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Gamma-aminobutyric acid and brain-derived neurotrophic factor content in the brain structures of rats with alcohol dependence and under exercise

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The state of alcohol dependence is usually accompanied by emotional disorders, such as anxiety, depression, and aggressiveness. They arise against the background of disturbances in central neurotransmission and neurotrophic processes. Exercise is effective in restoring some damaged brain functions. The aim of our work was to identify disturbances in the g-aminobutyric acid (GABA) and brain-derived neurotrophic factor (BDNF) regulatory systems and the possibilities of their correction by exercise in rats with alcohol dependence. Alcohol dependence was modeled by ingesting food with alcohol at a dose of 1.25 g/kg body weight for 30 days, followed by alcohol withdrawal for 10 days. In rats under alcohol withdrawal, we found an imbalance of GABAergic activity between the frontal neocortex, hippocampus, and amygdala, a decrease in BDNF concentrations in the frontal neocortex, hippocampus, and serum, accompanied by increased anxiety levels. Wheel running during alcohol withdrawal (30 min daily for 10 days) restored the balance of GABA content in the brain structures and the reduced levels of BDNF (excluding reduced GABA and BDNF content in the frontal neocortex), and also reduced anxiety. Exercise increased hippocampal weight, which was decreased in alcohol-dependent animals. The negative correlation was found between indices of hippocampal weight and GABA concentration in hippocampus in intact and alcohol-dependent animals, which persisted even after exercise. The findings suggest that exercise is effective in restoring GABAergic and BDNF signaling impaired by alcohol intake. Restoration of synchronizing GABAergic regulation and BDNF levels contributes to anxiety reduction in alcohol-dependent rats.

Key words: GABA; BDNF; amygdale; hippocampus; frontal neocortex; alcohol dependence; anxiety; exercise.

INTRODUCTION

One of the most common causes of emotional and mental disorders is alcohol abuse, and the development of alcohol dependence often accompanied by depression, anxiety or aggressiveness. Chronic toxic effects of ethanol disrupt many processes in the brain, but particularly dramatically – neurotransmitter, neurotrophic and hormonal-modulatory regulatory systems [1-3]. γ-Aminobutyric acid (GABA) and brain-derived neurotrophic factor (BDNF) are among the most abundant and the most prominently studied bioregulators in the brain. GABA is not only the main inhibitory neurotransmitter in the central nervous system but also takes part in the regulation of synaptic plasticity [4, 5]. BDNF is a neurotrophic factor that is involved in the regulation of local neuroplasticity and maintenance of function in different neuronal populations [6, 7]. GABA and BDNF are involved in many regulatory processes, as well as in the regulation of each other's structural and functional activity. Moreover, GABA and BDNF play multifactorial roles as both regulators and targets of stress hormone signaling in the brain in alcohol withdrawal [8, 9]. All this indicates the crucial role of GABA and BDNF in the development of

pathology in the CNS and makes them important targets for the correction of emotional and mental disorders arising from the development of alcohol dependence.

Recently, growing evidences suggest on the beneficial effect of exercise on the recovery of processes associated with impaired brain function, in particular, as a result of alcohol abuse, as well as on the attenuation of craving to substances with addictive potential [10-12]. Much attention in these studies is focused on the role of BDNF and GABA, predominantly in the hippocampus, which is not surprising since the hippocampus is one of the key structures involved in the formation of emotions and memory, as well as a zone of active neurogenesis. However, it has been demonstrated varying effects of exercise on the expression of BDNF and its TrkB receptor in different brain structures of mice in control animals and on the background of long-term alcohol intake [12]. Therefore, we focused our research on studying changes in GABA and BDNF content in rat brain structures responsible for the regulation of emotional-motivational behavior under the influence of alcohol dependence and exercise.

The aim of our study was to understand the nature and degree of involvement of GABA and BDNF of the neocortex and limbic system in the maintenance of alcohol dependence and related anxiety, and to evaluate the possibility of correction of the identified disturbances by physical exercise.

METHODS

All procedures with experimental animals were performed in accordance with the General Ethical Principles of Animal Experiments in Ukraine and the European Commission Directive (86/609/EEC).

The studies were carried out on 35 nonlinear adult laboratory male rats weighting 250-300 g in a chronic experiment in four groups: intact rats (n = 8), rats with alcohol dependence in the state of alcohol withdrawal (n = 8), rats with voluntary wheel running (n = 8), rats with alcohol dependence in the state of alcohol withdrawal and voluntary wheel running (n = 11). Alcohol dependence modeling was performed by voluntary intake of food containing 1 ml of 24.0% ethanol solution at a dose of 1.25 g/kg body weight for 30 days. The rats were tested for alcohol preference in individual cages for 10 min by choosing a piece of bread with alcohol or water every 7 days. Withdrawal of alcohol was carried out for 10 days. The exercises were performed by rat running in a wheel for small animals for 30 min daily for 10 days and were applied both to rats with alcohol withdrawal and to rats not exposed to alcohol. The animals were euthanized immediately after the last exposure to running wheel.

