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ALCOHOL, WITHDRAWAL SYNDROME AND MEDIATORS IN THE CENTRAL NERVOUS SYSTEM

ALKOHOL, APSTINENTSKI SINDROM I MEDIJATORI U CENTRALNOM NERVNOM SISTEMU

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Ključne reči

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Key words

alcohol, withdrawal syndrome, mediators in the central nervous system, catecholamine's

Abstract

The Alcohol withdrawal syndrome (AWS) reflects the neuro-biochemical adaptation of the organism to recurrent alcohol consumption and the symptoms are opposite of those caused by the substance. The core of the multiple abstinence pathology consists of changes in neuro-mediators. Ethanol rapidly crosses the blood-brain barrier and affects membranes, ion channels, enzymes and central nervous system (CNS) neurons.The material aims to analyze the data in the literature about the influence of the chronic alcohol use on the catecholamine levels, which are the basis for the intensity and duration of the alcohol withdrawal syndrome.To conclude: the catecholamine neurotransmission is the basis for the various symptoms of ethanol withdrawal. All patients with alcohol addiction develop AWS. Their pathogenesis is the plasma levels of adrenaline and noradrenaline. AWS is often of a short duration, but can quickly enter into a pre-delirium or delirium. In the pre-crisis period, the somatic manifestations are discrete – light tremor, tendency to tachycardia, minor increase in blood pressure (BP), skin moistening. It is during this period that an active observation is needed to capture these prodromal signs. In the meantime, the onset of treatment often prevents the onset of delirium tremens.

The withdrawal syndrome reflects the neuro-biochemical adaptation of the organism to recurrent alcohol consumption and the symptoms are reversed to the effect of the substance. Abstinent symptoms are a manifestation of established physical dependence. These are seen in all alcohol-dependent patients. The majority of patients develop rapid transient symptoms and in most cases their intensity is relatively weak [1].

Symptoms of alcohol withdrawal syndrome (AWS) are associated with dysfunctions such as: palpitations, rapid breathing, sweating, mild elevation, tremor, etc. Gastrointestinal symptoms like nausea and vomiting are seen in almost a third of the patients - Approximately 75% of patients recorded changes of the mood (as soon as AWS appear) [2]. The core of the multiple abstinence pathology consists of changes in neuro-mediators (NM). The alcohol (EtOH) alters their metabolism or the sensitivity of the receptor to them.

The material aims to analyze the data in the literature about the influence of chronic alcohol use on the catecholamine levels, which are the basis for the intensity and duration of alcohol withdrawal syndrome. Ethanol rapidly crosses the blood-brain barrier and affects membranes, ion channels, enzymes and central nervous system (CNS) neurons.

The alcohol affects the brain by changing the level of neuromediators. This is caused by:

1. Impact on CNS receptors:

Ethanol attacks the lipid component, composed mainly of phospholipids and encom-passing the major protein component of GABA-receptors. The processes of correct information transmission, chlorine ion infestation, blocking of glutamate - Ca^{++} system (blocking the excitation system) are violated. This causes disharmony in cell membrane permeability, stimulation of secondary mediators and disturbances in central cerebral mediation and hormonal secretion [3].

Blocking vasopressin leads to a general dehydration effect, both in the cells of the left brain and on stromal cells [4].

The withdrawal syndrome itself is brain-reactive, a property associated with hyper-glutamatergia. In the pathogenesis of the pathological pathway to alcohol and AAS, dopamine system disorders are of central importance [5,6].

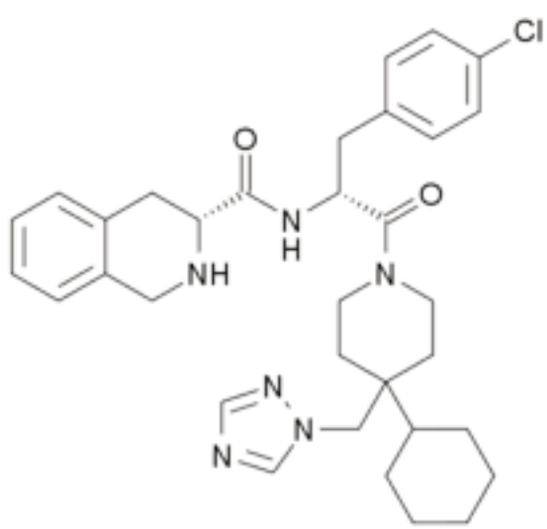
2. Pathological synthesis:

Ethanol oxidation (acetaldehyde synthesis, AcAD) is a process leading to intracellular accumulation of $NADH_2$ and $NADPH_2$ and is a prerequisite for a number of pathological syntheses that begin to run intracellularly [7].

