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CORRECTION OF PSYCHOLOGICAL AND NEUROLOGICAL SIGNS OF ALCOHOL HANGOVER IN RATS WITH ACETYLCYSTEINE

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The development of medications to treat alcohol hangover is important for a large number of people, especially those, who perform responsible and dangerous types of work. The severity of the hangover syndrome is determined by the toxic effect of acetaldehyde and its metabolic rate, which decreases with the depletion of glutathione, worsening and prolonging the hangover.

The aim of the article is to provide an experimental basis for use of acetylcysteine as a precursor of glutathione in treatment of psychological, neurological and cognitive symptoms of ethanol hangover.

Materials and methods. The study was performed in male Wistar rats. The ethanol hangover was modeled via an acute ethanol injection (i.p., 3 g/kg). After awakening, the animals were divided into 2 groups, receiving acetylcysteine (p.o., 1 mg/kg) or saline. The intact group of the animals received saline only. Before and after acetylcysteine or saline administration, the animals were assessed according to Combs and D'Alecy scale. The adhesive test, the open field test, the passive avoidance test and Morris water maze test were also performed twice. The liver glutathione level was assessed in sacrificed animals.

Results. The control group animals showed signs of neurological deficits and cognitive impairment, including a decreased locomotion, motor deficits and a memory decline. The rats administered with acetylcysteine after the ethanol intoxication, had a less severe impairment associated with an improved performance in the adhesive test, Morris water maze test and the passive avoidance test, and demonstrated an increased locomotion in the open field test. The liver glutathione content in the animals treated with acetylcysteine, was comparable to the glutathione content in the liver of the animals not exposed to the ethanol intoxication.

Conclusion. Against the background of an acute ethanol intoxication, an oral administration of acetylcysteine in the rats, promoted an increase in liver glutathione levels and led to a decrease in severity of neurological and cognitive deficits in the animals.

Keywords: ethanol, post-toxic state, hangover, acetylcysteine, rat, preclinical study

Abbreviations: ATP – adenosine triphosphate; WHO – World Health Organization; NAD – nicotinamide adenine dinucleotide; OP – Open field.

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КОРРЕКЦИЯ ПСИХОНЕВРОЛОГИЧЕСКИХ ПРОЯВЛЕНИЙ АЛКОГОЛЬНОГО ПОХМЕЛЬЯ У КРЫС АЦЕТИЛЦИСТЕИНОМ

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Разработка средств для устранения алкогольного похмелья важна для большого числа людей, в том числе связанных с выполнением ответственных и опасных видов работ. Тяжесть похмельного синдрома определяется токсическим действием ацетальдегида и скоростью его метаболизма, которая снижается при истощении запасов глутатиона, что приводит к утяжелению и пролонгации похмелья.

Цель. Экспериментальное обоснование применения ацетилцистеина в качестве предшественника глутатиона для снижения выраженности психоневрологических и когнитивных нарушений, возникающих на фоне алкогольной интоксикации.

Материалы и методы. Исследование проведено на крысах-самцах линии Wistar. Состояние «похмелья» моделировали путем однократного введения этанола (3 г/кг, в/б). После пробуждения животных разделяли на 2 группы: опытной группе однократно перорально вводили раствор ацетилцистеина (1 мг/кг), контрольной группе – физ. р-р. Интактной группе вводили физ. р-р. До лечения и спустя 3 часа поочередно оценивали уровень неврологического дефицита по шкале «Combs and D'Alecy», а также проводили тесты: Адгезивный тест, Открытое поле (ОП), УРПИ и лабиринт Морриса. После эвтаназии определяли уровень глутатиона в гомогенатах печени.

Результаты. У животных контрольной группы отмечались выраженные признаки психоневрологических и когнитивных нарушений, проявляющихся в низкой двигательной активности, нарушении мелкой моторики и когнитивных функций.

