



## ORIGINAL RESEARCH

## Hangover Syndrome: Pathogenesis and Treatment

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### Abstract

**Aim:** To discuss the state of art of pathogenesis and treatment of Hangover Syndrome (HS).

**Methods:** The review of the Russian and English language literature related to this problem.

**Results:** It was shown, that there is a significant gap in the understanding of pathogenesis of HS, which hamper the elaboration of means of metabolic correction of this condition. The target of majority of currently existing means of treatment of HS is one of the pathogenic mechanisms of HS. The effectiveness of majority of currently existing medicine is not supported by the results of clinical trials.

**Conclusions:** The actual task of future research is the detailed investigation of pathogenic mechanisms of HS. This will allow elaborating the comprehensive medicine for HS treatment targeting all links of its pathogenesis.

### Keywords

Hangover syndrome, Pathogenesis, Treatment

concentration, cognitive deficit) symptoms [5,10].

A study on volunteers who injected themselves with alcohol intravenously showed that the morning after self-administration of alcohol 78% of the participants experienced at least one hangover symptom [6]. The most common symptoms of HS were: Fatigue (67%), thirst (57%), and headache (32%) [6]. The symptoms of a HS appear 6-8 hours after the end of alcoholic excess and can be observed for 20 hours against the background of the absence of alcohol in the blood [10]. The existing gender and age specificity of HS is in the greater severity of symptoms in women [5], as well as its progression with increasing age [3].

Hangover is associated with a host of medical and socioeconomic problems. HS can pose a threat to health, as it provokes an increase in blood pressure and heart rhythm disturbances, which, in turn, can cause sudden death [11]. HS also carries significant socioeconomic implications. For example, in the United States, the annual economic losses due to decreased productivity associated with hangover syndrome are about \$179 million [5].

In experimental studies, it was shown that in the state of HS, the reaction time and the number of errors in the task performance increase [12,13]. Impairment of cognitive functions (attention, operative, retrospective and prospective memory, deficit of executive function) and psychomotor disorders noted in HS lead to a decrease in labor productivity increase the risk of industrial and road traffic injuries [14-16]. There is a direct relationship between the frequency of hangover and the likelihood of various kinds of problems in the workplace

### Introduction

Alcohol abuse causes significant damage to health and is associated with more than two hundred different diseases [1]. One of the most common negative consequences of alcohol abuse is the so-called post-intoxication, or hangover syndrome, which is a symptom complex of psychophysiological disorders that develop the morning after an alcoholic excess (heavy alcohol consumption) the night before [2-9]. The clinical symptomatology of HS varies greatly. In the classical form, HS manifests itself as a constellation of physiological (general malaise, headache, fatigue, nausea, dry mouth, thirst, lack of appetite) and mental (low mood, impaired



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[3]. A simulator study showed a significant impairment in the ability to drive in a state of hangover [17]. Meanwhile, 56.4% of heavy truck drivers in Denmark admitted driving in a state of hangover [6]. A biochemical marker survey of drivers admitted to a US hospital with injuries following a road traffic accident showed that 22% of them drank alcohol on the eve of the accident, although no alcohol was found in their blood [5].

Since HS is associated with alcoholic excesses, it is considered a sign of alcohol abuse [4]. This is confirmed by the fact that the severity of HS is positively correlated with the level of alcohol problems, assessed using the AUDIT test [5]. Symptoms of HS can resemble the clinical picture of mild withdrawal symptoms, which is one of the key diagnostic criteria for alcohol dependence [3]. However, unlike HS, withdrawal symptoms are manifested by more pronounced and varied symptoms (including neurological symptoms), which manifests itself against the background of a strong craving for alcohol [6]. Drinking alcohol greatly alleviates the symptoms of withdrawal symptoms [14]. HS is characterized by a lack of craving for alcohol, while an aversion to the smell of alcohol may appear which allows us to consider HS as a post-intoxication state [18]. Nevertheless, despite the differences in the clinical picture and pathogenic mechanisms, some authors consider HS as a harbinger of withdrawal symptoms [19].

Despite the significant damage to health and large economic losses associated with HS, the pathogenesis of this condition is not well understood. At the same time, understanding the pathogenic mechanisms of HS is necessary for the development of means for the prevention and treatment of this condition. Presumptive mechanisms of HS pathogenesis are: Alcohol-induced metabolic and endocrine disorders, oxidative stress, inflammation, disturbances in water-electrolyte balance and acid-base balance [7,8,20-23].

The severity of HS depends on a number of factors, one of which is the dose of alcohol taken the night before [5]. The important role of the dose of alcohol consumed as a predictor of HS severity is confirmed by the fact that its severity correlates with the maximum alcohol concentration in the exhaled air, as well as with the concentration of alcohol and methanol in urine [8]. It should be noted that HS develops in the absence of alcohol in the blood. One of the factors influencing the severity of HS is the ethanol metabolic rate. It was found that in individuals with a slow ethanol metabolism and, accordingly, with a high level of alcohol in the urine, HS is more pronounced than in individuals with a fast ethanol metabolism [22].

