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Review Article

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Cognitive Impairment Associated with Chronic Alcohol Dependence: Recent Advances in The Understanding of Disease Pathogenesis

Jiang Qingmei[1], Yin Changhao[2] and Zhu Xiaofeng[*1]

[1]*Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang*

[2]*Department of Neurology IV, Hongqi Hospital affiliated to Mudanjiang Medical University, Heilongjiang Province, Mudanjiang 157000, Heilongjiang*

[*]Corresponding author
Zhu Xiaofeng, Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang

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Abstract

At present, a large increase in global alcoholics, the resulting problems associated with alcohol dependence cognitive dysfunction has become increasingly serious, the domestic and foreign research shows that long-term excessive drinking seriously damage the body organs, this paper mainly study the influence of the alcohol dependence on the central nervous system, from signal transduction, oxidative stress and neuritic response, neurotransmitter release and its receptor, nutrition metabolism, brain structure change analysis of alcohol dependence summarized research progress to do related to the pathogenesis of cognitive impairment.

Keywords: Alcohol Dependence; Cognitive Impairment; Nervous System Changes; Oxidative Metabolism

The phenomenon of alcohol consumption is very common worldwide, with about 2 billion people. Long-term heavy use of alcohol can cause a variety of diseases and deaths, it not only has an effect on the digestive system, but also causes chronic irreversible damage to the central nervous system, such as a progressive decline in cognitive function. Studies have found that the risk of cognitive impairment after quitting drinking remains the same [1]. Approximately 74.7 million patients with cognitive impairment are projected to be accrued worldwide by 2030 [2]. This will cause a great burden on families, medical care, and society. The global cost of patients with cognitive impairment is expected to increase from $957.56 billion in 2015 to $2.54 trillion in 2030 [2]. The situation of cognitive dysfunction related to alcohol dependence in China is worrying, and its mechanism research is imminent.

Definition and Diagnostic Criteria of Chronic Alcohol Dependence

Chronic alcohol dependence (CAD) is an encephalopathy resulting from chronic alcohol consumption, which is mainly manifested as a psychological state that often has a strong craving for drinking. It can appear continuously or periodically. In order to avoid the discomfort caused by not drinking, self-compulsion drinking behavior [3]. In recent years, the number of chronic alcohol dependence patients in our country has grown rapidly. When they try to quit alcohol or reduce alcohol intake, they may be manifested as tremor, sweating, palpitation, increased blood pressure, increased heart rate and gastrointestinal symptoms in mild cases, and even fatal generalized seizures, hallucinations and delirium tremens in severe cases, drinking must be resumed to alleviate the above symptoms. A meta-analysis in 2017 found that light to moderate drinking should be protective [4, 5]. Light drinking corresponds to 4 glasses per week, 6g/day or 1 drink/week, no impairment of cognitive function was found, while excessive drinking of 23 glasses/week or 12.5g/day significantly increased the risk of cognitive dysfunction. In addition, qualitative analysis shows that the protective effect exists only in wine consumption [5]. The diagnostic points of "chronic alcohol dependence-related cognitive dysfunction": 1. Meet the ICD-10 criteria for the diagnosis of alcohol dependence; 2. The main risk factor is that multiple cognitive abilities caused by drinking are lower than normal people, may be accompanied by abnormal behavior; 3. exclude the possibility of delirium and other mental and psychological diseases. Improved neurocognitive function if patients abstain from alcohol for more than 3 months in a timely manner, which shows that it is necessary to save their cognitive deficits in the early stage of alcohol withdrawal and can benefit the most. In addition, the correlation with the history of drinking has been determined, which may help prevent and manage cognitive dysfunction in CAD patients in the future [6].

Pathogenesis of Chronic Alcohol-Dependent Cognitive Dysfunction

Alcohol refers to molecular ethanol. As an amphiphile, it is quickly absorbed from the stomach and duodenum after oral administration. When alcohol penetrates the lipid layer of the nerve cell membrane of the blood-brain barrier, the brain tissue is rich in lecithin. alcohol is easily combined with lecithin and

retained in brain tissue. Studies have confirmed that alcohol affects the normal function of the central nervous system [7]. Initially, neurons and glial cells made changes such as degeneration, necrosis, loss, and atrophy of nerve cell bodies, create lasting and irreversible damage. Gradually, it was found that such patients had less cognitive ability than before, so the research on the cognitive function mechanism of patients with chronic alcohol dependence-related cognitive dysfunction attracts attention.