У животных, которым вводили ацетилцистеин, нарушения психоневрологических и когнитивной функций были менее выражены, что проявлялось в улучшении мелкой моторики в Адгезивном тесте, повышении двигательной активности в тесте ОП. В тестах лабиринт Морриса и УРПИ, в которых оценивают сохранность памятного следа, большее количество животных успешно решили задачу, а уровень глутатиона в печени отвечал физиологической норме.

Заключение. На фоне острой алкогольной интоксикации введение ацетилцистеина, способствует восстановлению содержания глутатиона в печени и приводит к снижению выраженности нарушений психоневрологических и когнитивной функций у экспериментальных животных.

Ключевые слова: этанол, постинтоксикационное состояние, похмелье, ацетилцистеин, крысы, доклинические исследования

Список сокращений: АТФ – аденозинтрифосфат; АЦЦ – ацетилцистеин**;** ВОЗ – Всемирная организация здравоохранения; НАД – никотинамидадениндинуклеотид; ОП – Открытое поле; УРПИ – условная реакция пассивного избегания.

INTRODUCTION

An acute consumption of large quantities of ethyl alcohol, causes profound negative socio-economic consequences. According to the CDC data for 2010, economic losses due to the reduced labor productivity because of the alcohol consumption, amounted to $ 179 billion. Despite the large socio-economic costs and the costs of medical services spent on the treatment of the hangover syndrome and its consequences, this problem is of relatively little interest among the researchers. As a result, this extremely widespread symptom complex, still has many unexplained aspects in its pathogenesis. To improve the methods of its prevention or pharmacotherapy, a deeper understanding of the pathological processes that occur in the body during the development of a similar condition is necessary [1, 2].

Currently, this syndrome is defined as a general discomfort that occurs after the complete metabolism of previously taken alcohol (i.e. in the situation where alcohol cannot be detected in the blood). Neuropsychiatric disorders that occur after drinking large doses of alcohol, are not a steady state of the body, but a developing and slowly running process, which is especially important to consider by the people whose professional activities require attention and a high speed of decision-making at the risk of threatening situations (for example, drivers and operators of complex mechanisms) [3]. For an outsider, the presence of a hangover is dif-

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ficult to detect and distinguish from the symptoms of certain diseases (a tension headache, food poisoning, arterial hypertension), which, under certain conditions, can pose a threat to others. In particular, professional drivers who are in a state of post-alcohol intoxication, make significantly more serious errors when driving in simulation conditions (on a car simulator). They more often and by a larger amount exceed speed, ignore traffic signs, do not notice abrupt interference, take notice of emergency situations slower and/or inappropriately [4, 5]. It is important to note that in this state, irritability and aggressiveness often increase, which can be associated with a severe pain and/or increased levels of testosterone [6, 7]. Its metabolism occurs in the liver and can change with the depletion of intracellular substrates caused by an intensive biotransformation, first of the alcohol, and then of its metabolites. A hangover is characterized by the development of a complex of negative symptoms, the most common of which are: a headache, nausea, vomiting, diarrhea, chills, fever, drowsiness, tremor, irritability, aggressiveness [8]. In the groups whose employees, on condition of anonymity, reported performing their duties in the morning after drinking large doses of alcohol, interpersonal conflicts occurred more often, and the overall labor productivity was low [9].

Ethanol intake is an example of a voluntary, largely uncontrolled, consuming of the most common and probably the most studied psychotropic drug [10]. With a lot of stressful factors in modern life, antidepressant, psychostimulating, disinhibit and hedonic effects of ethyl alcohol, often become a cause of abuse. Although alcohol is often consumed in the doses that cause a hangover, there are no universal signs to determine a risk group. For this reason, negative phenomena associated with its use, can occur in absolutely any person (regardless of their social, financial or legal status, mental and physical level of development).

According to the results of some sociological studies, 75% of the people who had been consuming alcoholic beverages to the state of intoxication, had a hangover at least once, 15% of the respondents noted that the latest episode of this kind had taken place a month before. About 50% of the people who regularly take ethanol (those who consume one or two drinks per day; one drink is an equivalent dose of 50 g of pure alcohol [11]) have a habitual hangover. 40% of the people who openly report the fact of their frequent use of ethyl alcohol say, that they have neuropsychiatric post-toxic effects every month or more often. In patients with alcoholism, their prevalence is lower and amounts to 20–25%. Up to 87% of university students experience one or more hangover episodes during a year, while numerous studies have shown a negative impact of this symptom complex on their cognitive activity [12].

