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ВПЛИВ ТЕРАПЕВТИЧНОГО ВВЕДЕННЯ МУЛЬТИПРОБІОТИКА НА ГІПОТАЛАМО-ГІПОФІЗАРНО-НАДНИРКОВУ СИСТЕМУ І ЦИТОКІНОВИЙ ПРОФІЛЬ В УМОВАХ СТРЕСУ

Вивчали вплив мультиштамного пробіотика (МП) на вміст гормонів стресу (адренокортикотропний гормон (АКТГ) та кортизол) та вміст прозапальних (інтерлейкін (ІЛ) 1β та 12В р40) та антизапальних (ІЛ-4 та ІЛ-10) цитокінів за умов ерозивно-виразкових уражень, викликаних водно-іммобілізаційним стресом (ВІС). Встановлено, що МП суттєво прискорював відновлення функціонування гіпоталамо-гіпофізарно-надниркової системи за умов дії стресу, що відображалося у більш швидкому поверненні концентрації АКТГ та кортизолу до значень інтактних щурів. МП зменшував вміст прозапальних (ІЛ-1β та ІЛ-12В р40) та підвищував вміст антизапальних (ІЛ-4 та ІЛ-10) цитокінів в сироватці крові щурів після ВІС. Отримані дані свідчать, що одним з механізмів лікувального ефекту МП на ураження в слизовій оболонці шлунка, викликані стресом, є вплив на систему стресу та цитокіновий профіль.

Ключові слова: адренокортикотропний гормон, кортизол, цитокіни, стрес, мультиштамний пробіотик.

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ВЛИЯНИЕ ТЕРАПЕВТИЧЕСКОГО ВВЕДЕНИЯ МУЛЬТИПРОБИОТИКА НА ГИПОТАЛАМО-ГИПОФИЗАРНО-НАДПОЧЕЧНИКОВУЮ СИСТЕМУ И ЦИТОКИНОВЫЙ ПРОФИЛЬ В УСЛОВИЯХ СТРЕССА

Изучали влияние мультиштамного пробиотика (МП) на содержание гормонов стресса (адренокортикотропный гормон (АКТГ) и кортизол) и содержание провоспалительных (интерлейкин (ИЛ) 1β и 12В р40) и антивоспалительных (ИЛ-4 и ИЛ-10) цитокинов в условиях эрозивно-язвенных поражений, вызванных водно-иммобилизационном стрессом (ВИС). Установлено, что МП существенно ускорял восстановление функционирования гипоталамо-гипофизарно-надпочечниковой системы в условиях действия стресса, что отражалось в более быстром возврате концентрации АКТГ и кортизола до значений интактных крыс. МП сни жал содержание провоспалительных (ИЛ-1β и ИЛ-12В р40) и повышал содержание антивоспалительных (ИЛ-4 и ИЛ-10) цитокинов в сыворотке крови крыс после ВИС. Полученные данные свидетельствуют, что одним из механизмов лечебного эффекта МП на поражения в слизистой оболочке желудка, вызванные стрессом, является воздействие на систему стресса и цитокиновый профиль.

Ключевые слова: адренокортикотропный гормон, кортизол, цитокины, стресс, мультиштаммный пробиотик.

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THE EFFECT OF ACETIC ZINC ON SERUM ZINC LEVEL AND INTERLEUKIN 1β AND 6 LEVEL IN RATS EXPOSED TO ALCOHOL FOR 21 DAYS