The individual level of anxiety was determined using a multi-parameter method for assessing anxiety in rats based on the latent periods of behavioral reactions in response to created emotiogenic situations: “step-down” test, “pass-through-hole” test, time to leave the box, time to leave the “open field” center [13]. The individual anxiety level was calculated as a cumulative score of points obtained for each behavioral test. The level of anxiety was assessed in points (from 0 to 16) and was considered elevated with values above 7 points.

After brain removing, brain structures were extracted on ice according to the rat brain atlas [14], then were weighted and frozen in polypropylene tubes at -80ºC. The concentrations of GABA in homogenates of the hippocampus, amygdala, and frontal neocortex (FC), and BDNF in homogenates of the hippocampus, FC, prepared in ice-cold PBS (0.01 M, pH 7.4) followed by freeze-thaw cycle, and serum were determined using «Rat Gamma-Aminobutyric Acid (GABA)» ELISA kit («Puda Scientific CO, LTD», China), and «Rat BDNF (Brain Derived Neurotrophic Factor) ELISA Kit» (“Elabscience”, China) respectively according to the manufacturer’s protocols.

A statistical analysis was performed using «Statistica 6.0» software («Statsoft Inc.», USA,

2001). The data presented as the mean and standard deviation (x ± SD) for each group. One-way analysis of variance followed by the Tukey test was used to detect statistically significant differences between groups. Differences were considered significant at $P < 0.05$.

RESULTS

The individual anxiety level of alcohol-dependent rats increased on average 1.5 times (5.36 ± 0.31 points - baseline; 7.82 ± 0.55 points – under alcohol withdrawal ($F_{(2;\ 3.26)} = 4.12$; $P < 0.01$) (Fig. 1B). In alcohol-dependent rats with alcohol withdrawal, the GABA concentration in the amygdala increased by 23.9% ($F_{(2;\ 3.22)} = 4.80$; $P < 0.001$), whereas in the hippocampus it decreased by 30.1% when compared with the intact rat group ($F_{(2;\ 3.22)} = 3.46$; $P < 0.05$) (Fig. 2A). The decrease in GABA concentration in the FC of rats in alcohol withdrawal state was not statistically significant, although the ratio of the neurotransmitter content in the amygdala to that in the FC was 1.53 times higher than in the intact group. The ratio of GABA content in the amygdala to its content in the hip-

