Hypoglycemic and epigenetic effects of alcohol in the regulation of cognitive functions: experimental data and literature review

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Abstract: - This paper is devoted to the importance of relative functional hypoglycemia induced by long-term mental load and the epigenetic action of ethanol in the regulation of cognitive function and disruption of the error monitoring and processing system (EMPS) in people during the period of abstinence (sobriety). The study was carried out using biochemical and psychophysiological techniques as well as analysis of scientific data retrieved from the databases of Scopus and PubMed on the mechanism of action of alcohol on cognitive functions and the activity of EMPS, through its effects on glucose metabolism/blood glucose level, and the epigenome of brain cells. Based on our own research and analysis of the literature for the period 1940–2014, we present evidence about the role of hypoglycemia and epigenetic action of ethanol in the regulation of cognitive functions and EMPS in sober individuals. The acquired data confirm our previous hypothesis and indicate that long-term regulation of cognitive functions and the activity of EMPS caused by ethanol in sober individuals occur through its effect on the epigenetic profile and the "glycemic memory" of neurons.

Key-Words: - Hypoglycemia, glycemia, epigenetics, epigenostressor, error monitoring and processing system, cognitive function, ethanol (alcohol)

1 Introduction

Alcohol is the most common psychoactive substance used by humans in the world today. The negative and positive effects of alcohol consumption have been documented in a number of studies [1, 2]. But literature evidences over the past decades have shown that the negative effects of alcohol consumption supersede the positive effects. The negative social and health consequences of alcohol use and abuse have been repeatedly established [1-3]. Alcohol use causes of a number of mental and somatic disorders and diseases [1, 2]. Alcohol use is

the chief cause of many road accidents, aviation and other catastrophic disasters. The main factors leading to road traffic, flight and other accidents are human erroneous actions of the driver, pilot or pedestrian (so-called "human factor"), especially in a state of intoxication. Detection of erroneous actions (errors) and their timely correction in humans are controlled by the error monitoring and processing errors (EMPS). EMPS [2, 4, 5] is represented by neurons of the substantia nigra of the midbrain, the basal ganglia and the cerebral cortex. The chief players in EMPS are believed to be neurons of anterior cingulate cortex and dopaminergic system.

It is known that acute alcohol intoxication leads to disorders in cognitive function and activity of EMPS [4, 5]. The mechanism of disruption of EMPS by ethanol, in sober individuals (people in a state of alcohol abstinence), for example is not clear. Available evidence suggests possible direct disruption of EMPS caused by ethanol in humans in a state of acute or chronic alcohol intoxication or the disruption may be indirect [4]. We [2, 6] developed the hypothesis of indirect disruption of EMPS caused by ethanol. This indirect disruption persists over a period of time in a sober person. The main tenets of our hypothesis explain the indirect disruption of EMPS by ethanol through its effect on metabolic processes of neurons – regulation of the level of their main energy substrate (glucose) in the blood. Increased erroneous actions in sober people during mental work has been associated with the development of functional relative hypoglycemia or even neuroglycopenia, which in turn may determine the level of activity of dopaminergic neurons in the substantia nigra as a main component EMPS. The number of error commission and pattern of glycemic regulation in experimental condition at the initial testing and after 2 hours of mental work significantly vary in sober respondents and non-drinkers [1,2,6]. This identified fact is an open question that has not been addressed. Notwithstanding, however, it is likely that the discrepancies in error commission rate and pattern of glycemic regulation could be, possibly, explained by the pleiotropic action of ethanol (and its metabolites) and hypoglycemia (provoked by prolonged mental activity in a sober person) as exogenous and endogenous epigenetic factors in the regulation of EMPS.

Epigenetic factors can cause post-translational modifications of the DNA and nuclear proteins, and lead to relatively lasting changes in the pattern of gene expression [7, 8]. Epigenetic influence is involved in the development of various pathologies of the brain, including alcoholism [8-10], transgenerational transfer of some characteristics and behavior. This indicates that alcohol's action on the epigenetic profile of cells could induce long lasting effects (or "marks") on epigenetic regulation of functions in a sober person [8, 11, 12].