The aim of this study was to examine the effect of acetic zinc supplementation on dynamics of zinc level and inflammatory cytokines (IL-1β and IL-6) production in serum of rats subjected to ethanol exposure for 21 days.The zinc level in serum was determined by flame atomic-absorption spectrophotometry. The level of IL-1β and IL-6 in serum was measured by enzyme-linked immunosorbent assay (ELISA) kits ("Sigma", США). A significant gradual decrease of serum zinc level and elevation of the levels of circulating IL-1β and IL-6 were seen in the ethanol-fed animals been maximal on 16^{th} and 21^{th}. The changes of zinc level and IL-1 β and IL-6 production in ethanol-intoxicated rats were completely corrected after acetic zinc supplementation that was more evident at prolonged ethanol exposure. Zinc level in such animals has been demonstrated to increase and exceed the control by 4.2 and 4.9 times on 16^{th} and 21^{st} day of alcoholization. The IL-1β and IL-6 level diminished and normalized also at these stages of study. Our results suggest that acetic zinc supplementation recovers zinc pool in blood and normalizes inflammatory cytokine production that may be due to reduction of zinc deficiency and attenuating of oxidative stress thus leading to inhibition of inflammation.

Key words. Ethanol, chronic alcohol intoxication, zinc deficiency, inflammatory cytokines, interleukin 1β, interleukin 6, acetic zinc.

Introducton

Ethanol has a variety of detrimental effects on immune system including effects on cell mediated and humoral immune response. It decreases neutrophil infiltration and phagocytic capability, inhibits lymphocyte activation following antigen stimulation, and alteres cytokine production by T cells and macrophages [1]. Prolonged ethanol exposure can directly and indirectly lead to the suppression of immunity and increased susceptibility to infections. The alcohol effects are dose-dependent, long-term ethanol consumption has been associated with inflammation [2]. Alcoholic liver disease is a result of a pro-inflammatory effect of chronic ethanol exposure [3].

Ethanol affects the production of cytokines that involved in inflammatory responses in plasma and a variety of tissues including lung, liver, and very importantly brain [4]. Cytokines are regulatory proteins playing a key role in immune and inflammatory response to infection by pathogens and oncogenesis. Excessive alcohol abusers have increased circulating levels of the inflammatory cytokines such as TNF-α (tumor necrosis factor-α), IL-1β (interleukin 1) and IL-6 (interleukin 6) [5]. A significantly increased production of IL-1β, IL-6, IL 12, and TNF-α by unstimulated peripheral blood monocytes was demonstrated in patients with alcoholic liver disease [6].

Severe zinc deficiency has been observed to develop in patients who chronically abuse alcohol, it's is one of the most consistent biochemical observation in alcoholic liver disease (ALD) [7]. Zinc affects the function of immune system, because it is one of the most highly proliferative organs. Zinc is crucial for normal growth and function of T and B cells, macrophages, neutrophils, and NK cells [8]. Zinc directly influences on blood mononuclear cell, diminishing the production of cytokines (IL-1, IL-6, TNF-α and IFN-γ) [9]. Various immune disorders are associated with zinc deficiency [10]. Decreased serum zinc level is observed in chronic inflammatory or infectious diseases [9, 11].

Zinc has been successfully used to restore impaired immune functions in diseases accompanied by diminished plasma zinc levels (rheumatoid arthritis, acrodermatitis enteropathica, hemodialysis patients, elderly individuals) [10]. A dietary zinc supplement has been proposed as possibly being an efficient method to palliate zinc deficiency in alcoholism [12]. Studies using animal models have demonstrated that Zn treatment prevents alcohol-induced liver injury under both acute and chronic alcohol exposure conditions [13, 14]. Zn has a high potential to be used in the prevention and treatment of ALD [12]. It may be a completely new therapeutic tool for the selective suppression of lymphocyte functions [10] and inhibition of inflammation. In

comparison to conventional immunosuppressive drugs, zinc has the advantage of being most nontoxic, even in dosages well exceeding the recommended dietary intake [15]. Acetic zinc has the lowest toxicity among zinc salts.

However, the molecular basis of zinc effects on immunity in alcoholism is largely unknown. Altogether, these observations would support the importance of studying of acetic zinc effect on the production of pro-inflammatory cytokines in blood of rats chronically consumed alcohol. The circulating cytokines now may contribute to diagnostic biomarkers of excessive alcohol intake and alcoholism [4].