An intriguing phenomenon in terms of understanding the pathogenic mechanisms of HS is resistance to its development. It is known that about 23% of subjects do not develop HS even after drinking a large dose of alco-

hol [6]. The biological hypothesis suggests the existence of genetically determined differences in ethanol metabolism in persons experiencing HS and those resistant to it [24]. Twin studies have shown that the probability of occurrence of HS by 55.4% is determined by genetic factors [3]. It was found that the concentration of alcohol in the urine in the morning after alcoholic excess in persons with severe HS was significantly higher than in persons resistant to HS [5]. At the same time, the concentration of alcohol in the urine correlates with both the overall severity of HS and its individual symptoms [6]. Differences in the concentration of alcohol in the urine in persons with severe HS and those resistant to it indicate an important role of the ethanol metabolic rate in the pathogenesis of HS.

It has also been shown that HS resistance correlates with low sensitivity to the acute effects of alcohol [8]. It is known that low sensitivity to the acute effects of alcohol is a predictor of the development of alcohol dependence [25]. It was also found that resistance to HS is associated with the so-called festival style of alcohol consumption (drinking large doses of alcohol for a short period of time) [10]. The constellation of these factors suggests that persons resistant to the development of HS have a higher risk of developing alcohol dependence.

According to the psychological hypothesis, ethanol metabolism is the same in subjects with and without HS; however, subjects resistant to HS are less sensitive to its symptoms [8]. One of the studies showed no differences in demographic, psychological and a number of biological parameters (methanol, ethyl glucuronide, ethyl sulfate levels, proinflammatory cytokine levels, sensitivity to acute effects of ethanol) in persons with and without HS [26]. At the same time, it was found that people with borderline personality disorders are more likely to experience hangovers compared to the general population [5].

Alcohol has a hypoglycemic effect [26], which can cause the appearance of such symptoms of HS as fatigue, impaired attention, and headache. At the same time, the administration of glucose against the background of HS had no effect on the severity of its symptoms [27]. Alcohol-induced sleep disturbance may be a possible cause of cognitive decline the morning after a binge [1]. However, it was found that sleep disturbance does not correlate with the severity of HS [5]. The severity of HS symptoms largely depends on the effectiveness of sleep [6].

Changes in the composition of the intestinal microflora may play an important role in the pathogenesis of hangover syndrome [8]. It has been shown that chronic alcohol consumption leads to dysbiosis [7]. Alcohol-induced dysbiosis is characterized by an increase in the number of pro-inflammatory and a decrease in the number of anti-inflammatory bacteria [26]. In addi-

tion, by damaging the intestinal wall, alcohol increases the permeability of the intestinal barrier, which leads to increased absorption of toxic products [3]. The combined effect of dysbiosis and damage to the intestinal barrier is endotoxemia and an increase in the level of proinflammatory cytokines TNF- $\alpha$  and IL-6 [20]. It is assumed that anti-inflammatory cytokines of intestinal origin cause inflammation in the brain, which explains the symptoms of hangover from the central nervous system [5].

A number of studies have presented data indicating the involvement of the immune system in the pathogenesis of HS [1,20,26]. In particular, it was found that the level of cytokines (IL-10, IL-12, IFN- $\gamma$ ) in the blood significantly increases 13 hours after drinking alcohol [8]. In another study, it was shown that the peak level of pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IFN- $\gamma$ , TNF- $\alpha$ ) in saliva is observed 6 hours after the last dose of alcohol, and then, within the next 2-3 hours returns to normal [20].

The severity of the symptoms of HS may depend on the type of alcoholic drink consumed. Some alcoholic beverages contain a large amount of toxic impurities (methanol, fusel oils, higher alcohols, aldehydes), which can increase the severity of HS. It was found that the use of alcoholic beverages with a high content of impurities (bourbon, whiskey, tequila) is accompanied by a more severe HS than the use of beverages with a low content of impurities [28,29]. However, these data do not cast doubt on the fact that alcohol is the main etiological factor of HS. Additional pathogenic mechanisms of HS can be dehydration (alcohol increases diuresis), impaired mineral metabolism (a decrease in the level of calcium and magnesium in the blood plasma), alcoholic lactate and ketoacidosis (due to increased formation of acetoacetate and beta-hydroxybutyric acid) [7,8,20-23].