The aim of this work was to investigate the role of functional relative hypoglycemia, induced by long-term mental load as well as the epigenetic action of ethanol in the regulation of cognitive functions and activity of EMPS in a sober person.

2 Materials and Methods

The study was conducted with the voluntary, informed, written consent of 27 male students of the Belarusian State Medical University: 19 young men, who were social drinkers but were in their period of abstinence (sober persons) and 8 nondrinkers.

Mental load was induced for a period of 9 hours according to recommended protocol [1, 2]. It included determination of glycemia and cognitive functions (memory, attention, thinking) in the respondents on fasting in course of prolonged mental activities (at 2, 4 and 6 hours), followed by 75 g of glucose load after 2 hours of rest. A more detailed description of the study design used is reported [2].

Statistical and correlation analyses were performed using the Statistical Package for the Social Science, version 16 for Windows. The level of significance was set at $p < 0.05$.

To clarify our earlier formulated hypothesis [6] about the long-term regulation of cognitive functions and activity of EMPS by ethanol, induced by its influence on the epigenetic profile of neurons and their "glycemic memory", scientific data from databases of Scopus and PubMed between the period "1940 and 2014" were analyzed. The following keywords were used: epigenetics and memory (or cognition/cognitive function); epigenetics and alcohol (or glycemia); alcohol and memory (cognition/cognitive function); epigenetics and error monitoring (or processing); alcohol and error monitoring (or processing); glycemia and error monitoring (or processing). Literature search strategy and selection criteria were based on the relevance of the retrieved information to the subject of this paper. Methodological approach for the literature review stage was conducted according to a previous layout [13]. The reference list shows only a few of the published papers that were retrieved during the search processes.

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3 Results and Discussion

All students who participated in the study were divided into two groups: non-drinkers (those that did not consume alcoholic beverages of any kind) and sober respondents (those that consume alcohol, and with a frequency of 1 per month to 3 times a week. The reported dose of alcohol consumption by the respondents was from 10 to 60 (38 ± 4) ml per session dose, and monthly – 10-480 (94 ± 26) ml (values are in absolute ethanol).

TABLE 1. Number of errors (error commission) and their dynamics during mental work (M ± m) of non-drinkers and sober people, based on the attention test "correction probe" and the tests on memory and thinking capacity

Testing	Number of error commission on correction probe		Total number of error commission in the tests on "memory and thinking"	
	Non-drinkers	Sober respon-dents	Non-drinkers	Sober respon-dents
Initial	2.8 ± 0.8	15.2 ± 3.5 ☼	11.3 ± 0.9	13.2 ± 1.0
After 2 h of work	2.4 ± 0.7	18.2 ± 4.1 ☼☼	10.6 ± 0.8	14.7 ± 1.2 ☼
After 4 h of work	3.1 ± 0.7	25.1 ± 4.9 ☼☼	10.6 ± 0.7	14.0 ± 1.2 ☼
After 6 h of work	2.6 ± 0.7	33.2 ± 7.1 *☼☼	10.6 ± 0.6	14.4 ± 1.3 ☼
After 2 h of rest	2.5 ± 1.1	23.3 ± 4.2 ☼☼	10.6 ± 0.9	12.7 ± 1.5

Notes: sober respondents (n = 19) scored on the AUDIT test, 5.05 points, and the duration of their sober state ranged from 1 to 4 weeks before the study. The non-drinkers (n = 8) scored zero point on the test "AUDIT", meaning that they do not consume alcohol. *p <0.05; ** – p <0.01 compared with students in its own group at the initial testing; ☼ – p <0.05; ☼☼ – p <0.01 compared with similar data of non-drinkers at the same phase of testing. Values were calculated by Student's test.

Analysis of the number of errors in the test on attention and on memory and thinking (Table 1) during prolonged mental work on fasting showed significant differences in the performance of both groups of respondents. The level of erroneous actions on attention test (Table 1) in sober respondents was 5–13 times higher than that of non-drinkers at all phases of the study. On the tests on short-term visual and auditory memory, thinking and operant memory, significant differences between the performances of both groups of respondents during mental work were less pronounced (Table 1). This indicates that people who consume alcohol, even during the period of abstinence, suffers primarily from dysfunction of active attention.

