

Role of acetaldehyde in alcohol addiction: current evidence and future perspectives

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Abstract

The effects of alcohol have been widely studied during the past century, corroborating the idea that this tiny chemical compound acts throughout most of our neurotransmitter systems since it is capable of inducing addictive behaviour.

Two of the most serious problems of alcohol addiction are craving and relapse; several studies have demonstrated that relapse is related to the anxious state which occurs during withdrawal, and it has been proved that this behavioural modifications results from an alteration of the dopaminergic and serotonergic systems. An important role in the neurobiology of alcohol addiction is played by acetaldehyde (ACD), ethanol first metabolite.

Keywords

Alcohol; addiction; acetaldehyde; motivation; operant behaviour.

Our recent studies indeed, have demonstrated that ACD itself is able to induce CRH release from hypothalamic explants, underlying the central role played by ACD in alcohol-induced modifications of the HPA axis. Moreover, for the first time, this group has shown that ACD is able to induce and maintain an operant drinking behaviour after repeated abstinence periods, and in the presence of a conflict situation in rats, mimicking the same characteristics as alcohol. ACD is produced either peripherally or within the brain by alcohol dehydrogenase and catalase, respectively. Studies assert that the highest concentrations of catalase in the brain are mainly located in aminergic neurons suggesting that ACD could take part in alcohol action in those circuitries. Further investigations are then necessary to fully understand the molecular mechanisms underlying the neurochemical and behavioural modifications induced by ACD, as a mediator of alcohol activity in the brain.

Introduction

Today alcohol addiction is one of the most serious clinical and socioeconomic problems for many countries. Excessive drinking is a social emergency, especially if we look at young people; in fact in Europe, from 1998 to 2010, alcohol consumption among adolescents, aged between 14 and 20 years old, increased from 12.6% to 20.5%. It is not a controlled use of alcohol that must be criminalized, but its abuse, and the reason for that is the establishment of an addictive behaviour. As for other substances of abuse, alcohol addiction is a chronic relapsing brain disorder, characterized by neurobiological changes, leading to compulsive drug seeking and drug taking despite serious negative consequences, and by loss of control over drug use. The neuronal networks supporting the compulsive consumption of alcohol are the circuitries responsible for the positive reinforcement, which is to say the activation of the dopaminergic neurons of the ventral tegmental area (VTA) which project to the

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nucleus accumbens (NAC), where an increase in dopamine release (DA) occurs.

EtOH Effect on the self-administration Paradigm

One commonly used approach for modelling human alcohol consumption in rodents is the free-access paradigm with alcohol at various strength, where the amount of each fluid consumed is measured. Usually, at the beginning, rats prefer alcohol solutions of lower concentrations (<6%), because of their "sweet taste", over those of higher concentration¹. With this aim our research group has recently published a study which sought to examine ethanol intake and preference patterns in heterogeneous adult male Wistar rats, using a 3-bottle choice paradigm with water, 10%-ethanol solution, and white wine (10% v/v), for a four-week period.

Our results showed that during the three-bottle choice paradigm, adult male rats displayed an initial 47% alcoholic preference that decreased to a final 24% in the last two weeks.

Rat drinking patterns displayed an irregular trend, including dramatic peaks in the early days, followed by sharp drops in the following days. This irregular pattern may resemble the initial binge-like drinking behaviour observed in humans, as a function of the rewarding effects exerted by alcohol; this was then followed by a voluntary, and probably necessary, reduction in alcohol intake in order to recover from intoxication. It seems therefore, that rats with alcohol free-access (AFA) are able to control their alcoholic intake in order to avoid unpleasant effects, but enjoyed the reinforcing properties of alcohol.

When the animals were tested in the Morris water maze in order to assess the acquisition of spatial learning and memory tasks, interestingly, alcohol induced a facilitatory effect just in a task that required a new processing of spatial information. It was then hypothesized that AFA, was able to enhance spatial flexibility, when an unexpected change in the environment required an adaptive response in order to find a solution.

