ALCOHOL ADDICTION: A ROLE FOR ACETALDEHYDE

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SUMMARY

Alcoholism is a chronically relapsing disorder characterized by cycles of repeated high alcohol intake and negative emotional consequences of withdrawal thought to contribute to excessive drinking and susceptibility to relapse.

In the past years, the pharmacological and behavioural effects of alcohol, such as sedation, memory and learning impairment, were assigned to the main component of alcoholic drinks, ethanol.

Recently acetaldelyde, the first metabolite of ethanol, seems to exert biological activity, besides its adverse effects.

The aim of the present review is to elucidate the putative role of acetaldelyde in mediating the neuronal and behavioural features induced by ethanol intake.

Key words: alcoholism, ethanol, acetaldelyde

Today alcohol addiction is one of the most serious clinical and socioeconomic worries for many countries (23).

In the United States, alcohol abuse constitutes one of the three main causes of the onset of psychiatric disturbances such as anxiety and depression (8).

Alcohol addiction is caused by an excessive consumption of ethanol (EtOH), commonly considered the main psychoactive ingredient of alcoholic drinks. In particular, EtOH produces a wide range of behavioural effects ranging from psychomotor agitation, to increase in reaction times, attentional disturbances and impulsiveness.

These symptoms depend on neurochemical modifications regarding both the functionality of ionic channels activated by excitatory and inhibitory amino acids (glutamate and GABA) and the expression of membrane proteins and receptors (4).

However, the molecular mechanisms that undergo EtOH action in human beings are still widely debated. 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 nucleus accumbens (NAC), where an increase in dopamine release (DA) occurs.

Recently, it has been suggested that some of the effects induced by ethanol, are likely related to its first metabolite, acetaldelyde (ACD) (13).

This molecule is produced peripherally by the activity of alcohol dehydrogenase (7, 22, 12) and centrally by the catalase-H2O2 system (24), whose presence, in the central nervous system, has been demonstrated through the study of EtOH metabolism in brain homogenates (5) and in neuronal cultures (6).

ACD is metabolized into acetic acid by aldehyde dehydrogenase in the whole organism.

In the past, ACD has been taken into consideration for its adverse and toxic effects, particularly in relation to the treatment of alcoholism with “disulfiram”, a compound that irreversibly blocks both cytosolic and mitochondrial aldehyde dehydrogenase, resulting in the inhibition of ACD degradation.

Many studies have investigated the role of ACD in determining neurochemical and behavioural effects such as sedation, sleep induction (12), and temporary loss of memory (29).

RIASSUNTO

L'alcolismo è una malattia cronica recidivante, caratterizzata da ripetuti cicli di elevata assunzione di alcol con conseguenze emotive negative caratteristiche dell'astinenza, che conducono ad un eccessivo consumo della sostanza e a frequenti ricadute.

Negli scorsi anni, gli effetti farmacologici e comportamentali dell'alcol quali, sedazione, amnesia e peggioramento cognitivo, sono stati assegnati al componente principale della bevanda alcolica, l'etanolo.

Recentemente, l'acetaldeide, il primo metabolita dell'etanolo, sembra possedere attività biologica al di là dei più noti effetti avversi. Lo scopo di questa review è di chiarire il ruolo dell'acetaldeide quale mediatore delle alterazioni neurochimiche e comportamentali indotte dall'etanolo.

Parole chiave: alcolismo, etanolo, acetaldeide
It has also been reported that in alcohol abusers, ACD mediates addiction and craving\(^{(3)}\), thus playing a key role in the development of alcohol dependence\(^{(4)}\). In order to elucidate the role of ACD, pharmacological manipulations of EtOH have been performed.

In particular, it has been observed that the block of catalase, through a specific inhibitor, 3-amino-1,2,4-triazole (3AT), reverts both the reduction in locomotor activity\(^{(5)}\) and the hypnotic effect\(^{(6)}\), induced by high doses of EtOH. Moreover, the block of aldehyde dehydrogenase, induced by cyanamide, results in a large increase in ACTH plasma concentration, such to allow ACD to cross the blood-brain barrier and therefore to diffuse in the central nervous system. Many behavioural studies have inquired the reinforcing properties of ACD\(^{(7)}\).

In particular, rodents self-administer ACD in the VTA area which is the brain region mainly involved in the rewarding properties of drugs of abuse\(^{(8)}\).

The reinforcing activity exerted by ACD has also been confirmed from place-preference studies in which rats show to spend more time in the place where they were previously treated with ACD\(^{(9)}\)

Besides, ACD is able to modify neurotransmitter and peptidergic transmission.

For instance, 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\(^{(10)}\).

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 effect could be mediated by its conversion into ACD\(^{(11)}\).

It is not surprising that stress and its mediators, released by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, are involved in setting up alcohol addiction\(^{(12)}\). EtOH administration activates the HPA axis, and therefore releases ACTH and glucocorticoids\(^{(13)}\).

However it’s believed that the activation of the HPA axis induced by EtOH does not represent a direct effect on the pituitary gland, but it seems to occur through the stimulation of the paraventricular nucleus of the hypothalamus\(^{(14)}\).

Recent data of our research group demonstrate indeed that EtOH is able to stimulate CRF release from hypothalamic explants and that this effects is mediated by ACD.

To convalidate this hypothesis the hypothalamic oxidation of EtOH into ACD has been inhibited by 3AT. This compound in the presence of EtOH, completely prevents CRF release.

Furthermore, the administration of D-penicillamine, a molecule able to inactivate ACD, inhibited ACD-induced CRF release, pointing out how ACD is the primary mediator of EtOH activity on the HPA axis.

In conclusion, the repeated consumption of EtOH induces, through the formation of ACD, a readaptation of the neurotransmitter and peptidergic circuitries that contribute to the onset and the maintenance of alcohol addiction.

The study of the biological features that undergo animal behaviour following EtOH or ACD administration, may provide valid indications to clarify the molecular mechanisms responsible for alcohol effects in the CNS.

Moreover, through an accurate clinical evaluation of human psychological traits, together with a careful investigation of the structures mainly affected by alcohol use, it will be possible to highlight the most relevant elements of vulnerability, in order to arrange a more affective strategy aimed to the prevention and the treatment of alcohol abuse.

References

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