Pharmacotherapy is the only effective way to eliminate the effects of an acute excessive consumption of alcoholic beverages, but the modern pharmaceutical market has a limited number of drugs for the prevention and treatment of this state [13]. The situation is complicated not only by the lack of the general consensus of the professional community regarding the pathogenesis of a hangover, but also by the difficulties encountered in initiating and conducting preclinical studies.

One of the promising directions in the treatment of hangover is the development of the agents that accelerate the metabolism of acetaldehyde. Among the compounds with a similar effect, acetylcysteine, which is the precursor of glutathione, the most important regulator of the redox processes in cells, including hepatocytes, can be distinguished. Ethyl alcohol is metabolized to acetaldehyde, which has a general toxic effect, the manifestation of which is a hangover. Glutathione inactivates free oxygen radicals formed in the mitochondria of hepatocytes in the processes of their functioning, the formation of which depends on the intensity of the course of the redox reactions. Since the alcohol metabolism proceeds in several stages (alcohol – acetaldehyde – acetic acid), hepatocytes stay in conditions of intensification of metabolic processes for a long time when a large amount of them enters the human body, which is followed by the formation of a large number of reactive oxygen species and reactive metabolites inactivated by glutathione. In such a situation, a slowdown in the metabolism of acetaldehyde due to the depletion of the reserves of reduced glutathione is not excluded. Therefore, the use of substances that can increase the content of the latter, can promote the activation of natural detoxification systems, accelerate the metabolism of acetaldehyde and alleviate the hangover syndrome. The use of acetylcysteine, able to increase the content of reduced glutathione, may become promising for this purpose [14].

This study was planned to provide an experimental basis for the use of acetylcysteine as a precursor of glutathione in treatment of psychological, neurological and cognitive symptoms of ethanol hangover.

MATERIALS AND METHODS

Animals

All experiments were conducted in accordance with the animal research standards defined by the law of the Russian Federation and EASC technical standards for Good laboratory practice (GOST R 53434-2009 and GOST R 51000.4-2011). The study design and the protocol were reviewed and approved by the Department of the ethical, legal, and sociological expertise in medicine of the Volgograd Medical Research Center [registration number: IRB 00005839 IORG 0004900 (OHRP)] on May 20, 2019 (protocol number: 132).

The experimental study was performed on 30 male Wistar rats (300–350 g, obtained from mouse bank of

"Rappolovo"). In the vivarium, the animals were acclimated for 14 days before starting the experiment where the rats were kept during the experiment. They were housed at 20 ± 2°C and 40–60% humidity in a standard 12/12-h light–dark cycle with food and tap water *ad libitum*.

Study design

Before the acute ethanol administration, all the animals were trained in Morris water maze task and in the passive avoidance reflex conditioning test (for 4 and for 2 days, respectively). The animals able to find a platform in Morris water maze task and showing avoidance of dark compartment in the passive avoidance test, were divided into 3 groups (n = 10 in each). The groups were the following:

1. Intact group – normal saline (15 ml/kg, i.p.) + saline (5 ml/kg, p.o.);
2. Control group – ethanol (3 g/kg, i.p.) + saline (5 ml/kg, p.o.);
3. Experimental group – ethanol (3 g/kg, i.p.) + acetylcysteine (1 g/kg, p.o.).

The rats of the first (intact) group were administrated with saline (i.p. and p.o.). The rats of the control and experimental groups were given a single dose of 20% ethanol solution (3 g/kg, i.p.). Then (after awakening and fixing the initial parameters), a single dose of a physiological solution (LLC "Hematec", Russia) or an aqueous solution of acetylcysteine (CJSC "Sandoz", Russia) was administered (1 g/kg, per os). The volumes of the solutions for intraperitoneal and intragastric administration were 15 and 5 ml / kg, respectively.