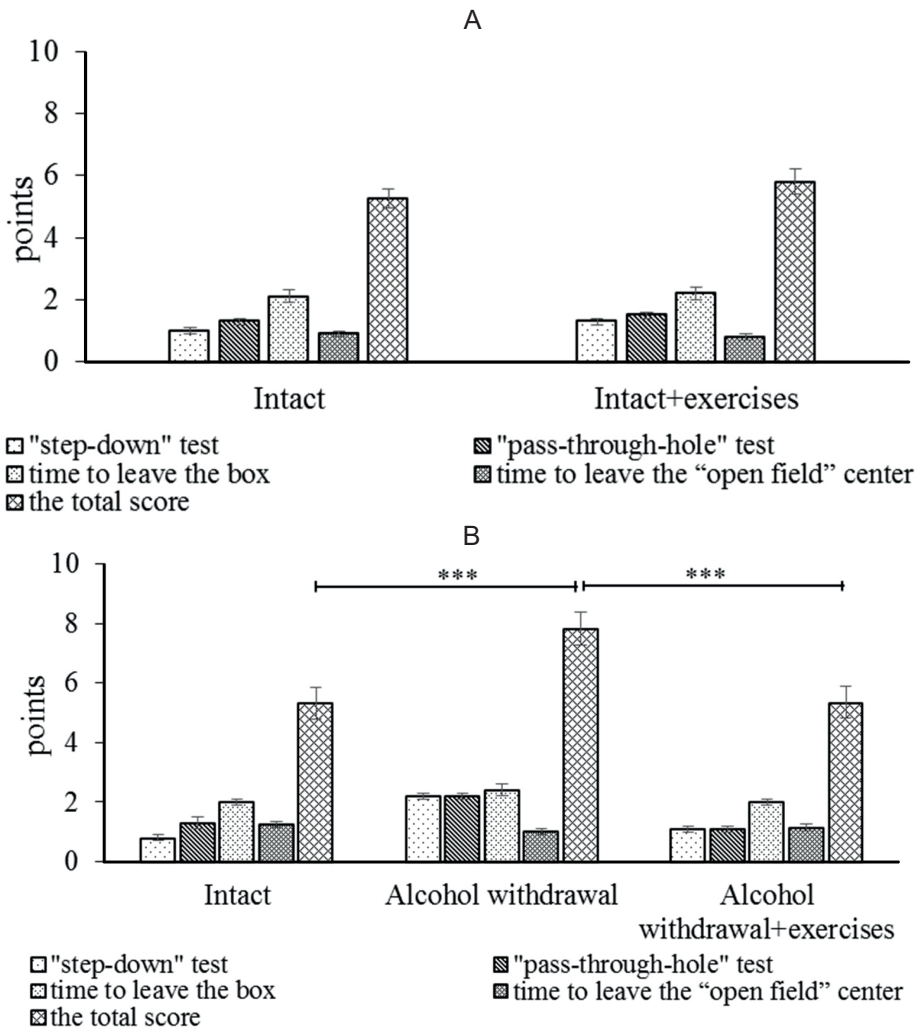

Fig. 1. Anxiety levels in rats under alcohol withdrawal and after exercises calculated based on results of tests: "step-down" test; "pass-through-hole" test; time to leave the box; time to leave the "open field" center; and the total score. A – in intact rats and in rats after running in a wheel for 30 min daily for 10 days. B – in intact rats, in rats under alcohol withdrawal without exercises, and after wheel running for 10 days under alcohol withdrawal. ***P < 0.01

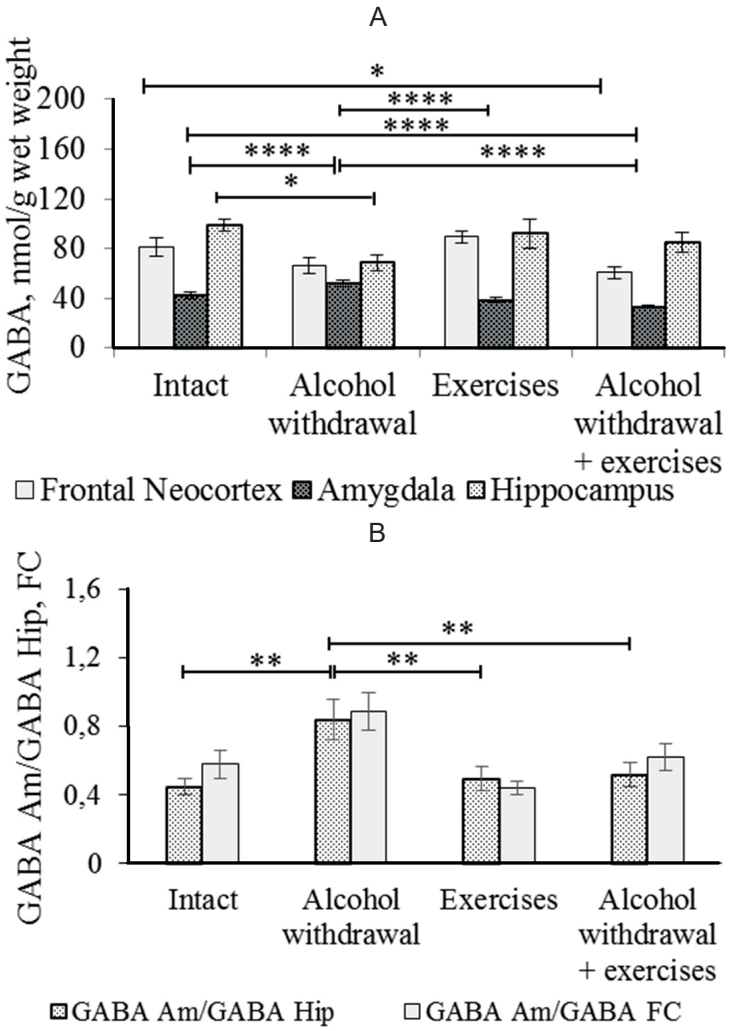

Fig. 2. GABA concentration and the ratio of GABA concentrations in the brain structures in rats under alcohol withdrawal, after running in a wheel for 30 min daily for 10 days and after wheel running for 10 days under alcohol withdrawal. A – GABA concentration in the frontal neocortex, amygdala, and hippocampus. B – the ratio of GABA concentrations between: amygdala and hippocampus; amygdala and frontal neocortex. Am – amygdala; Hip – hippocampus; FC – frontal neocortex. *P < 0.05, **P < 0.02, ****P < 0.001