Insufficient understanding of the pathogenetic mechanisms of HS complicates the development of scientifically proven effective means of its prevention and treatment. Nevertheless, at present, active work in this direction is being carried out in many countries of the world. The most promising approach to the development of methods for the prevention and relief of HS is the use of drugs that accelerate the metabolism of ethanol. Rapid elimination of ethanol and acetaldehyde from the body can reduce the severity of hangover [30-32].

An important area of research is the study of the effect of various nutrients on the severity of HS. It is known that food intake (especially fatty food) on the eve or during alcohol consumption slows down its absorption and reduces the peak blood concentration, thereby weakening the manifestation of HS symptoms [33]. Some vitamins (nicotinic acid, B vitamins, vitamin C) and trace elements (selenium, zinc, copper, magne-

sium, iron, vanadium), having a direct effect on alcohol metabolism, or through their antioxidant and anti-inflammatory properties, can affect the likelihood and severity manifestations of HS [34,35]. In particular, nicotinic acid (vitamin PP) in the body is converted to nicotinamide, which is part of NAD and NADP, which are involved in ethanol metabolism [26]. In a study on volunteers who do not suffer from alcohol dependence, it was shown that the use of nicotinic acid in the diet is negatively associated with the severity of the clinical symptoms of HS [32].

As for other vitamins, the data on their use for the relief of HS manifestations are rather contradictory. For example, Kahn, et al. found that oral use of vitamin B6 significantly reduced the severity of HS symptoms [36]. At the same time, Kelly, et al. showed that intravenous administration of a complex of B vitamins and vitamin C does not affect ethanol metabolism [34]. Laas conducted a double-blind, placebo-controlled study to investigate the effectiveness of the Morning Fit hangover remedy, which contains dry yeast and vitamins B1, B2 and B6 [37]. It was found that this agent does not reduce the level of alcohol and acetaldehyde in the blood and does not affect the severity of symptoms of PS [37]. The literature data on the use of microelements for the relief of HS are limited. In one of the few studies devoted to this problem, it was shown that the use of zinc in the diet reduces the severity of symptoms of HS [35].

Taking into account the increase in the level of proinflammatory cytokines after the consumption of alcohol in a large dose [20], a potentially promising way to stop PS is the use of drugs that reduce their level. Probiotics normalize the intestinal microflora, reduce the permeability of the intestinal wall, and reduce the production of proinflammatory cytokines [32]. It has been found that probiotics reduce the severity of inflammation in the nervous tissue caused by alcohol-induced endotoxemia [31]. It was shown that after a 3-month course of treatment with probiotics, alcohol abusers showed a decrease in the level of pro-inflammatory cytokines in the blood, and the symptoms of a hangover almost completely disappeared [31].

In the USA, a pilot clinical trial of the hangover drug JMI-001, which is a combination of a non-steroidal anti-inflammatory drug and an H1 receptor antagonist, was carried out [23]. It has been shown that taking this drug on the eve of alcohol consumption significantly reduces the severity of HS. In a recent study, it was found that intravenous administration of the peptide hormone ghrelin, produced by cells of the gastric mucosa, significantly reduces the severity of HS [38].

There is information in the literature on the effectiveness of using plant extracts for the relief of HS. In particular, Bang, et al., showed that *Acanthopanax senticosus* extract normalizes glucose levels, lowers C-re-

active protein levels, and also reduces the severity of HS symptoms such as fatigue, dizziness, and headache [39]. Kim, et al. found that the extract from the fruit of *Hovenia dulcis*, containing heteropolysaccharides and dihydromyricitin, significantly reduces the level of proinflammatory cytokines in the blood plasma and reduces the severity of hangover symptoms [40]. In a double-blind, placebo-controlled study, *Opuntia ficus indica* extract was shown to reduce C-reactive protein levels, increase heat shock protein synthesis, halve the likelihood of developing severe HS, and significantly reduce the severity of HS symptoms [41]. Another study showed that a blend of polyphenols from *Viscum album*, *Lycium chinense*, *Inonotus obliquus*, and *Acanthopanax senticosus* significantly reduced blood alcohol content two hours after drinking [42].

In conclusion, the heavy burden of medical and social problems and economic damage associated with PS necessitates the development of measures for the prevention and treatment of this pathological condition. A review of the literature data showed the existence of significant gaps in understanding the pathogenesis of HS, which complicates the development of means of metabolic correction of this condition. The target of most of the currently proposed treatments for HS is any one of the pathogenic mechanisms of HS. The effectiveness of most of the available drugs has not been confirmed by clinical trials. In addition, many of them have side effects that limit their use. Therefore, an urgent task for further research is a detailed study of the pathogenic mechanisms of HS, which will make it possible to develop a comprehensive treatment for HS that affects all links of its pathogenesis. An independent direction of research can be the development of means for the prevention of HS. It should be understood that the best way to prevent HS is to stop drinking alcohol.

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## Conflict of Interests

The authors declare no conflict of interests.

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