After the ethanol administration, the latent period of loss of the righting reflex (ability to stand up and lean on the limbs from the upside-down position) was recorded in the animals [15]. The duration of sleep in animals was 8 h ± 30 min.

Within 30 min after awakening the animals were assessed. Combs and D'Alecy scale, the adhesive test, the open field test, the passive avoidance test and Morris water maze test were performed. Then the rats (in accordance with the group) were administered with acetylcysteine or saline intragastrically. The animals, which did not wake up 8.5 hours after the ethanol administration, were excluded from the experiment.

3 hours later, all the tests were performed again: the signs of neurological deficits were assessed according to Combs and D'Alecy scale [16]. The adhesive test was used to assess the ability of the animals to feel and remove a duct tape applicated on the upper paws within 3 min of the observation [17]. The open field test was used to study locomotor and exploratory activities of the animals [18]. Cognitive functions were assessed in the passive avoidance test [18] and in Morris water maze test [19].

After euthanasia (decapitation under anesthesia with zoetil / xylazine at the dose of 20/8 mg / kg), liver tissue samples were taken from the animals for the subsequent analysis. The concentration of the reduced glutathione was assessed in the reaction with 5.5-dithiobis-(2-nitrobenzoic acid) [20]. All the reactions were performed in triplicates.

Statistical processing

The statistical processing was performed by methods of descriptive and analytical statistics. The distribution of quantitative values was evaluated using the Shapiro-Wilk test. The intergroup differences were assessed by a one-way analysis of variance using Newman-Keuls *post hoc* test. All the data were presented as the mean and standard error of the mean (unless otherwise indicated). The differences in the categorical data were evaluated by χ^2 test.

RESULTS

An intraperitoneal ethanol administration in rats resulted in the general anesthesia which lasted in average for 8 ± 0.5 hours. With regards to the latent period of anesthesia and to the total duration of this condition, the rats included in this study, were comparable.

The ethanol hangover in the rats was characterized by an inhibition of the total activity, a decrease of locomotion and somnolence (the animals spent more time with shut eyes, and their reactivity to mechanic stimuli was decreased). The results of the open field test reflected the general trends: the ethanol hangover significantly decreased the exploratory and motor activities in all the animals.

The decrease in the motor activity was also observed in the control animals 3 hours afterwards, while in the acetylcysteine-treated rats their motor and exploratory activities in the open field test increased (Figure 1). Thus, acetylcysteine promoted a restoration of the total activity in the rats exposed to the acute ethanol intoxication.

The signs of neurological deficits, assessed according to Combs and D'Alecy scale, were symptoms of severe neuropsychiatric deficiency after awakening in both ethanol-treated groups. The severity of neurological deficits decreased in 3 hours after the oral administration of saline and decreased significantly after the administration of acetylcysteine (Figure 2A).

In the adhesive test, the animals neglected a duct tape applicated on the volar side of the upper limbs. In 3 hours after the first testing and treatment of the animals undergoing acute alcohol poisoning (the oral administration of saline did not improve their sensory-motor function), only 2 of 10 animals were able to remove a duct tape (at least from one paw). In the group of acetylcysteine-treated rats, 7 of 10 animals were able to remove a duct tape ($p < 0.05$) using a shorter period of time ($p < 0.05$; Figure 2B).

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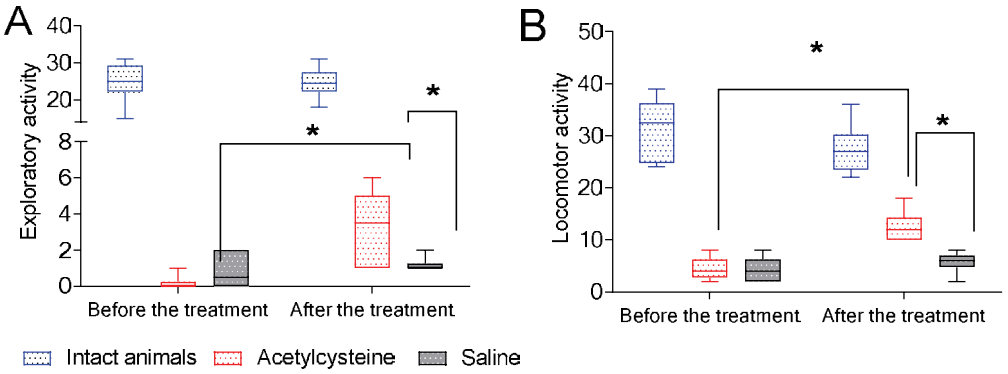