Neural Signal Transduction

The intracellular signaling cascades in the nervous system affected by alcohol consumption must take into account their effects on brain circuits. CSERVENKA and other studies have confirmed that patients with chronic alcohol dependence show significantly lower functional connectivity in the cingulate gyrus, thalamus and insula, and even some distant brain regions (such as cerebellum) and neural circuits (such as attention and emotional neural circuits) when performing commands [8]. In a study of gambling decision-making in Iowa, heavy drinkers made incorrect decisions compared with nondrinkers, and during decision-making, alcoholics had elevated insular and amygdala responses, which were positively correlated with drinking problems and urgency scores (a measure of impulsive behavior driven by negative emotions) [9]. LEE et al studies have shown that the alcohol treatment group causes cell loss and impaired function in the hippocampus [10]. Long-term alcohol consumption resulted in a more significant decrease in hippocampal volume than age-related normal degeneration alone. In addition, ZAHR et al found that the volume of hippocampal CA1 and CA4 areas was significantly reduced, while molecular layer and dentate gyrus were additionally reduced [11]. At the same time, long-term drinking seems to accelerate age-related degeneration in certain areas of the hippocampus. Once chronic alcohol dependence is formed, the reward mechanism (nucleus accumbens and caudate nucleus, etc.) and the motivational drive system (orbital Frontal cortex, etc.) related neuronal signal transduction are enhanced. The previous normal cognitive control loop changes, which is why chronic alcohol dependence cannot control alcoholism [10]. The above studies use high-quality neuroimaging data to determine brain function and changes in brain circuits. Based on these data, we should further study the intervention methods of brain circuits in the future in order to effectively control alcohol-dependent behaviors.

Oxidative Stress and Neuroinflammatory Response

Oxidative stress in the central nervous system means that the body is subjected to harmful stimuli, such as alcohol, and the imbalance between the oxidative and antioxidant systems leads to neuronal death. The indicators of oxidative stress observed in the study by Reddy et al were malondialdehyde (MDA) and protein carbonyls, which are products of more abundant lipid and protein oxidation, respectively [12]. The results showed that in rats with long-term alcohol treatment, the synaptic membrane The MDA and protein carbonyl levels increased significantly. Membrane proteins are important targets for oxidative attack. Membrane lipids and proteins are oxidatively damaged, leading to membrane dysfunction. The brain is more susceptible to alcohol-induced oxidative damage due to its higher fatty acid content. Free radicals can cause tissue damage. Studies have shown that patients with chronic alcohol dependence related cognitive dysfunction have reduced antioxidant enzymes, free radical dependence or antioxidant enzymes are inactivated, suggesting that alcohol causes the body to produce oxidation products and reduce antioxidant activity, and long-term exposure of neurons to such an environment will undoubtedly. It produces irreversible damage to the central nervous system and further affects cognitive function [13]. In addition, heavy alcohol consumption is associated with an increased inflammatory response, which is the result of a complex interaction between systemic inflammation and the nervous system. When some immune cells try to restore homeostasis in the central nervous system, they cause certain microglial gene transcription to change. For example, TNF-α plays an important role in inducing cell death and is released from microglia. It is worth noting that TNF-α also plays a huge role in the pathophysiological changes of neurodegenerative diseases, including Alzheimer disease related to cognitive decline, although its specific role on neurological dysfunction and injuries has not been fully elucidated [14, 15]. LOFTIS and other observed that within the frontal cortex, a large amount of alcohol intake may be related to the activation of microglia during the neural invasion of chronic viral infections, which can exacerbate immune pathological damage [16]. Recent studies by RUA et al found that when lymphocytic choriomeningitis virus infection occurs, intrinsic meningeal macrophages acquire viral antigens and interact with cytotoxic T lymphocytes[17]. At the same time, inflammatory monocytes infiltrate the meninges and persist for months after the virus is cleared. Alcohol causes the body to undergo oxidative stress and neuroinflammation. The body's functional regulation in this area cannot be completed in a short time. If alcohol dependence is formed and the pathological damage of the central nervous system is aggravated, it will pose a long-term threat to cognitive ability. The next step is to study more markers of oxidative stress and neuroinflammatory factors, which will help to delay the study of cognitive impairment.

Neurotransmitter Release and Its Receptors

Neurotransmitters are "messengers" in the brain and play a key role in completing the interconnection between neurons. Long-term drinking will lead to upregulation (glutamate) and downregulation of neuronal receptors related to alcohol withdrawal and cravings in the body, which are excitatory transmitters that directly and specifically bind to their receptors (N-Methyl-D-aspartate receptors) after release from nerve terminals. Studies have shown that the specific receptor N-Methyl-D-aspartate receptor (NMDAR) of CAD patients is more sensitive to glutamate, resulting in an excessive response to the glutamate pathway, manifested as increased postsynaptic excitability, which has a damaging effect on neuronal cells [18]. In addition, the calcium activated N-Methyl-D-aspartate receptor (NMDAR) plays a role in completing the proper connection between nerve cells in the synapse, which is related to the learning and memory cell mechanisms [19]. Therefore, it is important to consider the development of NMDAR dysfunction and various neuropsychiatric and addictive diseases including CAD-related cognitive impairments [20]. In the body, monoamine neurotransmitters, in addition to helping regulate human activity, mood, are more important for the regulation of cognitive function, such as serotonin (5-HT) [21]. Alcohol destroys the normal function of these neurotransmitters. The metabolic

pathway of alcohol is catalyzed by ethanol dehydrogenase to produce acetaldehyde. Acetaldehyde can inhibit the enzyme activity of 5-hydroxytryptamine (5-HT), resulting in an increase in the concentration of 5-HT; it further increases its corresponding receptors, these series of changes cause a burden on the regulation of central nervous system function [22]. It is well known that GABA receptors play an important role in various neurobehavioral responses to alcohol. Among them, GABA-A receptors are considered to be related to alcohol tolerance and addiction [23]. KuanZeng et al found that GABA-Aa5 expression increased in rats with alcohol through acetylation of histone H3K9 [24]. Moreover, this epigenetic modification can be inherited by the next generation, and eventually show similar spatial learning and memory barriers in the offspring. Any disease has environmental and genetic factors. In addition to the damage caused by each drinking, it also gradually affects the genetic modification of our body, showing the influence of alcohol on the cognitive ability of future generations.