A higher number of errors commission by sober people on attention test and a significant increase in its dynamics during mental work (Table 1) indicate a fairly long duration of the negative effects of ethanol on the effectiveness of mental activity and the respondents' state of active attention. These facts point to the long-term (at least 4 weeks sober state), negative modulation of EMPS by ethanol in humans.

TABLE 2. Scanning speed of the symbols and the dynamics of its change with respect to the initial value (M ± m) in non-drinkers and sober people on the attention test "correction probe"

Testing	Scanning speed of symbols, symbol/second		Dynamics, symbol/second	
	Non-drinkers	Sober respon-dents	Non-drinkers	Sober respon-dents
Initial	4.54 ± 0.22	5.57 ± 0.19☼☼	4.54	5.57 ☼☼
After 2 h of work	5.15 ± 0.22	6.59 ± 0.17**☼☼	+ 0.61 ± 0.09 *	+1.02 ± 0.07 **☼☼
After 4 h of work	5.58 ± 0.31 *	6.90 ± 0.14**☼☼	+ 1.04 ± 0.11 **	+ 1.33 ± 0.09 **☼
After 6 h of work	5.96 ± 0.47 *	7.37 ± 0.20**☼	+ 1.42 ± 0.15 **	+ 1.80 ± 0.12**
After 2 h of rest	5.69 ± 0.33 *	7.26 ± 0.20**☼☼	+1.15± 0.12*	+1.69 ± 0.12 **☼

Notes: Designations are the same as in Table 1.

Effectiveness of mental performance is often limited by the speed of task execution [14]. This limitation of speed of performance is necessary for the permanent monitoring of results and errors of ongoing/current activities (error monitoring) and timely correction of errors (error processing). Excessive increase in the speed of mental processes is often accompanied by an increase in the number of erroneous actions [2, 6, 14]. Retrieved research data have shown that the speed of scanning (viewing) through letters or symbols by sober respondents on attention test is 22.7–28.0% faster

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than non-drinkers, at all phases of the study on prolonged mental work on fasting (Table 2). Analysis of the dynamics of the increasing speed of viewing symbols during work and after rest led to further establish that this indicator in sober respondents is even more pronounced (23.1–67.2% higher) compared with non-drinkers.

Along with the increase in the speed of viewing symbols during mental performance (Table 2) of sober people, there was a sharp decline in mental effectiveness, as evidenced by the increase in the number of erroneous actions (Table 1). Similar results were obtained by other authors. Reference [14] showed that an increase in the speed of reaction in humans after acute alcohol administration is accompanied by increase of the number of erroneous actions.

reflecting dysfunction of attention and EMPS activity (Table 3).

Rank correlation analysis showed a pronounced increase in the dependence of the scanning speed (speed of reaction) on the frequency, single and monthly doses of alcohol in sober respondents at all phases of the experiment. This average strength of direct significant correlation in the Spearman test was observed in 100% of cases (Table 3) and corresponded to that of a larger sample of respondents from 54 young men in our previous study [2]. Linear correlation analysis showed that the main factor that caused increased speed of mental work in sober respondents was the single dose of previously consumed ethanol. The calculated direct contribution of the aftereffect of a single dose of ethanol on reaction speed of the sober respondents ranged from 19.9% (r = 0.446; p = 0.020) to 38.9% (r = 0.624; p = 0.001). Correlation analysis between the reaction speed and the number of erroneous actions showed the presence of an average strength direct relationship between these parameters (Table 3). The contribution of high reaction speed to reduced efficiency of attention ranged from 16.4% to 29.3% (Table 3).