This study was undertaken to examine the effect of acetic zinc supplementation on dynamics of zinc level and inflammatory cytokines (IL-1β and IL-6) production in serum of rats subjected to ethanol exposure for 21 days.

Materials and Methods

The research was conducted on white nonlinear rats (males) with body weight ranging from 180 to 200 g. Rats were kept under standard conditions with free access to animal chow and tap water. Animals were divided into 3 groups (n=10 per group), namely: (1) control; (2) chronic alcohol intoxication (animals were intragastrically treated with 40% ethanol (2 ml/100 g); one time per day for 21 days); (3) chronic alcohol intoxication and acetic zinc treatment (animals were simultaneously intragastrically treated with ethanol and acetic zinc (0.2 g /100 g that was considerably less than LD_{50}=0,278±0,049 for white rats) for 21 days). The development of chronic alcohol intoxication in rats was performed as described by M.H. Halilov and S.A. Zackirhodjayev [16].

Rats were sacrificed by cervical dislocation on next day after treatment with ethanol and acetic zinc for 4, 7, 11, 16 and 21 days. The protocol of animal experiment was approved by the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 18.III.1986). Blood samples were collected for further analyses. Serum was collected by centrifugation of whole blood sample at 1000×g for 10 min at 4°C and stored at – 80°C.

The zinc level in serum samples was determined by flame atomic-absorption spectrophotometer C115-M1 ("SELMICHROM", Ukraine) with deuterium background correction and digital analytical complex CAS-120 [17].

The level of cytokines (IL-1β and IL-6) was measured in serum samples by commercially available enzyme-linked immunosorbent assay (ELISA) kits ("Sigma", США). Samples were processed according to the manufacturer's instructions. Optical densities of each well were analyzed using a microplate reader. Samples were processed in triplicates, and were analyzed in batches to minimize inter-assay variability. The level of cytokines was determined by calibration curve plotted using the IL-1β and IL-6 standards.

All analyses were performed using the Microsof Exel 2007 software package, version 12 (Microsoft Corporation, USA). The Student's t-test was used for the evaluation of the statistical significance of the differences observed between two or more groups, respectively. P values less than 0.05 were considered statistically significant.

Results and discussion

Serum zinc level has been measured in rats intragastrically treated with ethanol for 4, 7, 11, 16 and 21 days. Zinc level progressively diminished at all stages of study and was less than control by 32%, 2 and 2.75 times on 4 th, 7 th, 11th day of ethanol exposure, respectively. The most essential decrease was observed on 16th and 21st day of ethanol exposure (by 3.2 and 3.7 times in comparison to the control) (Figure 1).

Simultaneous introduction of acetic zinc and ethanol to rats led to elevation of serum zinc level which exceeded the control at all stages of study. Results shown in Figure 1 indicate that zinc level increased by 2, 4.4. and 8.5 times on 4 th, 7 th, 11th day of alcoholization, respectively, comparative to untreated animals. An elevation was most evident on 16th and 21st day and made 12.9 and 18 times similarly to that observed in rats exposed to alcohol only. In this case zinc level exceeded the control by 4.2 and 4.9 times.