When female rats were exposed to the same experimental conditions, they drank more alcohol than males during the paradigm, reaching a preference of 55%. This pattern can be explained through the activation of the mesolimbic dopaminergic reward system, since it is reported that female rats display a greater release of dopamine in the NAcc following alcohol consumption when compared to males.²

When exposed to the MWM, in order to assess the effects of alcohol self-administration on learning and memory abilities, female rats showed a significant worsening with respect to control rats together with a significant decrease in both locomotor activity and explorative behaviour in the open field. It is widely reported that women tend to suffer from alcohol-related physical illness and display more severe cognitive and

motor impairments compared to men. Whether the effects observed in our study are related to metabolic or to pharmacodynamic mechanisms is difficult to say, but the topic is worth further investigation.

Alcoholism or Acetaldehydism?

Several studies in the last 30 years have investigated the role and the effects of acetaldehyde (ACD) as one of the mediators of the central and peripheral effects of ethanol. ACD derives from the peripheral metabolism of ethanol (EtOH) by alcohol-dehydrogenase (ADH) and is converted into acetic acid by aldehyde dehydrogenase (ALDH). Traditional views contend that acetaldehyde is an "aversive" compound responsible for the so-called "flushing syndrome", which is exploited therapeutically by disulfiram.^{3,4} A slow but measurable accumulation of ACD in the rat brain has also been demonstrated. Although other enzymes from the microsomal ethanol-oxidizing system (MEOS) such as CYP2E1, and alcohol dehydrogenase I (ADH I) are also present in the brain,^{5,6} but to a lesser extent than in the periphery; the biochemical data suggest that acetaldehyde is formed in the brain mainly by catalase, when ethanol is administered acutely.^{7,8} However, in sharp contrast with the idea of a toxic metabolite, recent data suggest that acetaldehyde is actually rewarding both in rodents and humans.⁹ Particularly, acetaldehyde induces "place preference";¹⁰ it is self-administered directly in the VTA area,^{9,11} and acts as other crucial cellular elements of drug-induced reward.^{12,13}

ACD and neuropeptides

The opioidergic system modulates some of the mechanisms which are at the base of the induction and the maintenance of addiction. Some experiments conducted on hypothalamic neuronal cultures have demonstrated that ACD stimulates, more than EtOH, the release of beta-endorphin.¹⁴ Interestingly, when the enzymatic oxidation of EtOH into ACD is blocked by the inhibition of cerebral catalase, beta-endorphin release is inhibited, suggesting that EtOH effects could be mediated by its conversion into ACD.¹⁵ Stress mediators, released by the activation of the hypothalamus-pituitary-adrenal (HPA) axis, are involved in setting up alcohol addiction.¹⁶ EtOH administration activates the HPA axis, and therefore releases ACTH and glucocorticoids^{17,18} through the stimulation of the paraventricular nucleus of the hypothalamus.¹⁹ Recent data of our group demonstrate indeed that EtOH is able to stimulate CRF release from hypothalamic explants and that this effect is mediated by ACD. To validate this hypothesis we showed that ACD was able to stimulate CRH release

in a dose-dependent manner. When the hypothalamic oxidation of EtOH into ACD by cerebral catalase was inhibited by 3-amino-1,2,4-triazole, this compound in the presence of EtOH completely prevented hypothalamic CRF release. Furthermore, the administration of D-penicillamine, an ACD-trapping agent, inhibited ACD-induced CRF release, demonstrating that ACD was the primary mediator of EtOH activity on the HPA axis. In conclusion, the repeated consumption of EtOH induces, through the formation of ACD, a rearrangement of neurotransmitter and peptidergic circuitries that contribute to the onset and the maintenance of alcohol addiction.

ACD and self-administration

It is still under debate whether, under physiological conditions, acetaldehyde formed in the liver is able to penetrate into the brain from the periphery because of the metabolic barrier presented by ALDH in the blood-brain barrier.²⁰ Studies showing central effects of peripherally administered ACD seem to validate this possibility.^{21,22}

Self-administration, within operant conditioning, is considered a valid experimental model to investigate drug-seeking and drug-taking behaviour in rats: the higher the frequency of the animal response, the more rewarding and possibly addictive, the test substance.²³ Although dopamine was originally proposed to mediate “reward”,^{24,25} recent studies indicate that dopamine is likely to have a more general role in the processing of behaviourally relevant positive and negative stimuli and the selection of appropriate responding.²⁶⁻²⁸ Addiction induces or modifies complex behavioural and neurobiological processes, including the different stimuli which lead to relapse. Indeed, more than 80% of addicts relapse to drug seeking and use after a period of withdrawal and abstinence. Understanding the neurobiological basis of drug seeking and relapse, following the deprivation effect, is a central issue of the research on addiction.²⁹