According to several notable neurobiochemical studies, AcAD (which is much more aggressive than ethanol) plays an extremely important role in the appearance of AWS and delirium tremens (DTs), mainly by its tendency to condensation with CNS mediators [7,8]. It stimulates the activity of some endogenous opioids in the brain, which, by chemical structure and by effect, are very similar to the molasses molecule and thus predispose the formation of dependence. Such are tetrahydropaproveloline, tetrahydroisoquinoline and betacarbone found in mesolimbic brain structures and having a direct relation to the effects of dopamine and serotonin. For example, beta-carbohydrates act as inhibitors of MAO {MAOIs} (harmin, charmalin, tetrahydrocharmine, etc.) [8,9].

In the first place, the acetaldehyde is condensed with dopamine (DA) to form a con-densate-salsalinol having a hallucinogenic effect. Furthermore, in its amine oxidation, tetra-hydroisoquinolines (THIQ, formul 1) are obtained. The latter are extremely stable compounds, practically non-degradable and accumulate in the CNS and play an important role in the occurrence of abstinent reactions [10].

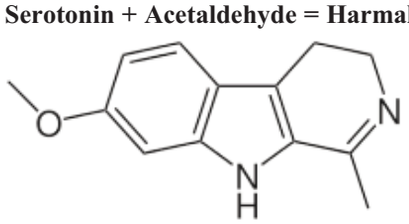
Dopamine + Acetaldehyde = Tetrahydroisoquinolines (THIQ)



Formula 1: Tetrahydroisoquinoline (THIQ)

Acetaldehyde is also condensed with 5-HT (serotonin):

Serotonin + Acetaldehyde = Harmaline



Formula 2: Harmaline

Harmaline degrades extremely slowly, stimulates the release of DA into the CNS; an inhibitor of cholinesterase and blocking MAOIs. Reduces melatonin synthesis and is a potent indole stimulator of the CNS. It determines the anxiety-hallucinogenic symptom [11,12,13].

3. Chronic alcohol use deficits:

Chronic alcohol use leads to disorders in hepatocyte metabolism. The latter is charac-terized by: reduced synthesis of aldehyde-dehydrogenase (due to depletion or inadequate glutathione); high levels of homocysteine due to impaired methylation; change in the alkaline-acidic state of the body with a tendency to acidosis (changes in the metabolism of carbohy-drates, lipids and proteins); general dehydration of the body as a consequence of a vestibular blockage; common enzyme deficiency induced by impaired amino acid uptake and protein synthesis [4,14,15,16]. Ethanol leads to hypovitaminosis of water-soluble vitamins and zinc deficiency (Zn). Their absorption, storage and distribution are impaired. Among the most affected vitamins are B1, B6, D, E. At the same time, vitamin B deficiency and associated impairment in the function of thiamine and pyridoxine-dependent enzymes involved in the metabolism of bio-genic amines [17,18,19,20].

Of course, other factors contributing to the emergence of AWS and DTs, such as amyl alcohol as a result of the degradation of the carbon skeleton of branched chain amino acids (BBAAs), can not be ignored. It is present in almost all alcoholic beverages [21].

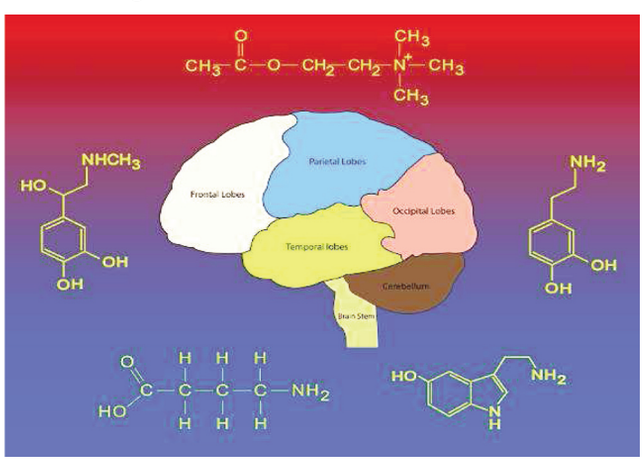


Fig. 1*: Main neurotransmitters in the CNS and impact zones (Internet)*

AWS is triggered by the activation of the hormonal and mediator units of the sympa-thetic part of the nervous system. The effect of EtOH unlocks changes in plasma levels of catecholamine's (CA). The most important role in the pathogenesis of AWS is the change in catecholamine's exchange (dopamine and noradrenaline) - CA concentrations in biological fluids are increasing, which determines the activation of dopaminergic and noradrenergic neurons [17,22,23].

With the development of alcohol intoxication (stress response), the level of adrenaline (A) is gradually decreasing, with that of noradrenaline (NA) increasing. In the case of a stress reaction such as chronic alcohol use, the secretion of adrenaline and noradrenaline is increased. EtOH tem-

porarily stimulates the noradrenergic system, causing a rush of energy followed by a decrease in its activity. The catecholamines activate the cardiac beta-adrenergic receptors in the smooth musculature. Adrenaline and noradrenaline accelerate metabolism and favor the conversion of glycogen into the liver in glucose and thus increase its blood concentration. EtOH affects the metabolism of NA, and its concentration in the brain affects the attunement to alcohol [24].