Figure 1 – Effect of acetylcysteine on exploratory (A) and locomotor (B) activities in the open field test performed by the rats exposed to acute ethanol intoxication

*Note: * – p < 0.05 (one-way ANOVA with Newman-Keuls post-test); the compared groups are connected with horizontal lines; the exploratory activity was defined as a sum of vertical postures and nose-poking acts; the locomotor activity was defined as a number of crossed sectors of the open field.*

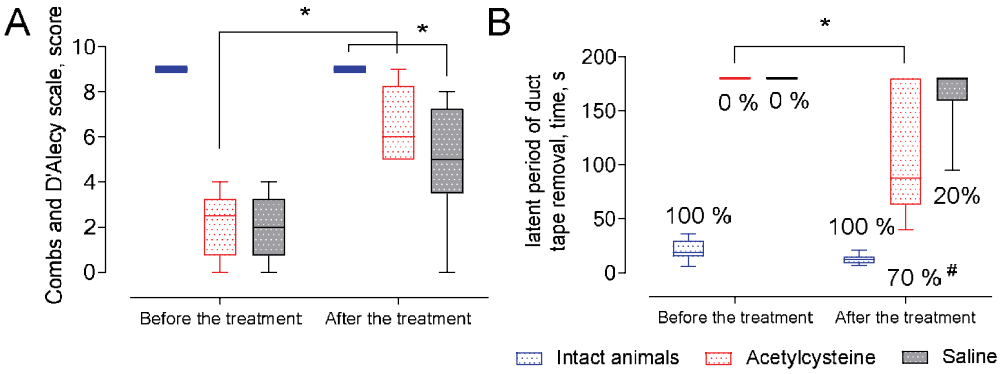

Figure 2 – Effect of acetylcysteine on neurological deficits assessed according to Combs and D'Alecy scale (A) and a latent period of the duct tape removal in the adhesive test (B) in the rats exposed to acute ethanol intoxication

*Note: * – p < 0.05 (one-way ANOVA with Newman-Keuls post-test); # – p < 0.05 (χ^2); % – a number of the animals in the group, which removed the duct tape from one paw; the compared groups are connected with horizontal lines.*

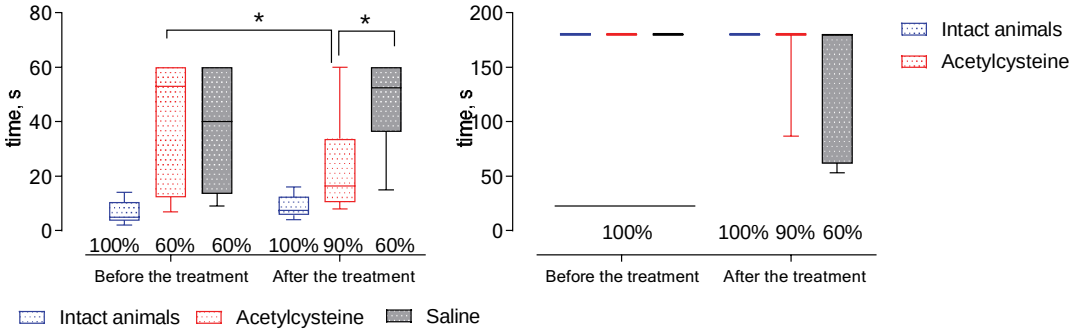

Figure 3 – Effect of acetylcysteine on the latent period of platform finding in Morris water maze (A) and on the latent period in the passive avoidance test (B) in the rats exposed to acute ethanol intoxication