TABLE 3. The relationship between the indicators of ethanol consumption, the number of errors and speed of scanning the letters on the attention test at initial, in the course of mental work and rest

Correlating pairs	Rank (ρ) and linear (r) correlation				
	Initial	2 h of work	4 h of work	6 h of work	2 h of rest
Per session ethanol dose – number of error on attention test	ρ=0.354 P=0.070	ρ=0.548 * P=0.003	ρ=0.609 * P=0.001	ρ=0.577 * P=0.002	ρ=0.542 * P=0.004
Frequency of alcohol use – number of errors on attention test	ρ=0.592 * P=0.001	ρ=0.711 * P=0.000	ρ=0.764 * P=0.000	ρ=0.772 * P=0.000	ρ=0.685 * P=0.000
Monthly ethanol dose – number of errors on attention test	ρ=0.467 * P=0.014	ρ=0.630 * P=0.000	ρ=0.684 * P=0.000	ρ=0.676 * P=0.000	ρ=0.599 * P=0.001
Per session ethanol dose – scanning speed on the attention test	ρ=0.427* P = 0.026	ρ=0.597* P = 0.001	ρ=0.650* P = 0.000	ρ=0.445* P = 0.020	ρ=0.477* P = 0.012
Frequency of alcohol use – scanning speed on the attention test	ρ=0.506* P = 0.007	ρ=0.650* P = 0.000	ρ=0.604* P = 0.001	ρ=0.395* P = 0.042	ρ=0.511* P = 0.006
Monthly ethanol dose – scanning speed on the attention test	ρ=0.463* P = 0.015	ρ=0.617* P = 0.□01	ρ=0.634* P = 0.000	ρ=0.408* P = 0.035	ρ=0.475* P = 0.012
sca□ning speed – number of errors on the attention test	r = 0.541* P = 0.004	r = 0.486* P = 0.012	r = 0.411* P = 0.037	r = 0.347 P = 0.083	r = 0.405* P = 0.040
	ρ = 0.367 P = 0.060	ρ = 0.611* P = 0.001	ρ = 0.601* P = 0.001	ρ = 0.377 P = 0.057	ρ = 0.465* P = □.017

Rank correlation analysis identified the most frequent and pronounced significant relationship of indicators of alcohol consumption with the state function of attention in 96.7% of cases (Table 3), short-term visual and auditory memory in 40.0% and 6.7%, respectively, thinking and operant memory in 23.3% of cases. These findings support the notion that active attention is the most vulnerable function to the long-term negative effects of alcohol. During mental work, the relationship of indicators of alcohol consumption and the number of errors on attention test significantly increased,

The obtained evidence suggests a long duration of conserved effects of exogenous ethanol (up to 4 weeks – after complete elimination of the consumed ethanol from the blood). The results also support the notion that ethanol is responsible for disrupting feedback mechanisms, and thus, inhibits the

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function of detection of (monitoring) erroneous actions by EMPS [5]. As a result of disruption of EMPS activity, the reaction speed of mental performance increases (Table 2), but its effectiveness is sharply reduced (Table 1).

The lack of statistical significance of the relationship between speed and quality characteristics of the test on attention after 6 hours of work (Table 3), and the significant changes in the dynamics of the relationship of the indicators during mental work indicate the importance of taking into consideration other factors, in particular, the processes of learning and energy supply of the working brain. A significant increase in reaction speed in both groups of respondents (Table 2) during periods of retest indicates a phenomenon of learning. However, the most effective learning occurred in non-drinkers, as the process of acceleration of performed standard tasks (Table 2) were not accompanied by an increase in the number of error commission (Table 1). In sober respondents, learning process was less effective, because the increase in reaction speed by 30% (Table 2) was accompanied by a sharp increase in the number of error commission by 118% (Table 1). One of the chief reasons for this phenomenon may be disorders of energy supply of the working neurons. This, in particular, shows that there is tendency to a decrease in the number of error commission in the sober respondents after 2 hours of rest following administration of 75 g of glucose (Table 1).

In standard conditions, the main energy source for the functioning of the nervous system is glucose [15, 16]. The consumption of glucose by the brain, from the blood in a state of rest is 5–7 g/h and increases by 1.1–2.0 times (up to 12 g / h) during functional activation (such as in mental activity), depending on the type and intensity of work [17, 18]. Research has shown significant differences in the dynamics of glycemia and the absolute level of glucose in the blood after 4 and 6 hours of mental work between indicators of the non-drinkers and sober respondents (Table 4 and Fig. 1). In non-drinkers, there was a continuous significant increase in blood glucose throughout the period of mental work (Table 4), which can be described as a phenomenon of working functional hyperglycemia. In sober respondents, increase in glycemia was observed only after the first 2 hours of mental work. After 6 h of mental work from the start of the experiment, significant hypoglycemia (–0.55 ± 0.24 mmol/l in relation to the initial level) was observed. Moreover, some of the respondents even had neuroglycopenia as blood glucose was less than 3 mmol/l. Such a state of lowering blood glucose during mental work may be described as functional relative hypoglycemia.

