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COGNITIVE IMPAIRMENT DUE TO ALCOHOL ABUSE: CURRENT STATUS OF RESEARCH

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Alcohol abuse causes significant changes in cognitive functioning. These effects are related to the fact that ethanol and acetaldehyde, its first metabolite, affect the the brain's neurotransmitter systems. Long-term abuse may lead to the dysexecutive syndrome (DES) exhibited through emotional, behavioral and cognitive symptoms. Alcohol has a specific dose-dependent effect on memory that serves as a block of memory consolidation, i.e. transition of the short-term memories to the long-term storage. This effect displays either as reversible amnesias of events from the alcohol abuse period (blackouts), or as an irreversible fixation amnesia within Korsakoff's syndrome. Refs 34.

Keywords: cognitive functions, alcohol, amnesia, blackouts, dysexecutive syndrome.

К ВОПРОСУ О КОГНИТИВНЫХ НАРУШЕНИЯХ ПРИ УПОТРЕБЛЕНИИ АЛКОГОЛЯ

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Употребление алкоголя вызывает значительные изменения когнитивного функционирования. Эти эффекты связаны с влиянием как этанола, так и его первого метаболита ацетальдегида на нейромедиаторные системы головного мозга. При длительном злоупотреблении может возникнуть синдром исполнительского дефицита, проявляющийся эмоциональными, поведенческими и когнитивными симптомами. Также алкоголь имеет специфическое дозозависимое влияние на функцию памяти в виде блокирования консолидации воспоминаний, т. е. перехода ее из кратковременной в долговременную. Это проявляется либо обратимыми амнезиями периода алкогольного опьянения (блэкаутами), либо необратимой фиксационной амнезией в рамках синдрома Корсакова. Библиогр. 34 назв.

Ключевые слова: когнитивные функции, алкоголь, амнезии, блэкауты, синдром исполнительского дефицита.

Cognitive functions are mental processes involving symbolic operations such as perception, memory, creation of imagery, thinking and also facilitating efficient decision-making in various situations [1]. Cognitive functions encompass intelligence, visual spatial orientation and executive functions [2].

Judging by their group name, psychoactive substances may affect cognitive functioning. Substance-induced effects may be qualified according to such criteria as *time of onset* and *duration*. For instance, depending on the onset of the effects, there are changes occurring at the moment of intoxication and impairments resulting from systematic substance

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use. Depending on the duration of manifestations, changes may be either persistent (even after a single use) or temporary.

Ethanol is one of the most wide-spread substances, the use of which results in significant negative consequences both for users and people in their environment. Alcohol use may affect cognitive processes severely. Herein we are reviewing the recent understanding of mechanisms and manifestations of the influence of alcohol on human cognitive functioning.

Pathogenesis of Cognitive Impairment in Alcohol Abuse

The effects of alcohol abuse include those relating to the effect of ethanol, and those relating to the effect of acetaldehyde (ACD), its metabolite. Research shows that ACD is pharmacologically active and influences mental processes. ACD is the first metabolite of ethanol and is responsible for development of many subjectively unpleasant sensations while using alcohol. These sensations, and first and foremost, dysphoric response, are protective in relation to the development of alcohol dependence syndrome [1]. Some authors also noted that ACD might be involved in pathogenesis of other alcohol-related effects: elevated activity, drowsiness, amnestic disorders, and interferes with the reward system's functioning [3–6]. Nevertheless, the blood-brain barrier (BBB) formed by endothelial cells in brain vessels containing aldehyde dehydrogenase (ALDH) effectively inhibits permeation of ACD into the brain. Currently, most specialists share the opinion that no, or little, ACD gets into the brain during alcohol intoxication [7–10]. To this end, it is important to understand the mechanism underlying the existence of ACD in the brain. The research showed that catalase [11] and P450 cytochrome (its CYP2E1 fraction) [12] fulfilled the function of metabolizing ethanol due to the absence of alcohol dehydrogenase (ADH) in the brain. It was assumed that catalase was responsible for the synthesis of 60–70 % of ACD in the brain, and CYP2E1 — of 10–20% of ACD [12; 13]. According to the research, ACD that was formed in the brain was catabolised further with ALDH [11].