*Note: * – p < 0.05 (one-way ANOVA with Newman-Keuls post-test); % – a number of the animals able to find a platform (A) or avoided a dark compartment of the passive avoidance test apparatus (B); the compared groups are connected with horizontal lines.*

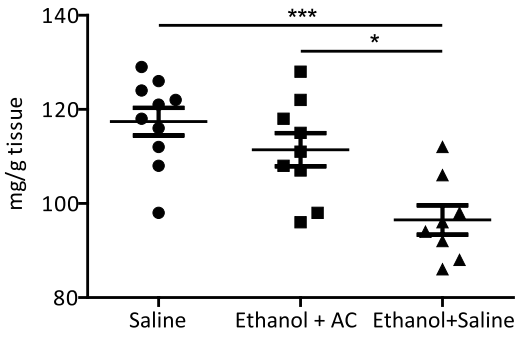

Figure 4 – Effect of acetylcysteine on the liver glutathione content in the rats exposed to acute ethanol intoxication

*Note: AC – acetylcysteine; data shown as means of triplicates, grand mean and standard error of mean; *, *** – p < 0.05, p < 0.0001 (one-way ANOVA with Newman-Keuls post-test); the compared groups are connected with horizontal lines.*

Before the ethanol administration, all the animals were trained in Morris water maze for 4 days to find a platform, and 2 days before the ethanol administration they passed a fear conditioning procedure based on the passive avoidance reflex. All the rats exposed to the ethanol intoxication ~~had~~ increased the period of platform finding in Morris water maze (Figure 3A). In the passive avoidance test, the animals demonstrated decreased locomotion without any exploratory activity, thus the assessment of the avoidance reaction could not be performed.

No changes in Morris water maze task and in the passive avoidance test performance were observed in the saline-treated animals within 3 hours after awakening. The rats treated with acetylcysteine, showed a better performance in both tests (Figure 3A, 3B). The observed results suggest that acute ethanol intoxication is associated with memory decline which could be partially rescued with the acetylcysteine administration.

At the end of study, the animals were sacrificed, and liver tissues were sampled for glutathione content detection. In the animals administered with ethanol and saline, the liver glutathione content reached 96.5 ± 3.11 mg/g tissue (*vs* 117.4 ± 2.95 mg/g tissue in intact rats; p < 0.0001). In the acetylcysteine-treated rats, the liver glutathione content reached 111.4 ± 3.52 mg/g tissue, which was higher than in the animals treated with ethanol and saline (p < 0.05; Figure 4). Thus, an oral administration of acetylcysteine led to an increase in liver glutathione content, which could reduce the severity of ethanol intoxication.

DISCUSSION

In modern society, alcohol abuse is a widespread problem due to the increase in stress load and the availability of alcohol. Although a hangover is a frequent adverse event of ethanol intake, this condition is not well understood in terms of current medical knowledge. Negative consequences of ethanol hangover include economic costs associated with inefficient work or study [1, 2].

An oxidation of ethanol by alcohol dehydrogenase leads to the formation of acetaldehyde, which turns into acetate. Both of these sequential and then parallel reactions could affect the balance between nicotinamide adenine dinucleotide (NAD) and NADH, indirectly decreasing the amount of reduced glutathione [21]. An increase in NADH causes a number of metabolic disorders, including hyperlactacidemia, which promotes acidosis and reduces uric acid excretion. This leads to secondary hyperuricemia, which is aggravated by alcohol-induced ketosis and enhances the acetate-mediated breakdown of ATP. An increase in NADH also prevents gluconeogenesis, thereby promoting hypoglycemia, increase in α-glycerophosphate levels, inhibition of the Krebs cycle. This is followed by inhibition of fatty acid oxidation, which promotes steatosis and hyperlipidemia. Acetaldehyde is a cytotoxic substance which inhibits the recovery of alkylated nucleoproteins, inhibits the activity of key enzymes and significantly decreases the efficiency of the oxygen metabolism in mitochondria. In addition, acetaldehyde contributes to cell death by depleting the level of reduced glutathione, causing lipid peroxidation, and an increase in the toxic effect of free oxygen species. By binding to microtubule tubulin, acetaldehyde blocks the secretion of proteins. The result of an increase in protein, lipids, water and electrolyte cell content is an increase in the size of hepatocytes. Acetaldehyde-protein adducts promote collagen production and can act as neoantigens that stimulate the immune response. The decrease in reduced glutathione, caused by ethanol, also contributes to damage to hepatocyte organelles and decreases the utilization of xenobiotics [21, 22].