Linear and rank correlation analysis showed a negative average strength or strong relationship between parameters of alcohol consumption and blood glucose in the respondents during mental work. The negative effects of alcohol increased during mental work and its contribution to the dynamics of blood glucose (relative functional hypoglycemia in working sober respondents) ranged from 18.1% ($r = – 0.425$; $p = 0.027$) to 64.8% ($r = – 0.805$; $p < 0.001$). Given that most of the sober respondents occasionally consumed alcohol [2] and in some cases tend to break their dietary regimen [19], skipping breakfast, thus, we can assume that episodes of relative functional hypoglycemia occur somewhat regularly and can significantly disrupt energy supply needed for the working neurons and their functional activity.

TABLE 4. Concentration of blood glucose and its dynamics (M ± m) in relation to the initial level in non-drinkers and sober respondents

Time of blood glucose sampling	Glycemic level, mmol/l		Dynamics of glycemia, mmol/l	
	Non-drinkers	Sober respon-dents	Non-drinkers	Sober respon-dents
Initial	4.24 ± 0.19	4.54 ± 0.15	–	–
After 2 h of work	4.91 ± 0.15 *	4.82 ± 0.13	+ 0.67 ± 0.08 **	+ 0.28 ± 0.10 *⚙
After 4 h of work	5.40 ± 0.18 **	4.52 ± 0.11 ⚙⚙	+ 1.16 ± 0.17 **	- 0.01 ± 0.14 ⚙⚙
After 6 h of work	5.78 ± 0.13 **	3.99 ± 0.18 *⚙⚙	+ 1.54 ± 0.16 **	- 0.55 ± 0.24 *⚙⚙

Notes: designations are the same as in Table 1.

Spearman and linear Pearson correlation analysis revealed a significant negative relationship between blood glucose level and the number of erroneous actions on the test “correction probe” on attention after 4 hours ($\rho = – 0.683$, $p = 0.000$; $r = – 0.364$, $p = 0.034$) and 6 hours ($\rho = – 0.619$, $p = 0.001$; $r = – 0.398$, $p = 0.022$) of mental work. In the same periods, respondents had the most pronounced differences in the dynamics of blood glucose (Table 4), in reaction speed (Table 2) and mental effectiveness, including monitoring and processing of error (Table 1). Thus, the higher the level of blood glucose, the lower the error commission, and hence, the more efficient the mental performance and functionality of the EMPS. The relationship of

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glycemia and the number of erroneous actions of the respondents at baseline testing and after 2 hours of mental work remains an open question.

Therefore, the presence of long-term changes in cognitive functions and activity of EMPS in sober people at the initial testing and during the first 2 hours of mental work, as well as the limited role of hypoglycemic mechanism in these changes (dysfunctional states) require a possible explanation. One of the explanation, as revealed by the analysis of the literature, may be epigenetic effects of ethanol and/or its metabolites (functioning as epigenostressor) as well as their impact on "glycemic memory" of cells through the development of a functional relative hypoglycemia during continuous mental work (Table 4, Fig. 1).

Epigenostressor is a substance that causes changes in the epigenetic profile of cells [7, 20]. Epigenostressor can regulate the expression of transcription factors in cells (including neurons and glial cells). Epigenetic modification (methylation, acetylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation, etc.) caused by these epigenostressors determine the degree of remodeling of protein-DNA complexes in chromatin, regulate gene expression and, therefore, the functional activity of cells, their properties and life cycle [6, 8, 21-28]. Accumulating research data indicate global role of epigenetic regulation in cognition, nutrition, mental stress, behavior, glycemic regulation and their dysfunctions [29-36]. Cognitive functions, mental activity and behavior, glycemic, and environmental influences/factors such as nutrition, alcohol, are associated with epigenetic modifications [28-36].