Alcohol stimulates the dopamine (DA) metabolism, and its chronic use leads to an increase in the number of dopamine receptors. This fact is the main cause for the development of the physical and the psychological dependence on ethanol [25]. These effects on dopamine and norepinephrine are closely related to the effects of EtOH on serotonin (5-HT). In chronic use, decreased synthesis of 5-HT and its release, reduced susceptibility of neurons to 5-HT is observed. Interesting data is tainted by the risk of alcohol dependence on the serotonin trans-porter activity [26].

A number of authors find an increase in the concentrations of free and conjugated forms of dopamine (DA) in the blood of alcohol-dependent patients [4,5,6]. They establish a direct correlation between the rate of increase in DA and the severity of alcohol withdrawal syndrome. In the case of an increase of DA with 250-300 %, in relation to the norms, alcohol demiter (DTs) develops. At the end of the withdrawal syndrome, the DA concentration in the brain reaches normal levels. The reason for the increased level of dopamine is the accelerated synthesis of catecholamines, with continued ethanol misuse [27].

In patients with AWS and DTs, monoamine oxidase (MAO) activity, the monoamine degrading enzyme (including DA) was found to be nearly 2-fold lower than that of the healthy persons and in patients who are in a period of prolonged remission [28].

In addition to MAO, dopamine beta-carboxylase, which converts dopamine into noradrenaline, is a factor determining the formation of alcohol dependence [29].

In an extensive article, authors put forward arguments in support of the hypodermic [11]. Increased homobanilic acid (HVA) levels, a major product of dopamine metabolism, have been reported during delivery. Increased DA activity is probably key to the formation of alcohol hallucinations. Studies suggest that there is a correlation between increased DA acti-vity and the weight of AWS [5,11,13,30].

There are also publications in the literature with the opposite view. These findings are based on the hypothesis that depressive syndrome is characteristic of AWS and it is logical to expect hypodopaminergy and hyposeerotinergy [31].

In experiments with rats, it was found that alcohol use during AWS rapidly restored the decreased levels of DA and 5-HT in nucleus accumbens [5,6]. Alcohol-dependent individuals carrying the A1-allele of the DRD2 gene have decreased density of postsynaptic D2- receptors, which is a prerequisite for low dopamine neurotransmission. These patients showed increased symptoms of depression during AWS [32].

To summarize, dopamine neurotransmission may be the cause of various symptoms of ethanol withdrawal. On the one hand, decreased DA activity probably causes depressive and dysphoric manifestations, and the increased induces hallucinations. According to Morikawa and Morrisett, this can be interpreted with the existence of different alcoholic phenotypes with heterogeneous neurobiological mechanisms [14].

To conclude: the catecholamine neurotransmission is the basis for the various symptoms of ethanol withdrawal. All patients with alcohol addiction develop AWS. Their pathogenesis is the plasma levels of adrenaline and noradrenaline. AWS is often short-lived, but can quickly enter into a divisive or divisive consciousness. In the pre-crisise period, the somatic manifestations are discrete - mild tremor, tendency to tachycardia, minor increase in blood pressure (BP), skin moistening. It is during this period that active observation is needed to capture these prodromal signs. In the meantime, the onset of treatment often prevents the onset of DTs.

Sažetak

Alkoholni apstinentski sindrom je odraz neurobiohemijske adaptacije organizma na ponovljenu konzumaciju alkohola, a simptomi koji se javljaju su suprotni onima koji su uzrokovani supstancom. Razlog apstinentske pojave nalazi se u promenama u neuromedijatorima. Etanol brzo prelazi krvno-moždanu barijeru i utiče na membrane, jonske kanale, enzime i neurone centralnog nervnog sistema (CNS). Cilj rada je analiza podataka u literaturi o uticaju hroničnog korišćenja alkohola na nivoe kateholamina, koji su osnova intenziteta i trajanja alkoholnog apstinentskog sindroma. Da zaključimo: neurotransmisija kateholamina je osnova za razne simptome alkoholne apstinencije. Svi pacijenti sa zavisnošću od alkohola razvijaju alkohlni apstinentski sindrom. Za patogenezu ovog oboljenja su odgovorni nivoi adrenalina i noradrenalina u plazmi. Apstinentski sindrom je često kratkog trajanja, ali može brzo ući u pre-delirium ili delirijum. U periodu pre krize, somatske manifestacije su diskretne - blagi tremor, tendencija ka tahikardiji, blago povećanje krvnog pritiska, vlaženje kože. Tokom ovog perioda potrebno je aktivno posmatranje kako bi se uhvatili ovi prodromalni znaci. U međuvremenu, početak lečenja često sprečava pojavu delirium tremensa.

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