pocampus was also 1.87 times higher in alcohol withdrawal rats than in the intact group ($F_{(2; 3.22)}$ = 4.17; P < 0.02) (Fig. 2B). Wheel running of rats not exposed to alcohol did not change the level of anxiety (5.25 ± 0.32 points – baseline; 5.80 ± 0.48 points – after wheel running) and had no significant effect on GABA content and its ratios in brain structures. However exercises during alcohol withdrawal led to a reduction in anxiety (7.82 ± 0.55 points – under alcohol withdrawal; 5.35 ± 0.53 points – after wheel running; $F_{(2; 3.26)}$ = 3.84; P < 0.01). At the same time, the balance of inhibitory activity between the amygdala and the hippocampus was restored ($F_{(2; 3.22)}$ = 3.43; P < 0.02) by reducing the elevated levels of GABA in the amygdala ($F_{(2; 3.22)}$ = 9.03; P < 0.001) and some restoring the reduced GABA levels in the hippocampus. In the FC, exercise did not cause recovery of the reduced during chronic alcohol intoxication GABA content (Fig. 2B).

Changes in BDNF levels as a result of alcohol withdrawal were similar: a decrease in the hippocampus by 27.1% ($F_{(2; 3.23)}$ = 3.35;

$P < 0.01$), and in blood serum by 22.6% ($F_{(2;\ 3.23)} = 5.22$; $P < 0.01$) (Fig. 3A). Wheel running of rats not exposed to alcohol led to an increase in the BDNF concentration in the FC by an average of 55.3% ($F_{(3;\ 2.85)} = 3.18$; $P < 0.01$) with no significant changes in the hippocampus and blood serum. Exercise had a different effect on alcohol-dependent rats in a state of alcohol withdrawal. Despite recovery of hippocampal ($F_{(2;\ 3.23)} = 5.24$; $P < 0.01$) and serum ($F_{(2;\ 3.23)} = 4.42$; $P < 0.01$) BDNF concentrations, neurotrophin level in the FC did not recover.

After wheel running for 30 min during 10 days, an increase in the weight of the hippocampus of animals was noted in rats that did not take alcohol, by 7.9%, (unreliably) and in rats with alcohol dependence, by 20.5% ($F_{(2;\ 3.23)} = 3.31$; $P < 0.05$) (Fig. 3B). Correlation analysis showed that in intact animals, hippocampal weight was negatively correlated with the concentration of GABA in the hippocampus. The same relationship was noted in rats in the state of alcohol withdrawal. Interestingly, the increase in hippocampal weight and the recovery of reduced GABA levels after wheel running did not change this relationship (Fig. 4).