Administration of ethanol to rats at a dose of 88 mM, which corresponds to the dose of "binging" for humans, leads to a change in DNA methylation of genes on chromosomes 7, 10 and X, which play an important role in the cell cycle, cell growth, apoptosis, and degeneration [7, 25, 28]. Thus, [7, 28] confirmed an increase in ethanol methylation (hypermethylation) of genes that play a role in metabolism (Cyp4f13) and reduced methylation (hypomethylation) of genes associated with the development (Nlgn3, Elavl2, Sox21 and sim1), including imprinting of the gene Igf2r [25]. Hypermethylation of genes on the chromosomes 10 and X in embryos of rats exposed to alcohol was especially pronounced [25, 28]. Metabolites of ethanol (acetaldehyde, acetate, phosphatidyl ethanol, ethyl esters of fatty acids) can also affect the epigenetic profile of cells [7, 28]. The concentration of these metabolites regulates the activity of enzymes involved in DNA methylation and histone modification – DNA methyl transferases, histone acetyl transferase, histone deacetylase, histone methyltransferases and histone demethylase. Metabolites of ethanol can regulate the quantity of substrates and cofactors of these enzymes [28]. Thus, ethanol and its metabolites may contribute to the modification of histones and result in the initiation of transcription [7]. These epigenetic modifications can affect cell proliferation and differentiation, and remodeling of neural connections [8]. It is assumed that changes in the medial prefrontal cortex observed in alcoholism are due to remodeling of neurons in this region of the brain [8]. A recent study by [24] also showed a significant methylation of genes in neurons of different parts of the cerebral cortex caused by ethanol administration. Researchers report post-translational changes in neurons of the major components of EMPS: substantia nigra and the anterior gyrus cinguli [8] under the influence of ethanol accompanied by increased activity of the enzyme catechol-O-methyltransferase and the activation of dopamine receptors types 1, 2, 3 & 4 [8, 9, 21, 37].

Remodeling effect of ethanol and its metabolites as epigenetic factors affecting neurons of EMPS can also occur through the modulation of neural differentiation with muscarine-sensitive nicotinic acetylcholine receptor subtype 1 or 3 [11]. Activation of neuronal muscarine-sensitive nicotinic acetylcholine receptor by ethanol (and / or its metabolites) can lead to individual characteristics of their differentiation, including up-regulated differentiation of cells [7, 38]. All these processes lead to the remodeling of neural connections, caused by the action of ethanol and its metabolites, and the acceleration of signal transmission through the already established connections that can manifest as increased speed of mental performance, for example, an increased reaction speed on attention test (Table 2). At the same time, up-regulated differentiation of neurons caused by the action of ethanol and its metabolites, probably, reduces their plasticity and ability for effective learning and detection of erroneous actions (Table 1). As a result, speed increases significantly (Table 2), and mental effectiveness is sharply reduced (Table 1), which leads to disruption of formation of long-term memory [26].

It is known that the major energy substrate for the nervous system is glucose [15, 16, 17, 39, 40]. However, the optimal level of performance is provided in certain neurons within a given level of glycemia. Neurons are very sensitive to decreasing blood glucose level [17, 18, 39, 40, 41, 42].