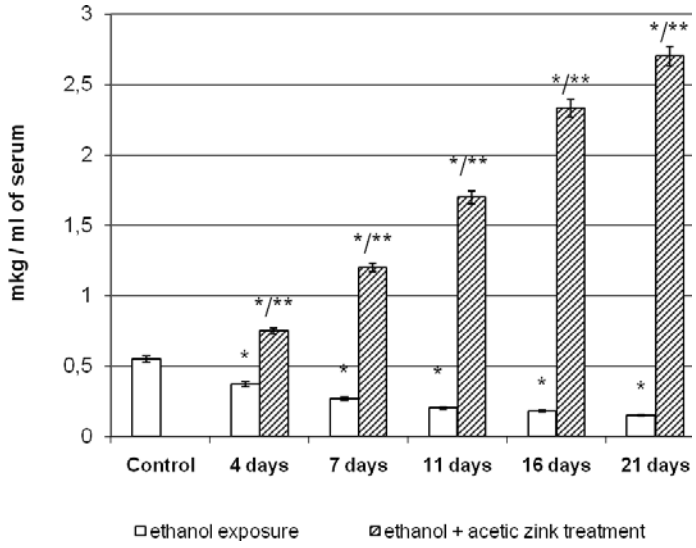

Figure 1. Serum zinc level in rats exposed to ethanol and acetic zinc for 21 day

* – P ≤ 0,05 in comparison to the control group, ** – P ≤ 0,05 in comparison to the group, treated with ethanol only

It seems clear that ethanol causes a notable fall in the level of zinc in serum of rats. We may assume that zinc deficiency develops in alcoholized rats and deepens after prolonged ethanol exposure. Our results are in agreement with findings of other authors. Chronic alcohol feeding associated with inflammation is characterized by low plasma zinc levels or a noticeable zinc deficiency [18, 7]. Even the shot-term ethanol treatment (for 5 days) has been shown to decrease the zinc level in serum of rats [19].

The physiologic plasma zinc concentration represents a very mobile and immunologically important pool [10]. The observed by us decrease of zinc level in ethanol-intoxicated rats likely reflects a redistribution of serum zinc into the liver. Such redistribution according to the findings of Singh et. al., occurs within the inflammation, caused by increased production of inflammatory cytokines, mainly IL-1 and IL-6, and the subsequent induction of zinc-binding metallothionein in hepatocytes [20].

In the present study, acetic zinc administration to ethanol-intoxicated rats restored zinc level in serum and it even exceeded the control value. The effect of this drug was more evident in rats exposed to ethanol for a longer time (for 16 and 21 days). We can assume that acetic zinc treatment restores the reserves of zinc in organism and might be a tool for alleviating of zinc deficiency.

Zinc is considered to be an antioxidant, membrane-stabilizing and anti-inflammatory agent. It has a role in the prevention of free radical-induced injury during inflammatory processes, decreasing reactive oxygene species (ROS) generation via inhibition NADPH oxidase [9]. It also inhibits NF-kB activation and this results in a decrease in production of inflammatory cytokines [8].

Chronic alcohol exposure has been reported to augment secretion of inflammatory cytokines by PBMC [6]. Several studies in human and animal models have confirmed that increases in the production of inflammatory cytokines such as IL-1, IL-6, TNF-α and IFN-γ are associated with decreased zinc status [9].

In line with this, the circulating level of cytokines IL-1β and IL-6 was measured in ethanol-intoxicated rats treated with acetic zinc. It was found that the ethanol-fed rats produced much higher levels of IL-1β and IL-6 than the control rats, and this increase was progressively intensified by prolonged ethanol exposure. The elevation of IL-1β serum level was insignificant in animals treated with ethanol for 4 and 7 days, it averaged 12% and 20%, respectively, in comparison to control animals (Figure 2). The level of this cytokine increased more significantly after more long ethanol exposure for 11, 16 and 21 days and its value exceeded the control by 58%, 71% and 76%, respectively.

The serum level of IL-6 weakly increased at early stages of alcohol intoxication (for 4 and 7 days), exceeding the control by 19% and 35%, respectively (Figure 3). In contrast to IL-1β, IL-6 level dramatically rose by 2, 2.3 and 2.6 times in comparison to control in rats exposed to ethanol for 11, 16 and 21 days, respectively.

Simultaneous treatment of rats with ethanol and acetic zinc led to gradual reduction of IL-1β and IL-6 level in serum at all stages of study. The observed decrease was insignificant in animals treated with zinc for a few days, but this preparation evoked more substantial effect when has been introduced for a longer time (16 and 21 days).

