

Acetaldehyde as the first hit of addictive behaviour

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Abstract

Unhealthy alcohol use is common in the Western society, which puts risk of health consequences, causing multiple behavioural injuries. Increasing evidence focuses on acetaldehyde, the first metabolite of ethanol, as the mediator of the several behavioural actions of alcohol, including its rewarding and motivational effects. In particular, acetaldehyde induces dopamine release in the nucleus accumbens modulating primary alcohol rewarding effect, drug seeking, and relapse behaviour. Recent behavioural studies point at acetaldehyde as a drug of abuse since its oral self-administration is induced and maintained in an operant/conflict paradigm. These findings provide further evidence on the role played by the acetaldehyde as a mediator of the effects of alcohol and focus attention on this molecule to arrange a more effective strategy, aimed at the prevention and treatment of alcohol abuse. Thus, the aim of this review is to summarize latest results on the role of acetaldehyde as the mediator of ethanol-central effects focusing on its capacity to induce an addictive behaviour.

Introduction

Alcohol is regularly consumed, ranging from 8 to 10% of heavy alcohol use (an average of ≥ 14 drinks per week in males and ≥ 7 drinks

per week in females).¹ Alcohol abuse represents a substantial and growing health problem in Western societies and it is the third risk factor for cardiovascular disease, cirrhosis of the liver and various cancers (WHO). The central effects of alcohol (ethanol, EtOH) are mediated by the interaction with different neurotransmitters, ionic channel, membrane proteins and receptors.²⁻⁴ EtOH abuse is associated with impairments of intellectual functions, memory, verbal and non verbal learning, visual motor coordination, cognitive flexibility, executive functions, problem solving, decision making, perception and information processing speed.⁵⁻¹¹ In the last years, EtOH dependence has been defined as a chronic relapsing and remitting disease, and it is well known that EtOH is able to influence emotional behaviour and cognition in humans in a dose-dependent manner,¹² time and modality of administration.¹³ An important role in the neurobiology of ethanol addiction is played by acetaldehyde (ACD), ethanol first metabolite detected and analyzed by HPLC/MS, that allows a quantitative and qualitative analysis.^{14,15} It derives from ethanol oxidative metabolism, which occurs by peripheral alcohol dehydrogenase, and by central catalase and CYP2E1.¹⁶⁻¹⁸ High blood levels of ACD enter the brain, likely overwhelming the aldehyde dehydrogenase present in the blood-brain barrier.¹⁹ Muggironi and colleagues showed experimental evidences on the involvement of ACD in the neurobiological mechanism supporting the motivational effects of EtOH.²⁰ Several studies have recently focused on ACD as the mediator of rewarding and motivational properties of EtOH.^{21,22} In particular, it has been reported that ACD acts in the mesocorticolimbic system, affecting dopamine (DA) neurotransmission with an increase of the neuronal firing in the ventral tegmental area (VTA), stimulating DA release in the nucleus accumbens (NAc) shell.²³⁻²⁵ In the last decades, several research groups have focused their attention on the role of ACD as a compound with potentially addictive effects, suggesting that ACD itself mediates addiction and craving,^{8,26,27} thus playing a key role in the development of alcohol dependence.^{28,29}

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Search methods

The authors' 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 EtOH-related addictive behaviour*. Through this simple strategy, we identified more than 10000 using two primary sources to identify relevant information: PubMed and Scopus (last accessed via PubMed and Scopus on March, 2016).

Role of acetaldehyde in addictive behaviour

The involvement of ACD as the *primum movens* of motivational and addictive properties of EtOH has been postulated by experiments conducted on manipulation of brain catalase activity. There is a positive correlation between brain catalase activity and natural propensity to drink EtOH in rodents, as shown by Amit and Aragon.³⁰ In agreement with past researches, these results confirmed that brain catalase activity and voluntary ethanol intake are unidirectionally and causally related,³¹ suggesting that brain catalase activity may be part of an enzymatic system, which controls the production and elimination of acetaldehyde in the brain.^{16,32} In particular, the administration of the irreversible inhibitor of catalase, 3-amino-1,2,4-triazole is able to decrease EtOH intake, the induction of an ethanol-induced conditioning-taste aversion to saccharine,³¹ and to antagonize ethanol-induced narcosis and lethality in ethanol drinking rats.³³⁻³⁵ Experimental evidence supports the idea that ACD itself is able to induce addictive like behaviour in rats. Indeed, early studies, have demonstrated that rats self-administer 1 to 5% (v/v) ACD directly into cerebral ventricles into VTA,^{28,36} and that its intracerebroventricular (icv) infusion induces conditioning-place preference.^{37,38} Rodd-Henricks and coauthors confirmed these data, pointing out that ACD is able to induce a self-administration behaviour directly into VTA, in alcohol-preferring rats.²⁹

Several studies highlighted the central effects and role of ACD in the establishment and maintenance of addictive behaviour, even when administered in rats, other than icv. Moreover, systemic ACD injections induce significant stimulus preferences;³⁷ intragastric administrations produce conditioning-place preference,³⁹ and rats self-inject ACD.⁴⁰ Recently, Cacace and co-authors have investigated the ability of ACD to induce and maintain oral-self administration behaviour in an operant conditioning paradigm,⁸ and the induction of a relapse behaviour upon the introduction of repeated deprivation phases. Furthermore, several studies sustain the role of ACD as a drug of abuse, showing that ACD-rats emitted a high number of lever presses during the extinction phase, also that an increase in the lever presses during the reinstatement one, moreover a higher emission of punished responses during the conflict paradigm,²² sustaining that ACD itself is able to induce an operant-drinking behaviour.