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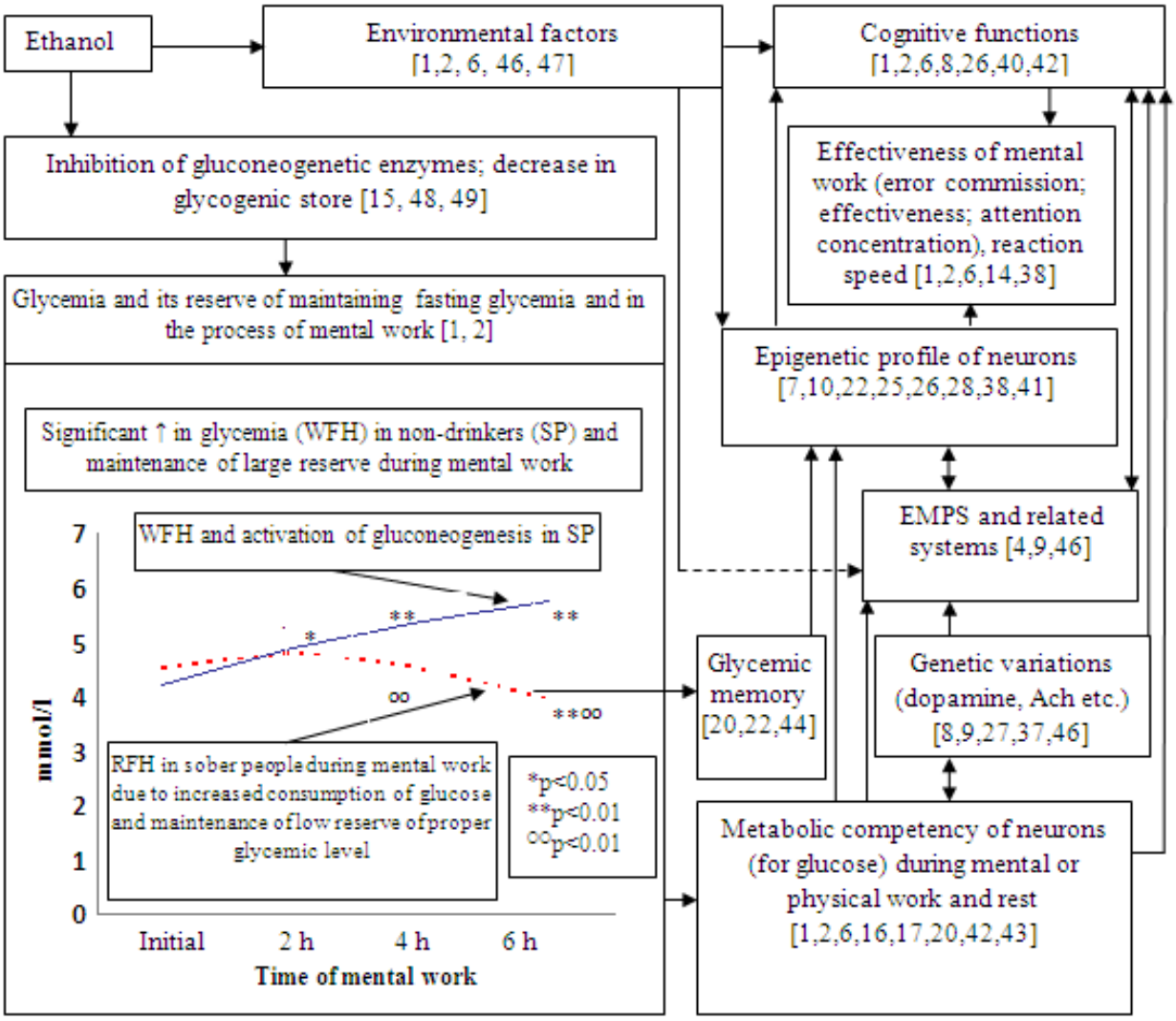

Figure 1: Scheme of the regulation of cognitive functions and EMPS by ethanol in sober people. Significance level: * – relative to baseline; ^{OO} – in relation to the corresponding value in nondrinkers. WFH – working functional hyperglycemia. ACh – acetylcholine. FRH – functional relative hypoglycemia. EMPS affects the state of cognitive function, thereby determining the effectiveness of mental activity. In turn, EMPS activity depends not only on the state of cognition and genetic variations of neurotransmitter systems (dopamine and others) in the brain, but also on the conditions of metabolism in neurons and glial cells, and above all, on the level of glycemia, which determines the level of glucose in the brain. Ethanol as an environmental factor affects cognitive function and EMPS directly (acute effect following alcohol administration), and by alteration in the epigenetic profile of neurons or blood glucose levels and the "glycemic memory" of cells formed during the occurrence of FRH in sober respondents during prolonged mental work.