When rats were treated with acetic zinc and ethanol for 4, 7 and 11 days, the serum level of IL-1β decreased by 12%, 23% 34%, respectively, in comparison to animals exposed to alcohol only (Figure 2). Treatment with drug for 16 and 21 days diminished IL-1β level by 40% and 43%, respectively. It should be noticed that level of this cytokine came to normal at last stage of study.

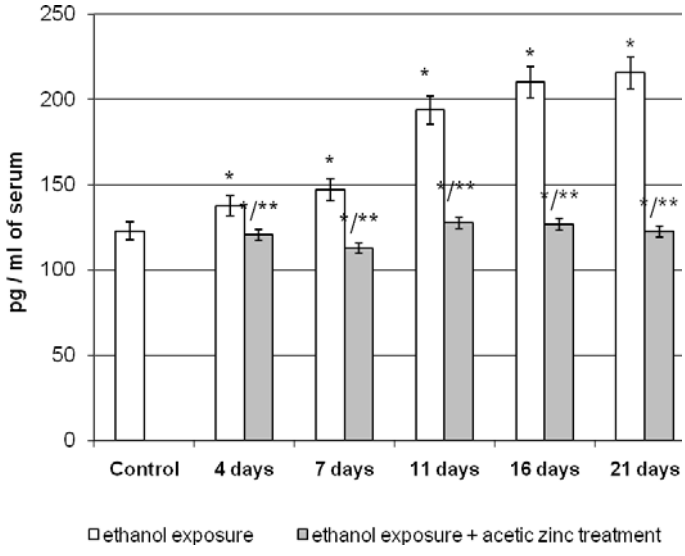

Figure 2. Serum level of IL-1β in rats exposed to ethanol and acetic zinc for 21 day

* – P ≤ 0,05 in comparison to the control, ** – P ≤ 0,05 in comparison to the group, treated with ethanol only

Short-term treatment of rats with acetic zinc and ethanol (for 4 and 7 days) hasn't been observed to alter the serum IL-6 level significantly. In the first case it didn't differ from such in alcoholic animals, in the second case it decreased by 11% (Figure 3). The level of this cytokine diminished by 45%, 53% and 60% in rats subjected to zinc administration for 11, 16 and 21 days, respectively, in comparison to alcoholic animals that haven't been treated with preparation. Thus, the diminishing of Il-6 level was most evident in rats treated with acetic zinc for a longer time (16 and 21 days), similarly to IL-1β. Both IL-1β and Il-6 levels normalized on 16th and 21st day of zinc treatment.

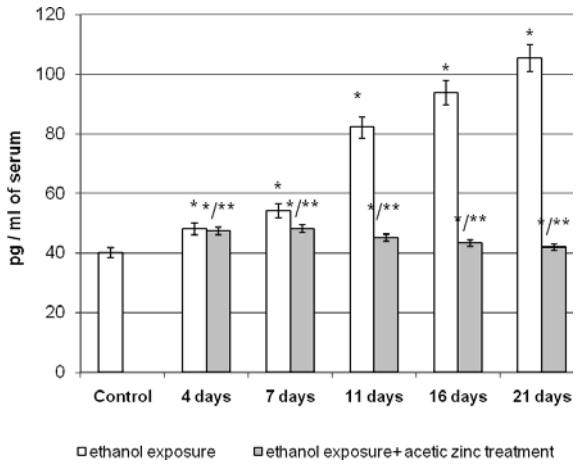

Figure 3. Serum level of IL-6 in rats exposed to ethanol and acetic zinc for 21 day

* – P ≤ 0,05 in comparison to the control, ** – P ≤ 0,05 in comparison to the group, treated with ethanol only

Studies in experimental human model provided a possible mechanism by which zinc deficiency may affect cell-mediated immunity adversely [8]. It was observed that the production of inflammatory cytokines (IFN-γ, TNF-α and IL-1β) by activated monocytes/macrophages is increased as a result of zinc deficiency [9]. Such augmentation leads to the generation of increased amounts of reactive oxygen species (ROS) and developing of the oxidative stress. Chronic alcoholism is also associated with an increased intracellular production of inflammatory cytokines [5, 6].

