order to assess the role of ACD in the modulation of ERK, have demonstrated that the inhibition of EtOH metabolism by 4-MP, and the sequestration of newly formed ACD by DP prevent ERK activation by EtOH, just blocking ERK phosphorylation by ACD. Furthermore, many studies have focused their attention on the role of DA in the activation of ERK via D1-receptors in the Nacc and extended amygdala. In particular, it has been reported that treatment with SCH 39166, a D1 receptor antagonist, prevents ACD-elicited ERK activation⁽⁵⁴⁾ and ACD-induced conditioning place preference⁽⁵⁰⁾. The clear influence of D1 receptor activity on ACD-induced ERK activation provides further evidence of ACD incentive properties, whose contribution must be taken into account in studying and treating ethanol-related behaviours.

Conclusions

The functional data obtained by different research groups in the last years emphasize the role played by ACD as the mediator of consumption, tolerance, and reinforcement induced by EtOH intake. Nevertheless, despite recent progress in ACD- and EtOH-related addictive behaviour research, several outstanding questions remain. Indeed if the elucidation of ACD mechanisms of action in the induction and maintenance of the operant drinking behaviour have emphasized the direct and indirect (through the endocannabinoid system) involvement of DA transmission^(11,14), a central need is the comprehension of the relationship and degree of overlap between ACD's addictive, emotional and cognitive properties.

In addition, more observations are necessary in order to fully understand the intrinsic mechanisms by which the formation of ACD from EtOH can be able to induce a readaptation of the neurotransmitter and peptidergic circuitries that contribute to the onset and the maintenance of alcohol addiction.

In conclusion, in order to quantify the contribution of ACD to the central effect of EtOH, the study of ethanol metabolism, with a focus on brain catalase and CYP2E1, may help clarifying the elements of individual vulnerability to alcohol addiction, in order to arrange a more effective and tai-

lored strategy aimed to the prevention and the treatment of alcohol abuse.

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