Hyperglycemia is also accompanied by stress influence on the function of neurons [16, 18, 43]. The increased concentration of intracellular glucose causes processes characteristic of oxidative stress and / or pro-inflammatory state, in particular, an increase in the secretion of reactive oxygen species [20, 22, 44, 45].

Pioneering studies on the effect of subsequent changes in glycemia on the ability of cells to keep track "remember" of the previously established glycemic level (i.e. glycemic memory") was directed towards certain cells. "Glycemic memory" is associated primarily with endothelial cells ("glycemic memory" of endothelial cells – caused by the effect of hyperglycemia) [20, 22, 44, 45]. Sequential and chronic hyperglycemia around endothelial cells causes malfunction, and by paracrine mechanisms induce epigenetic modifications in cells, such that the level of glycemia cannot return to the original level even after normalization of glycemia. This effect in

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endothelial cells is called “glycemic (metabolic) memory” [44, 45]. The authors of [22] suggested another name “hyperglycemic memory” for this phenomenon and related the increase of glycemia in diabetes with suppression of methylation (H3K9m2 and H3K9m3) on promoter p65. Siebel and co-workers [20] have shown that hyperglycemia can lead to significant transcriptional changes in vascular endothelial cells by activating NFkB p65 promoter through modulation of epigenetic profile of cells. Increased gene expression NFkB p65 activates NFkB-dependent proteins, such as MCP-1, which are involved in the development of vascular lesions in diabetic patients [20].

Mechanisms of development of “glycemic memory” of cells, according to [44] are: non-enzymatic glycation of cellular proteins and lipids; excessive accumulation of reactive oxygen and nitrogen in cells; and, possibly, their combined action. Advanced glycation products cause translocation of the transcription factor NF-κB to the nucleus and subsequent NF-kB-mediated gene expression [8, 44].

Given the importance of glucose to the functioning of brain cells, and based on the accumulating evidences of literature data, we can assume that in neurons and glial cells, not only epigenetic modifications caused by hyperglycemia is possible, but also post-translational changes during hypoglycemia (acute, chronic). The data of [23] suggest that hypoglycemia is associated with methylation of genes H19 and LIT1. Reference [43] indicate an increase in the ratio of NAD + / NADH and ADP / ATP in hypoglycemia as a basis for changes in DNA methylation and histone modifications. In this situation, there is increase in the flow of amino acids and ketone bodies in neurons and gliocytes for energy production [43]. Hypoglycemia with a shift in cellular metabolic substrates may be accompanied by epigenetic modifications in neurons [43], which may underlie the formation of “glycemic (hypoglycemic) memory”. After prolonged mental work on fasting, alcohol users (even sober people after a considerable period following alcohol use) may experience relative functional hypoglycemia (Table 4, Fig. 1). Frequent hypoglycemia among students may exacerbate the effect of the direct action of acute toxic doses of ethanol on the epigenetic profile of neurons and glial cells, and promote the formation of “glycemic (hypoglycemic) memory”. This epigenetic modifications may even be more pronounced for people who usually skips breakfast, especially when we consider the fact that approximately 40% of young adults may experience hypoglycemia due to their skipping of breakfast [19]. Thus, the efficiency of mental performance and regulation of error commission by EMPS may be reduced already at baseline compared to the non-drinkers (Table 1).

4 Conclusion

The results of this study and analysis of the literature confirmed the previously formulated hypothesis about the long-term negative modulation of EMPS activity and effectiveness of mental performance caused by ethanol in a sober person. Our findings (Fig. 1) suggest that the modulating effects are carried out through alcohol’s effect on the epigenetic profile and “glycemic memory” of neurons. Ethanol may be regarded as a long-term epigenetic stressor (epigenostressor) and a factor contributing to the development of hypoglycemia in a sober working individual, especially in conditions of prolonged mental work on fasting, and the formation of “glycemic (hypoglycemic)” memory of cells. Epigenetic influence of ethanol (in acute toxic effect) or its metabolites on neurons, with subsequent functional relative hypoglycemic attacks (leading to the formation of “hypoglycemic memory” of cells), can increase the speed of mental work and negatively affect the functioning of EMPS in sober respondents.

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