As could be expected, ethanol induced a significantly increased production of IL-1β and IL-6 analyzed in a group of rats with alcohol intoxication. This observation indicates that secretion of inflammatory cytokines by peripheral blood monocytes of alcoholic rats could be increased. Such effect could be related to the activation of these cells. This is consistent with observations about the activation of human monocytes and macrophages in chronic alcoholic individuals [21]. Such activation could represent a risk factor for the development of systemic inflammatory syndrome [22].

An increase of the production of inflammatory cytokines IL-1β and IL-6 in ethanol-intoxicated rats may reflect the cell-mediated immune dysfunctions and might be due to decrease of zinc level in blood. The observed effect was adversely affected in long-term alcohol exposure that is associated with amplification of zinc deficiency.

We have demonstrated the ability of acetic zinc to inhibit the production of inflammatory cytokines IL-1β and IL-6 in blood, which was simulated by alcohol. This preparation is more efficient when introducing to animals subjected to prolonged ethanol exposure (for 16 and 21 days).

Zinc is considered to affect directly the cytokine production [10, 11]. This preparation could also attenuate oxidative stress in alcoholic animals that is in line with findings concerning the antioxidant properties of this microelement. Zinc was demonstrated to induce the production of metallothionein, which is a scavenger of ˙OH [8]. It also competes with iron and copper ions for binding to cell membrane, thus decreasing the production of ˙OH, inasmuch as these ions catalyze the production of ˙OH from H_2O_2.

The beneficial effect of zinc preparation is associated with reducing of oxidative stress and inhibition of the production of inflammatory cytokines. Dietary zinc supplementation has been observed to prevent hepatocyte apoptosis in mice subjected to long-term ethanol exposure [13]. The action of zinc was assumed as suppression of oxidative stress and death receptor-mediated pathways (NF-R1, FasL, Fas, Fas-associated factor-1, and caspase-3).

Oral administration of zinc chloride has antioxidant effect on stomach and intestine of rats treated with ethanol [12]. This preparation prevented and reversed alterations of thiobarbituric acid reactive substance and reactive species levels, total protein SH content, superoxide dismutase and catalase activity induced by ethanol [14].

Oral administration of Zn(II)-curcumin complex has been reported to adjust the inflammatory cytokine-mediated oxidative damage to the gastric mucosa in the rats exposed to ethanol [23]. This drug prevented formation of ulcer lesions induced by ethanol, inhibited TNF-α and IL-6 expression, increased the activity of SOD and reduced MDA levels in gastric mucosa.

We can assume that acetic zinc inhibits inflammation in alcoholic animals via restoring zinc pool in organism and thus removing the outcomes of zinc deficiency. The observed augmentation of zinc level in blood of alcoholic animals subjected to acetic zinc treatment is evidence of such assumption.

Altogether, our results suggest that acetic zinc supplementation has some benefit by recovery of zinc pool in blood and diminishing the secretion inflammatory cytokines thus restoring impaired immune function in alcoholism.

Conclusions

Alcoholization led to zinc deficiency in blood and augmentation of the production of inflammatory cytokines IL-1 β and IL-6 in rats that is most evident at long-term ethanol exposure (for 21 days). Acetic zinc supplementation recovers zinc pool in blood and normalizes cytokine production that may be due to reduction of zinc deficiency and attenuating of oxidative stress thus leading to inhibition of inflammation. This preparation had beneficial effect when it has been used in prolonged alcohol intoxication.

These results support and extend on previous observations [12], suggesting the high potential of zinc be developed as an effective agent in the prevention and treatment of alcoholism.