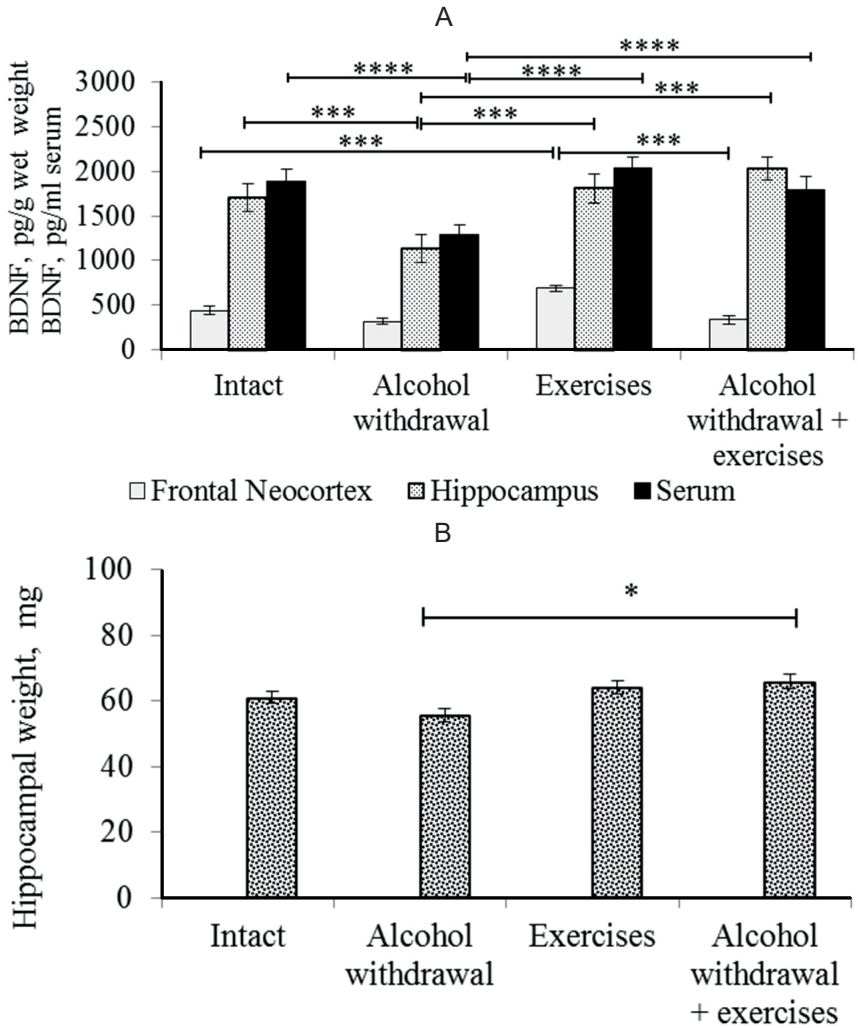

Fig. 3. BDNF concentration in the brain structures and serum, and the hippocampal weight in rats under alcohol withdrawal, after running in a wheel for 30 min daily for 10 days and after wheel running for 10 days under alcohol withdrawal. A – BDNF concentration in the frontal neocortex; hippocampus; and serum. B – hippocampal weight. *P < 0.05, ***P < 0.01, ****P < 0.001

DISCUSSION

Alcohol consumption affects multiple neurotransmitters and neurotrophic systems in the brain, in particular GABA and BDNF regulatory mechanisms. Acute alcohol exposure increases BDNF expression, as well as increases presynaptic GABA release and enhances postsynaptic $GABA_A$ receptors function in brain structures. Thus, ethanol produces a tonic $GABA_A$R-mediated current in many CNS neurons, which determines the antidepressant and anxiolytic properties of alcohol intake [1, 15-17]. The effects of acute alcohol intake are reversible, while chronic alcohol consumption has dramatic consequences, as alcohol withdrawal does not lead to full recovery of impaired functions, and the effects of chronic ethanol are critical for the development of ethanol dependence.

Chronic ethanol exposure induces many neuroadaptive changes within GABAergic synapses in a brain region-specific manner. Both increases and decreases in GABA release are observed in several brain regions [16, 17]. The amygdala is an important center for the regulation of emotional motivational behavior and states of dependence on substances with an

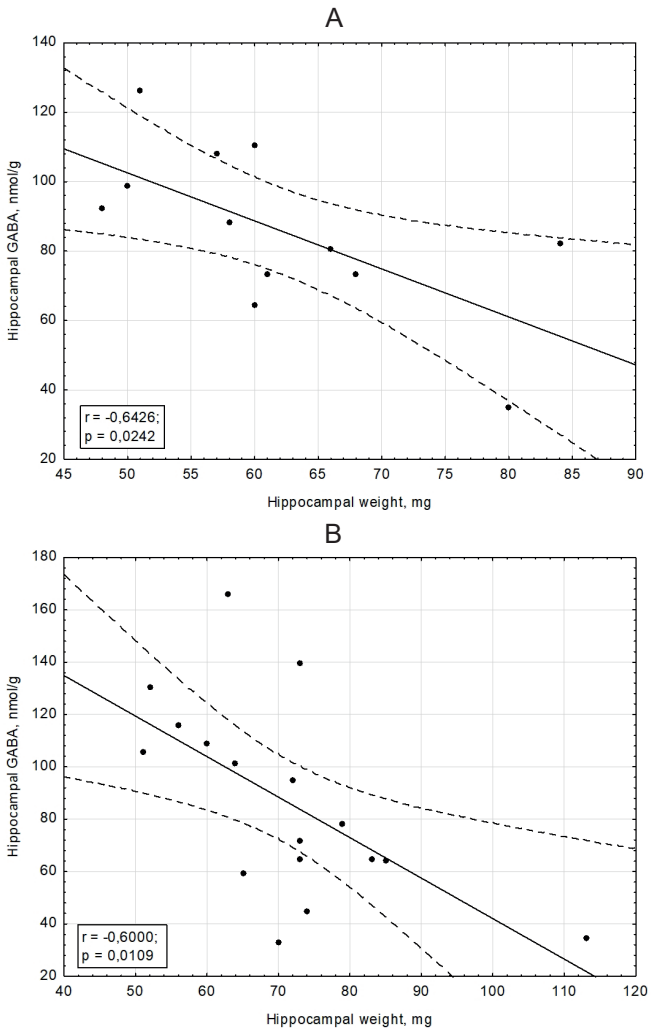

Fig. 4. Correlations between the hippocampal weight and GABA concentration in the Hippocampus. A – in intact rats and in rats under alcohol withdrawal without exercise. B – in rats after running in a wheel for 30 min daily for 10 days and after wheel running for 10 days under alcohol withdrawal