ACD exerts its effects both directly affecting catecholamine systems through activation of neuronal calcium channels, and due to ACD condensation with noradrenalin, serotonin, endorphins (with formation of such pharmacologically active substances as salsolinol and harmaline). Furthermore, ACD is able to competitively interact with noradrenalin, dopamine and serotonin receptors. These substances cause corresponding mental responses: stimulation, impairments in perception, and a decrease in anxiety. Harmaline stimulates transformation of serotonin into melatonin, this being one of the mechanisms behind the wake-sleep cycle impairment in prolonged alcohol abuse [14].

Acute and chronic effects

During intoxication, ethanol affects mental functioning in different ways depending on the blood alcohol concentration (BAC). Its effects usually start with general dysinhibition, lowered concentration, talkativeness, increased communicativeness, poor self-control, and, furthermore, increased pain threshold. As BAC grows, the response time decreases; the ability to control one's actions gets lost; the ability to identify logical connections between events and phenomena (reasoning) gets impaired. Further on, as intoxication intensifies, motor deficits become more relevant than mental ones. Abilities relat-

ing to understanding and memorizing the occurring events suffer significantly. Besides, emotional fluctuations may become markedly expressed [15].

The range of cognitive deficits in chronic alcohol abuse is much wider. However some recent research demonstrated that mild and moderate alcohol consumers showed better results in cognitive skill testing as compared to both heavy users and abstainers [16; 17]. Heavy alcohol use was associated with a large number of cognitive deficits [17]. Changes in the cognitive functioning were found in 50–80 % of alcohol-dependent patients displaying no signs of neurologic complications [18]. The research identified 4 profiles of alcohol-dependent patients in terms of cognitive functioning: 1) patients without cognitive deficits, 2) patients with an isolated deficit in executive functions, 3) patients with an executive deficit accompanied with memory deficits and unimpaired overall functioning, 4) patients with global cognitive impairment and problems in overall functioning [19].

Dysexecutive Syndrome

Executive functions play an important role in cognitive functioning as mental processes managing mental activity in cases when involuntary or instinctive behavior is inefficient or impossible [20]. Most authors identify three main executive functions: inhibition (including self-control, inhibitory control and selective attention), working memory and cognitive flexibility (including mental processing and closely relating to generation of ideas and creativity) [21]. These basic functions create the ground for development of higher order cognitive skills such as reasoning, problem solving and planning [22]. Developed cognitive skills are necessary for successful adjustment to the social environment, development and self-actualization.

Alcohol abuse may cause the so called dysexecutive syndrome (DES). It was assumed that DES develops as a result of impaired activity of the central executive in the working memory system [23]. It affects planning, abstract thinking, flexibility, and behavioral control. DES is common to a wide range of neurodegenerative disorders such as dementias of different etiology, posttraumatic brain changes etc.

DES includes three relatively independent domains: emotional, behavioral and cognitive deficits [24].

- *Emotional* deficits involve difficulty in inhibiting various feelings, e.g. anger, excitement, sadness, disappointment etc. People with DES may also display increased aggression and difficulty in accepting another person's perspective.
- *Cognitive* deficits include weakened control of impulsive behavior, higher level of egocentrism and stubbornness. Severe cognitive deficits may be accompanied with such phenomena as automatic utilization of objects in a proper way but in inappropriate circumstances. For example, sitting in front of a pen and a sheet of paper during a clinical interview, a patient with DES, starts painting even though if it is not envisaged by the plan of the interview. Another behavioral manifestation is stuck-in perseveration when a patient fails to switch attention from one object to another. If this patient is asked to name forest trees, they will name a birch tree and fail to name other kinds even if they know them. When asked the following question, they will still try to give the answer to the former one.
- *Cognitive symptoms proper* include a short attention span and related difficulties while reading and following the storyline and focusing on the object of conversation.

Working and short-term memory is impaired. The range of cognitive deficits in DES may be quite wide and dependable on various factors: the nervous system damage localization, personality, intelligence and life experience. Deficits in the assessment of memory retrieval accuracy and related autobiographic memory retrieval are also common to people with DES [25].

In addition to symptoms that occur in DES of any etiology, DES in lasting alcohol abuse has its specific features. These are poor impulse control, impaired encoding and retrieval of information. These deficits lead to difficulties in learning new information. Specific impairments also include lower levels of autonoetic consciousness, that is, the ability to imagine past, potential future or counterfactual situations and model possible behaviors [26].