Affect the Body's Metabolites

The characteristics of an alcohol-based diet: Alcohol is high in calories, but low nutritional value, resulting in reduced nutrient intake and excessive excretion, all of which cause malnutrition in alcohol-dependent people, An important cause of metabolic disorders [25]. However, one of the most obvious reasons is that excessive drinking interferes with the absorption of vitamin B1 (i.e., thiamine) [26]. As a result, it will first affect the nervous system and cardiac tissue led by oxygen consumption during glucose metabolism, while the transport process of thiamine through the blood-brain barrier is changed, thereby reducing the amount of thiamine that enters the brain through passive diffusion, insufficient supply of neurons in the brain, eventually leads to selective death of neurons, and accelerates the damage of central nervous system function[27]. Among them, including memory loss, motivation loss and brain damage. The loss of thiamine is related to the decline in alcoholic cognitive ability. The typical disease is Wernicke-Korsakoff syndrome, with the main symptoms of decreased memory in patients, manifested as inability to consolidate short-term memory into long-term memory, inability of patients to do anything beyond their usual habits [27]. There are cognitive impairments and abnormal activity in severe conditions [28]. Experiments have shown that mice chronically exposed to alcohol and/or thiamine deficiency show impaired memory and cognitive ability [29]. These mice showed defects in the hippocampus-dependent memory function. The hippocampus of the mice had fewer neurons in the CA1, CA3, and dentate gyrus regions of the mouse hippocampus and lower densities of wide dendritic spines in these regions, indicating memory deficits observed by WKS at necropsy. Rats that consumed alcohol orally exhibited behavioral deficits and similar loss of brain function [30]. WE is considered a medical emergency, and patients need immediate intramuscular or intravenous thiamine to prevent further progression. Supplementation of thiamine according to conventional prescriptions has proven successful in the treatment strategy for patient groups at risk of thiamine deficiency [31]. Thiamin therapy should be supplemented with electrolyte administration, because they are necessary cofactors for the enzyme to work properly [27]. At present, it is unclear whether long-term high-circulation thiamine will adversely affect health, so we have put forward requirements for future thiamine treatment of cognitive impairment related to alcohol dependence [31].

Changes in Brain Structure

Animal studies have found that excessive alcohol intake can cause structural changes in the brain, and is consistent with patients with memory and learning disabilities. In the CHANRAUD study, when performing the same spatial memory task, the activation of brain areas (bilateral prefrontal cortex) associated with executive control in patients with CAD-related cognitive dysfunction weakened, and CAD and healthy control groups showed different brain area activation patterns, the control group mainly activates the occipital parietal lobe system involved in the dorsal visual cortex involved in visual spatial memory, while the CAD-related cognitive dysfunction patient group activates the ventral visual cortex involved in declarative memory suboccipital temporal and limbic systems, which confirms that alcohol damages the normal brain function execution circuit, resulting in changes in the activation pattern of the brain area [32]. Also in the tapping task, PARKS et al found that alcohol-dependent patients perform poor frontal lobe activation when performing finger tapping tasks, and the contralateral parietal lobe activation may reflect the impairment of the right hemisphere visual spatial function, according to the comparison of brain activation, CAD patients may not activate the frontal cerebellar network normally as in the healthy group, but complete the finger tapping task by recruiting parietal lobe function [33]. In addition, the researchers found that CAD patients showed more brain area activation in the left frontal lobe and upper right cerebellum when performing oral memory tasks [34]. It has been clarified that in simple tasks of CAD patients, even if the normal neural circuit function is impaired, more compensatory neural mechanisms in the brain area can achieve near-normal performance, so the future treatment direction can be further studied to restore brain area activity and enhance the function of compensatory brain area activities and provide patients with opportunities for recovery.

Summary and Outlook

The problem of CAD-related cognitive dysfunction has become one of the most prominent public problems in the world. It has caused a burden on personal health and social medical care and national progress. The mechanism of alcohol-related cognitive impairment was studied to understand the effects of chronic dependence on brain circuits, oxidative stress, neurotransmitter release and receptors, affecting body metabolites, and changes in brain structure. At the same time, the next step was also proposed to address the requirements of alcohol-related cognitive impairment in many aspects, providing a theoretical basis for the treatment of cognitive impairment, and also promoting the study of cognitive impairment interventions.

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