Acetylcysteine was originally patented in 1960 and licensed for use in 1968. It is included in the WHO List of Essential Medicines, the most effective and safe medi-

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cines needed in the health system, as a drug used in case of paracetamol (acetaminophen) overdose and for mucolytic therapy [23]. This compound acts as the precursor of L-cysteine, from which the antioxidant glutathione is formed. Glutathione contains a peptide bond between the amino group of cysteine and the carboxyl group of the glutamate side chain. The value of glutathione in a cell is determined by its antioxidant properties. In fact, glutathione does not only protects the cell from toxic free radicals, but also generally determines the redox characteristics of the intracellular environment. In the cell, thiol groups are in a reduced state at the concentration of about 5 mmol/L. Such a high concentration of glutathione in the cell, leads to the fact that it restores any disulfide bond formed between the cysteine residues of intracellular proteins. In this case, the reduced form of glutathione turns into oxidized. Oxidized glutathione is restored under the action of the enzyme glutathione reductase, which is constantly in the cell in an active state and is induced by oxidative stress. The ratio of the reduced and oxidized forms of glutathione in the cell is one of the most important parameters that determines the level of oxidative stress, which increases during alcohol consumption and the development of an ethanol hangover [22, 24].

Acetylcysteine administration contributes to the replenishment of glutathione, which plays an important role in neutralizing reactive oxygen species and, together with oxidized glutathione and S-nitrosoglutathione, binds to the NMDA and AMPA receptors (through their γ-glutamyl fragments) and can be endogenous neuromodulator. At millimolar concentrations, they can also modulate the redox state of the NMDA receptor complex [25].

Glutathione modulates the NMDA receptor by acting on the redox site. L-cysteine also serves as a precursor of cystine, which is a substrate for antiportheracin glutamate on astrocytes. Therefore, cysteine could increase the release of glutamate into the extracellular space, where it acts on mGluR 2/3 receptors, and at higher doses of acetylcysteine – on mGluR 5 [26]. With regards to this fact, that hangover is accompanied by depression of neurotransmitters, the restoration of neurotransmitter balance can contribute to a faster restoration of neurocognitive functions. Acetylcysteine also exerts some anti-inflammatory effects, which could be due to inhibition of NF-κB transcription factor and due to modulation of cytokines synthesis [27].

Available preclinical and limited clinical data suggest that acetylcysteine is able to normalize glutamate neurotransmission to the *nucleus accumbens* and other brain structures, in part due to an increased expression of excitatory amino acid transporter 2, known as glutamate transporter 1, in addicted individuals. In adults with cocaine dependence, acetylcysteine modulates the neurotransmission of glutamate, which is not observed in people without dependence [28]. This study, in conjunction with the data presented, suggests that acetylcysteine could have a double effect related to the hangover symptoms: facilitation of the metabolism of xenobiotics and a neuroprotective effect, which helps to reduce alcohol craving. Acetylcysteine, acting as a modulator of glutamate and dopamine neurotransmission with a pronounced antioxidant effect, is a promising candidate for further development of a medication for correction of ethanol hangover.

CONCLUSION

An oral administration of acetylcysteine in rats suffering from acute ethanol intoxication promoted an increase in liver glutathione levels and led to a decrease in severity of neurological and cognitive deficits in animals. With regards to the obtained results, acetylcysteine could be used as a perspective medication for ethanol hangover treatment.

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AUTHOR CONTRIBUTIONS

All authors had equally contributed to the research work.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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