Alcohol and memory

Memory is a general name of a complex of cognitive abilities and higher mental functions relating to accumulation, storage and retrieval of knowledge and skills. All higher animals have memory in any form. Human memory is the most developed [27; 28]. Currently, Atkinson-Shiffrin's model of memory elaborated by Baddeley is most widely-used. According to that model, memory consists of three structures: sensory memory having low volume and storing recent memories (several sensory structures are working simultaneously); working memory and long-term memory that can store a large amount of information for a long time up to the death [29]. According to Baddeley, short-term memory is a part of working memory ensuring connectivity between a long-term memory and new information being obtained. Working memory includes the visuo-spatial sketchpad, the phonological loop, the central executive, the episodic buffer and other subsystems [23]. The central executive coordinates other cognitive processes. It establishes connections between information coming from different sources, and controls the focus of attention.

S. S. Korsakoff was the first who identified the specific effect of ethanol on memory. In 1887, he described a specific syndrome characterized with impairments in memory and consciousness that later received his name. There is evidence that alcohol affects memory in other ways as well. K. Bonhoeffer (1901) described palimpsests (*Greek* «παλίμψηστον» — a manuscript page from which text was scrapped off) — amnesias relating directly to alcohol intoxication and exhibiting as a failure to retrieve memories of some events from the period of intoxication. This term has been extensively used in the Russian scientific literature, although foreign authors prefer using the term "blackout" that had been introduced by E. M. Jellinek (1941).

Blackout is an amnesia relating to the events from the period of alcohol intoxication when the person was able to behave actively. Blackout should be differentiated from amnesia of the switched off consciousness period due to the alcohol-related coma. The latest review showed that about 50 % of alcohol users had blackouts [30]. Two phenomenological types of blackout were described [31]:

1) *Fragmentary (off-and-on) blackout.* It is difficult to clearly identify its beginning and end. People can't recall memories of certain brief events from the intoxication period usually being unaware that they had an amnestic episode. They regain memories of these events either spontaneously or being reminded of them.

2) *En block blackout*. It has a clear onset (patients are aware that they remember nothing after some point in time) and ends in sleep. It is subjectively perceived as a feeling of "lost time", and in most cases, the memories can't be recovered. This type of blackout is 4 times as rare as fragmentary blackout.

Another alcohol-related memory impairment was called the "Cocktail Party Memory Deficit" (CPMD). The term refers to mild unconscious deficits in memory consolidation after using low doses of alcohol exhibiting as difficulty in memorizing new information under the influence of alcohol [32].

In general, ethanol-related effects on memory can be characterized as a dose-dependent continuum suggesting that alcohol selectively blocks the function of new memories consolidation (i.e. transition of memories from the short-term memory to the long-term), with this effect being directly related to BAC [33]. CPMD exhibiting as difficulty in memorizing new information occurs at minimum doses of alcohol. At the BAC levels close to the individual tolerance threshold, consolidation is blocked completely but is still reversible, and a fragmentary (palimpsest) or en block blackout occurs. Chronic alcohol intoxication results in an irreversible blockade of consolidation, and the clinical picture of the Korsakoff's syndrome evolves.

The research showed that the CA1 region containing pyramidal cells connecting the hippocampus to the neocortex was responsible for memory consolidation in the hippocampus [34]. The animal experiments demonstrated that use of ethanol resulted in the blockade of NMDA-receptors, impairing long-term potentiation (the main mechanism of memory consolidation). Some cells of the hippocampal CA1 region were blocked even at a minimal alcohol dose causing partial impairment of consolidation. At a higher dose, all CA1 cells got blocked. Therefore, ethanol's effects on memory rest on a specific physiological mechanism relating to impairment of the CA1 region of the hippocampus.

Conclusion

The research into alcohol-related cognitive deficits becomes increasingly important year by year. The reviewed data provide that there is a wide range of cognitive deficits in alcohol dependence that should be taken into account in clinical practice. The assessment of cognitive impairments in alcohol-dependent patients has established itself as a routine practice in the Addiction Medicine. The recent research findings and the daily practice of cognitive impairment assessment help to improve both medication and psychotherapeutic programs for alcohol-dependence treatment.

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