addictive potential. The amygdala is the site of integration and evaluation of emotional significance of ascending information from subcortical structures and descending regulatory influences from cortical areas. GABAergic interneurons in the amygdala are important components for keeping a balance between neuronal excitation and inhibition. The principal glutamatergic neurons of amygdala are firmly regulated by GABAergic inhibitory neurons. Disturbances of GABAergic inhibition in the amygdala can lead to emotional dysregulation such as increased anxiety and mental disorders [18]. Roberto et al. [16] found that GABA transmission was increased in the amygdala as a result of chronic alcohol exposure and remained so during acute withdrawal. A partial explanation for this can be found in the fact that chronic ethanol alters the expression of specific GABA receptor subunits at both the transcriptional and translational levels in several brain regions in different way [19].

Steroid hormones also have the ability to alter GABAergic mediation in a specific manner. Liu et al. [20] have shown that chronic stress exposure triggers enduring loss of tonic but not phasic $GABA_A$ receptor currents in amygdala, which is dependent on stress-evoked corticosterone production with subsequent glucocorticoid receptors activation. It appeared that the enduring loss of tonic inhibition in mice exposed to chronic stress was not due to changes in GABA diffusion or activity of GABA transporter. The exact cellular mechanisms for this are not yet known. However, this could be due altering the expression of the δ subunit of the $GABA_A$ extrasynaptic receptor by activating the glucocorticoid receptors which results in a loss of tonic inhibition in the basolateral amygdala (BLA) and correlates with the increased anxiety-like behavior [20, 21].

It is well known that states of alcohol dependence and withdrawal are stress states associated with hyper-production of glucocorticoids [22]. Therefore, the above-mentioned results may explain our findings about an increase in the GABA content in the amygdala of alcohol-dependent rats with elevated anxiety levels. Apparently, GABAergic dysfunction in the rat amygdala during alcohol withdrawal may be associated not only with the increased concentration of the inhibitory neurotransmitter in a whole amygdala but with GABA imbalance within the amygdala evoked by disturbances particularly in extrasynaptic GABAergic regulation.

It has been shown that stress-derived neurosteroid hormones have different effects on GABAergic transmission in different brain regions. For example, chronic administration of dexamethasone upregulates GABA release from GABAergic neurons in the amygdala [23], but chronic stress reduces the number of parvalbumin-positive GABAergic neurons in the hippocampus [24]. We detected multidirectional changes in GABA content in brain regions of alcohol-dependent rats in the state of alcohol withdrawal: a decrease in the hippocampus and an increase in the amygdala. The ratio of GABA content in the amygdala to its content in the hippocampus and in the frontal cortex increased compared to intact rats. Therefore, we suppose that not only disturbances in GABAergic transmission within the amygdala, but also imbalance of GABAergic activity between the amygdale and frontal neocortex and between the amygdala and hippocampus, in which GABAergic influences of the amygdala dominate, contribute significantly to the maintenance of alcohol dependence and anxiety.

Amygdala has a highly complex organization of the internal network of GABAergic neurons, which mutually influence each other, and the principal glutamatergic neurons. The central mechanisms underlying fear and anxiety states are similar in animals and humans, with fear and anxiety processes are mediated by partially overlapping neuronal substrates. Their relationships are largely unexplored. However, some assumptions can be made based on the data already available. BLA has a quite compact organization of intermingled fear neurons and extinction neurons that form discrete neuronal circuits regulating the expression and extinction

of fear response. Fear and extinction neurons are differentially connected with the hippocampus and the medial prefrontal cortex, two brain areas implicated in fear and anxiety responses [25, 26].

The fear expression and renewal of extinguished fear are hippocampus dependent. The neural circuit for regulating fear expression includes direct hippocampal glutamatergic input to the BLA, which selectively targets fear neurons and/or to the central amygdala. The other indirect projection to the BLA consists of a circuit of excitatory neurons from the hippocampus to the prelimbic cortex, where they switch to glutamatergic neurons targeting BLA cells. Excitation of these neurons is synchronized [25-28].

The neural circuit for regulating fear extinction includes bi-directional connections between the BLA and infralimbic cortex. Extinction pathways could directly inhibit fear pathways locally within the amygdala or on subdivisions of the medial prefrontal cortex, and specific GABAergic neurotransmission plays an important role in this process. Hippocampal GABAergic long-range projection neurons have been suggested to coordinate and synchronize rhythmic activity patterns with other brain regions [25-27, 29].

Thus, our findings about the decrease in GABA concentration in the hippocampus and frontal cortex of rats during alcohol withdrawal may reflect the attenuation of synchronizing inhibitory influences in these brain areas, this may contribute to the disinhibition of fear neurons in BLA and fear expression [26]. This explains the state of increased anxiety in alcohol dependent rats, as shown in our current study. The described mechanisms can play an important role in maintaining the state of alcohol dependence, namely, the desire to relieve anxiety with the next dose of alcohol.