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ВПЛИВ ОЦТОВОКИСЛОГО ЦИНКУ НА РІВЕНЬ ЦИНКУ ТА ІНТЕРЛЕЙКІНІВ 1β І 6 У СИРОВАТЦІ КРОВІ ЩУРІВ, ПІДДАНИХ ДІЇ АЛКОГОЛЮ УПРОДОВЖ 21 ДОБИ

Метою роботи було вивчити дію оцтовокислого цинку на динаміку рівню цинку та продукції прозапальних цитокінів (IL-1β і IL-6) у крові щурів, підданих дії етанолу упродовж 21 доби.Рівень цинку у сироватці крові було визначено атомно-адсорбційною спектрофотометрією. Рівень IL-1β і IL-6 було визначено з використанням наборів для імуноферментного аналізу (ELISA) ("Sigma", США).Було встановлено значне поступове зниження рівню цинку та підвищення вмісту IL-1β і IL-6 у сироватці крові тварин, яким вводили етанол, що набувало максимуму на 16-у і 21-у добу. Зміни рівню цинку та продукції IL-1β і IL-6 у тварин з алкогольною інтоксикацією повністю коректувалися після введення цинку, що було найбільш вираженим при тривалій дії етанолу. Показано, що рівень цинку у таких тварин зростав і перевищував контроль у 4,2 і 4,9 рази на 16-у і 21-у добу алкоголізації. Вміст IL-1β і IL-6 знижувався і нормалізувався на цих же етапах експерименту. Наші результати свідчать про те, що введення оцтовокислого цинку відновлює пул цього металу у крові і нормалізує продукцію прозапальних цитокінів, що може бути наслідком усунення цинкового дефіциту і пригнічення оксидативного стресу і, як наслідок, зменшення запалення.

Ключові слова. Етанол, хронічна алкогольна інтоксикація, цинковий дефіцит, прозапальні цитокіни, інтерлейкін 1β, інтерлейкін 6, оцтовокислий цинк.

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ВЛИЯНИЕ УКСУСНОКИСЛОГО ЦИНКА НА УРОВЕНЬ ЦИНКА И ИНТЕРЛЕЙКИНОВ 1β I 6 В СЫВОРОТКЕ КРОВИ КРЫС, ПОДВЕРГНУТЫХ ВОЗДЕЙСТВИЮ АЛКОГОЛЯ В ТЕЧЕНИЕ 21 СУТОК

Целью работы было изучить действие уксуснокислого цинка на диамику уровня цинка и продукции провоспалительных цитокинов (IL-1β и IL-6) в крови крыс, которых подвергали действию этанола в течение 21 суток. Уровень цинка в сыворотке крови был определен атомно-адсорбционной спектрофотометрией. Уровень IL-1β и IL-6 был определен с использованием наборов для иммуноферментного анализа (ELISA) ("Sigma", США). Установлено значительное постепенное снижение уровня цинка и повышение содержания IL-1β и IL-6 в сыворотке крови животных, которым вводили етанол, что достигало максимума на 16-е и 21-е сутки. Изменения уровня цинка и продукции IL-1β и IL-6 у животных с алкогольной интоксикацией полностью корректировались посля введения цинка, что было наиболее выраженным при длительном действии этанола. Показано, что урівень цинка у таких животных возростал и превышал контроль в 4,2 и 4,9 раза на 16-е и 21-е сутки алкоголизации. Содержание IL-1β и IL-6 снижалось и нормализировалось на этих ж етапах эксперимента. Наши результаты свидетельствуют о том, что введение уксускокислого цинка восстанавливает пул этого металла в крови и нормализирует продукцію провоспалительных цитокинов, что может быть результатом устранения цинкового дефицита и угнетения оксидативного стресса и, как следствие, уменьшение воспаления.

Ключевые слова: этанол, хроническая алкогольная интоксикация, цинковый дефицит, пртивовоспалительные цитокины, интерлейкин1β, интерлейкин 6, уксуснокислый цинк.