These experimental evidence, in accordance with previous reports and confirmed by further results,^{22,41} suggests that ACD may be considered as a drug of abuse. Sure enough, in an operant drinking behaviour, rats increase their ACD self-administration intake during reinstatement, following periods of forced abstinence. Furthermore, they increase lever presses for ACD when the reward is delivered together with an aversive stimulus. These studies, taken together, show that ACD is a strong reinforcer, whatever the route of administration is.

Behavioural effects of acetaldehyde

The impairment in learning and memory and cognitive functions, induced by long-term consumption of EtOH, may be attributed to a neurotoxic injury that induces a chronic degeneration of cholinergic basal forebrain neurons, and hippocampal cholinergic function, comparable to those observed in Alzheimer's disease.⁴²⁻⁴⁴

ACD is generally considered responsible for the harmful effects of EtOH occurring through modulation of neurotransmissions pathways in the CNS.^{4,18,45-47} In particular, ACD induces perturbation of cholinergic neurotransmission,^{48,49} a considerable reduction in choline acetyltransferase (ChAT) expression as a marker of acetylcholine (Ach) expression, in the frontal cortex as well as in the hippocampus and

plays a role in the pathogenesis of Alzheimer's disease.^{18,50,51} Jamal and colleagues have analyzed the effects of acute intraperitoneal administration of EtOH in Aldh2 knockout mice,⁵² a model of aldehyde dehydrogenase 2 deficiency in humans, to elucidate the role of ACD in the perturbation of cholinergic function. The authors showed that EtOH administration was able to induce a decrease in ChAT mRNA and protein levels in aldehyde dehydrogenase 2 knockout mice (Aldh2-KO) but not in wild type mice, suggesting a role for ACD in the mechanism of EtOH action. Moreover, it has been reported that ACD binds the Apolipoprotein E, a protein directly involved in the alterations of brain morphology and in learning and memory processes, promoting the formation of adducts.^{53,54} In particular, a polymorphism of mitochondrial aldehyde dehydrogenase gene (ALDH2 1/2 polymorphism) may cause the accumulation of ACD which could have a role in Alzheimer's disease, probably due to an altered modulation of the Apolipoprotein E.^{50,55} ACD induces different effects not only on cognitive function, in fact several reports have showed that ACD central administration, or locally formed ACD, is able to increase locomotor activity,⁵⁶⁻⁵⁸ while its intraperitoneal injection induces locomotor stimulant effects.¹⁹ Moreover ACD administration in the hypothalamic arcuate nucleus, a brain area known for its lower presence of ALDH, produces a long lasting induction of locomotion.⁵⁸ Interestingly Escrig and coauthors have found a relationship between anxiogenic effects produced by intraperitoneal high doses of ACD (100 mg/kg) and corticosterone levels,⁵⁹ as marker of endocrine responses, pointing out the role of ACD as mediator of EtOH consumption-induced stress response by.^{60,61} These findings are corroborated by previous *in vitro* studies showing that the inhibition of ALDH by cyanamid produces a significant increase in CRH mRNA in the paraventricular (PVN) and propiomelanocortin (POMC) mRNA in the anterior pituitary,⁶² and that ACD itself is able to induce, in a dose-dependent manner, CRH release from incubated hypothalamic explants.⁶⁰ These findings can better clarify the implication of ACD in the modulation of central neurotransmitters and peptidergic circuits, contributing to the onset and the maintenance of the emotional and cognitive effects induced by alcohol consumption. Furthermore, in the last year many researches point out to the attention on the role played by the endocannabinoid system in the modulation of ethanol-related central effects. Endocannabinoids (ECs) through the activation of the cannabinoid receptor 1 (CB1) broadly localized in the CNS, cause presynaptic inhibition of neurotransmitters release, such as gamma-aminobutyric (GABA),^{63,64} influencing dopamine transmission in the ventral striatum, amygdala and anterior cingulate cortex modulating the motivation approach towards substances of abuse. In particular the antagonist of ECs are able to reduce motivational and reward properties of ACD as mediator of ethanol addiction.²²

Conclusions

In the last years, several data commented the possibility that ACD may actually initiate and perpetuate EtOH reinforcement. Furthermore, different researches address the attention to the pivotal role of ACD in the modulation of the central effects of EtOH, since it mediates its consumption, tolerance and reinforcement. ACD might constitute the *first hit* in EtOH reinforcement, able to establish and maintain addictive behaviour, involving DA transmission in direct and indirect ways. This highlights the relationship and degree of overlap between acetaldehyde's addictive, emotional and cognitive properties. It suggests the real contribution of ACD in central effects of EtOH, driving the studies on ethanol metabolism. This may clarify the elements of individual vulnerability to alcohol addiction to arrange effective strategies aimed to prevent and treat alcohol abuse.

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