BDNF is a local neurotrophic regulator, and a crucial factor for proper synaptic plasticity and connectivity in the adult brain. Alcohol abuse is perceived by the body as stress. Stress-induced changes in BDNF signaling lead to altered synaptic plasticity due to increased methylation of BDNF DNA, leading to decreased BDNF expression, which ultimately raises the risk of increasing both anxiety and alcohol consumption. Chronic alcohol treatment leads to a long-lasting reduction of cortical BDNF expression, specifically in the medial prefrontal cortex [15, 30].

In our research, we found the same decrease in BDNF concentration in the hippocampus, frontal neocortex, and serum by 23 to 28% in alcohol-dependent rats during alcohol withdrawal. These data indicate that the attenuation of BDNF expression both in the brain and in the periphery of the body as a result of long-term alcohol exposure is persistent and remains for 7-10 days after alcohol withdrawal, which does not contribute to the full recovery of brain function during this period.

Despite the similar direction of changes, we did not find a clear correlation between the levels of GABA and BDNF content in the brain, which is one of the evidences of the complexity of interaction between these regulators. BDNF influences the development and functioning of the GABAergic network, which in turn controls BDNF levels. BDNF regulates the maturation of GABAergic synapses, genes transcription of $GABA_AR$ subunits, the expression of the presynaptic GABA synthesis enzyme GAD65 (glutamic acid decarboxylase), and GABA transporters (GATs). The surface expression of the major GABA transporter-1 (GAT-1) is carried out by both neurons and astrocytes. However, the neurotrophin was found to inhibit GAT-1-mediated GABA transport at the nerve endings, suggesting that this effect delays GABA uptake by the nerve terminal, thereby enhancing synaptic efficiency of GABA [8, 31]. In turn, GABA may decrease the glutamate-induced augmentation of BDNF mRNA expression [9]. However, the trophic effect of GABA is manifested in particular in that it triggers the release of BDNF after stimulation of $GABA_A$ and GABAв receptors [8].

The decrease in BDNF concentration in the hippocampus, frontal cortex and serum indicates a general weakening of neurotrophic function,

which does not recover after 7-10 days of alcohol withdrawal in alcohol-dependent rats. Apparently, this effect, initially caused by the toxic effect of ethanol, is one of the important reasons for the imbalance of the GABAergic activity of the brain and the weakening of its synchronizing influences, leading to increased anxiety.

The role of the voluntary exercise in the correction of psycho-emotional disorders has been extensively studied for last decades. Various studies show that exercise by different mechanisms leads to stimulation of neurogenesis, which actively contributes to the restoration of emotional and cognitive functions. Regulatory mechanisms of neuroplasticity are closely related to the activation of glutamatergic and neurotrophic processes [32].

The GABAergic system is also a component of mechanisms of neuroplasticity and neurogenesis. Neurogenesis plays a particularly important role in the hippocampus, where the active formation of new neurons takes place. The GABAergic system of the hippocampus is involved in this process in different ways through the system of its specific receptors [33-35]. The local hippocampal glutamatergic circuitry stimulates proliferation of neural progenitor cells. At this stage, local parvalbumin interneurons contribute to inhibition of local glutamatergic circuitry through tonic GABAergic signaling. Progenitor cells proliferation is suppressed largely by activation of $GABA_B$ receptors [34, 35]. BDNF signaling reduces the excitability of parvalbumin-positive interneurons [8], thereby supporting glutamatergic stimulation of neurogenesis. GABA is known to act as an inhibitory neurotransmitter in mature neurons mainly through $GABA_A$ receptors. However, in immature cells, activation of $GABA_A$ receptors elicits a depolarization of the membrane potential. This excitation initiates an increase of $[Ca^{2+}]_i$ and the expression of NeuroD, a positive regulator of neuronal differentiation. Thus, GABA activates the process of progenitor cells differentiation [33].

In our experiment, wheel running led to recovery of the disturbed balance of GABA content in the brain structures, reduced BDNF levels in the hippocampus and serum, as well as to decrease in anxiety. Previously, we have shown that wheel running also leads to a decrease in the level of alcohol dependence in rats [22]. Thus, our data demonstrated a positive effect of exercise on functioning of GABA and BDNF signaling impaired by long-term alcohol intake.