With this aim we recently wished to evaluate: whether oral ACD could induce a self-administration behaviour in an operant conditioning paradigm; hence its reinforcing properties on the maintenance of this behaviour; and the induction of a relapse behaviour upon the introduction of repeated deprivation phases. Our results showed that ACD, was able to induce an operant drinking behaviour according to a FR-1 schedule, and moreover ACD-drinking rats displayed a higher number of lever presses and greater amount of volume ingested, when compared to water-drinking rats.³⁰ Drug self-administration is directly under rat control, and the frequency and amount of drug self-administration are widely used to infer drug hedonic properties: positively reinforcing drugs will be readily and avidly self-administered. Though explored according to other experimental paradigms, ACD reinforcing properties have already been reported in other research employing a

self-administration pattern of consumption.^{9,31,32} Those studies showed that ACD self administration is easier to establish than ethanol self-administration,³³ indicating that ACD is a stronger reinforcer than its parent drug ethanol, whatever the route of administration, systemic or central. On the other hand, it has been suggested that ACD is able to cross the blood-brain barrier after a single systemic administration.³⁴ Moreover when ACD-deprived rats underwent a re-presentation of ACD, and their ACD intake over baseline drinking was measured, in accordance with evidence of increased alcohol consumption following periods of abstinence, ACD-drinking rats displayed a higher number of lever presses and a significant increase in liquid intake compared to controls. Moreover when ACD intake during the different relapse sessions was compared to basal ACD intake, a significant effect of deprivation was recorded. Interestingly, ACD intake in the second and third week of relapse was significantly higher than in the first week. The increase in ACD intake might be caused by an increase in the reinforcing value of ACD; alternatively ACD itself may be acting as a cue or as a priming stimulus, as reported with alcohol. The alcohol deprivation effect in long-term voluntary alcohol drinking rats is used as a measure of craving; i.e. high motivation to drink alcohol as a measure for relapse-like behaviour.³⁵ Therefore, these findings suggest a motivated operant drinking behaviour which reflects an incentive demand for the drug, apart from any other possible reason than motivation.

ACD and motivation

In contrast to experimental models involving spontaneous, threatening stimuli, in the Geller-Seifter procedure rats suffer from the “conflict” between the drive to drink and the fear of the shock: this usually leads to a suppression of a conditioned response for reinforcement. Punishment-based procedures have been thus employed for the identification and characterization of the anti-conflict properties of several drugs, including ethanol.³⁶ Here we report the observation of the effects of ACD in a modification of the Geller-Seifter procedure, where a negative reinforcer was introduced in the operant behaviour so that together with ACD solution, a mild electric foot-shock was elicited following each lever press (in press).

The presentation of the aversive stimulus, in the CTR group, had a dissuasive effect, and led to a dramatic decrease in the number of punished responses, according to the principles of behavioral psychology.³⁷ In ACD-drinking rats, instead, such a reduction was not observed, and the number of punished responses was significantly augmented. Usually, the unpunished

component of the test is poorly interested by the anxiolytic activity of the drugs unless when high doses are employed causing sedation and motor in coordination that is responsible for the decrease in the unpunished responses. In our study ACD was also able to increase the unpunished responses, although at a lesser extent than the punished ones. This was against a lack of effect on locomotor activity as resulted by the experiments in the open field. Therefore the effects exerted by ACD in increasing both the punished and the unpunished responses might be due to a prevalent motivational effect.

Studies based on the use of ADH- or ALDH inhibitors, of catalase inhibitors, or of ACD- sequestering agents, have consistently shown that the effects of ethanol on locomotor activity anxiety HPA axis activation and motivation appear to be mediated by ACD. The modulation of alcohol-derived ACD, either by reducing its production and / or by using sequestering agents, may exert a profound influence on the reinforcing and discriminative effects of alcohol, and might also accelerate the development of more effective therapeutic interventions to reduce the incidence of alcohol abuse and alcoholism.

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