One of the characteristics of the physiological state of the organ is its weight. With the development of alcohol dependence, the weight or volume of the hippocampus most often decreases with varying degrees of certainty. In our studies, we have always observed a decrease in hippocampal weight in a group of alcohol-dependent rats. In this study, however, the decrease was not statistically significant. Running in a wheel had a significant effect on hippocampal weight: a 7.9 % increase in alcohol-free rats and a 20.5 % increase in alcohol-dependent animals.

Analyzing the results obtained, we can conclude that the increase in hippocampal BDNF levels due to exercise contributes to the stimulation of neurogenesis.

At the same time, we have identified an interesting pattern. The correlation between hippocampal weight and GABA concentration always remained negative in intact animals and regardless of the decrease in hippocampal weight and GABA content in alcohol-dependent rats or of the increase in hippocampal weight and recovery of GABA levels as a result of exercise. Thus, it can be hypothesized that GABA also plays a role as a neurogenesis-restraining factor.

The GABAergic system plays an important regulatory (synchronizing) role in maintaining the emotional activity of the brain, which is disturbed during the development of alcohol dependence. The imbalance of GABAergic activity between the neocortex, hippocampus, and amygdala with a decrease in the GABA level in the neocortex and hippocampus may indicate a disturbance of the synchronizing GABAergic control at the level of these structures and activation of fear neurons in the amygdala. Increased GABA content in the amygdala may

hinder the rapid adaptive switching of fear and extinction neurons, which is expressed in the protracted nature of anxiety in alcohol-dependent rats after alcohol withdrawal.

The revealed disturbances of GABAergic activity are accompanied by a long-term weakening of BDNF neurotrophic function, which does not recover after alcohol withdrawal for up to 10 days, resulting in misalignment of synchronized brain activity, which can be expressed, as in our experiment, in an increased anxiety level.

The use of voluntary wheel running has demonstrated its effectiveness in correcting the imbalance of GABAergic influences in brain structures and normalizing of BDNF levels disturbed by long-term alcohol intake. Increased hippocampal weight and BDNF concentration in the hippocampus reflect an activating effect of exercise on neurogenesis in this brain structure.

Negative correlation between the hippocampal weight and GABA concentration in the hippocampus in all examined groups may indicate the importance of the restraining effects of GABA in the regulation of neurogenesis.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ВМІСТ ГАММА-АМІНОМАСЛЯНОЇ КИСЛОТИ ТА МОЗКОСПЕЦИФІЧНОГО НЕЙРОТРОФІЧНОГО ФАКТОРА В СТРУКТУРАХ ГОЛОВНОГО МОЗКУ ЩУРІВ ІЗ АЛКОГОЛЬНОЮ ЗАЛЕЖНІСТЮ ТА ПІСЛЯ ФІЗИЧНИХ НАВАНТАЖЕНЬ

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Стан алкогольної залежності зазвичай супроводжують емоційні розлади, такі як тривожність, депресія, агресивність. Вони з'являються на тлі порушень центральних нейромедіаторних та нейротрофічних процесів. Фізичні вправи ефективні у відновленні деяких пошкоджених функцій мозку. Метою нашої роботи було виявлення порушень у регуляторних системах системах γ-аміномасляної кислоти (ГАМК) і мозкоспецифічного нейротрофічного фактора (BDNF) та можливості їх корекції фізичним навантаженням у щурів із алкогольною залежністю,яку моделювали за допомогою вживання їжі з алкоголем у дозі 1,25 г/кг маси тіла протягом 30 днів, з подальшою відміною протягом 10 днів. У щурів з відміною прийому алкоголю виявлено дисбаланс ГАМК-ергічної активності між фронтальним неокортексом, гіпокампом і мигдалиною, зниження концентрації BDNF у фронтальному неокортексі, гіпокампі та сироватці крові, що супроводжувалось підвищенням рівня тривожності. Біг у колесі під час відміни алкоголю протягом 10 днів по 30 хв щоденно відновлював баланс вмісту ГАМК у структурах головного мозку та знижував BDNF (за винятком зниження обох показників у фронтальному неокортексі), а також зменшував тривожність. Фізичні вправи збільшували масу гіпокампа, яка була зменшена у алкогользалежних тварин. Виявлено негативний кореляційний зв'язок між показниками маси гіпокампа та концентрації ГАМК у гіпокампі інтактних та алкогользалежних тварин, який зберігався навіть після фізичних вправ. Отримані результати дають змогу вважати фізичні вправи ефективними для відновлення ГАМК-ергічної та BDNF- сигналізації, порушених вживанням алкоголю. Відновлення ГАМК-ергічної синхронізації та вмісту BDNF сприяє зниженню тривоги у алкогользалежних щурів.

Ключові слова: ГАМК; BDNF; мигдалеподібне тіло; гіпокамп; фронтальний неокортекс; алкогольна залежність; тривога; фізичні вправи.

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