Glycemic Allostasis during Mental Activities on Fasting in Non-alcohol Users and Alcohol Users with Different Durations of Abstinence

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Abstract

Glycemic allostasis is the process by which blood glucose stabilization is achieved through the balancing of glucose consumption rate and release into the blood stream under a variety of stressors. This paper reviews findings on the dynamics of glycemic levels during mental activities on fasting in non-alcohol users and alcohol users with different periods of abstinence. Referred articles for this review were searched in the databases of PubMed, Scopus, DOAJ and AJOL. The search was conducted in 2013 between January 20 and July 31. The following keywords were used in the search: alcohol action on glycemia OR brain glucose OR cognitive functions; dynamics of glycemia, dynamics of glycemia during mental activities; dynamics of glycemia on fasting; dynamics of glycemia in non-alcohol users OR alcohol users; glycemic regulation during sobriety. Analysis of the selected articles showed that glycemic allostasis during mental activities on fasting is poorly regulated in alcohol users even after a long duration of sobriety (1-4 weeks after alcohol consumption), compared to non-alcohol users. The major contributor to the maintenance of euglycemia during mental activities after the night’s rest (during continuing fast) is gluconeogenesis.

Keywords: Abstainers, Abstinence, Alcohol, Alcohol users, Fasting, Glycemic allostasis, Mental activities, Sobriety

Introduction

Glycemic allostasis is the process by which blood glucose stabilization is achieved through the balancing of glucose consumption rate and release into the blood stream under a variety of stressors. It involves glucose acting as a peripheral signal for the secretion of the respective hormones by pancreatic β- or α-cells or other involved cells.[1,2] Different types of stressors to varying degrees are constantly acting on blood glucose or its regulatory systems. The actions of stressors are consistently been counterbalanced by the organism’s organs and systems by maintaining a set point. Depending on the shift in glycemia, or activity of stressors, the organs and systems (central controlling system – central nervous system; peripheral controllers – liver, kidney, adrenals, intestine, pancreas, etc.) are mobilized for the maintenance of blood glucose within a narrow range.[2-7] However, these organs and systems themselves are vulnerable to the actions of other agents. For instance, the liver and kidney which are one of key peripheral controllers of blood glucose are largely affected by alcohol.[2,8,9] Recent data show that over 90% of many countries’ inhabitants consume alcohol.[10,11] Alcohol abuse is a social, legal, health problem world-wide.[10] At present, much is known about the acute and chronic effects of alcohol consumption in large doses. The actions of alcohol (especially acute and chronic alcohol use in hazardous doses) on glycemia had been documented decades ago.[12,13] However, information on the action of small to moderate alcohol doses are scanty.

Researchers have studied the changes accompanied by blood glucose during fasting; however, inconsistencies in data reporting remain unsolved.[14-17] Furthermore, there is a paucity of data on the pattern of changes of blood glucose on fasting when controlling for other variables (e.g. gender, level of mental states/activities, functional status, alcohol consumption). For instance, since glucose is the major substrate...
for brain functions, during mental activities, the amount of glucose needed by the brain will increase. However, during fasting in a condition of increased mental activities, the pattern of changes accompanied by blood glucose is fully not understood. Furthermore, the changes in blood glucose on fasting during increased mental activities (compared to resting, or basal state of brain functioning) for different groups of people (adolescence, young adults, adults, men, women, alcohol users, non-alcohol users, etc.) are not exactly known. Hypothetically, however, it is logical that a further decrease in the blood glucose concentration would be observed during intensive mental work on fasting.

In this paper, we review the pattern of change of glycemic levels during mental activities on fasting in non-alcohol users and alcohol users with different periods of sobriety (abstinence).

Materials and Methods of Literature Search

Data sources

In this study, two parallel data sources were utilized: Our research data,[18] and peer-reviewed articles from scientific databases.[1-17,19-77]

Data from our recent study[18] were critically examined. The study was carried out through a written consent of the participants (males) with approval from the Ethics and Research Committee of the Belarusian State Medical University. The experiment which took 6 h and 30 min on fasting, involved 8 non-alcohol users and 19 alcohol users who reported different durations of sobriety (14 alcohol users reported 1-2 weeks of sobriety, whereas 5 reported 3-4 weeks of sobriety). Participants completed various questionnaires alcohol use disorders identification test, etc., texts followed by questions, neuropsychological questionnaires and batteries of tests for analysis of higher integrative brain functions.

Blood glucose levels were determined at intervals of 2 h, including the initial level. A detailed design of the experiment is outlined in our previous publication.[18,78]

Peer reviewed articles on the effect of various alcohol doses on the blood and brain glucose levels and cognitive functions, the pattern of change of blood glucose level during mental activities on fasting in non-alcohol users and alcohol users with different periods of sobriety from scientific databases.

The databases of AJOL, Scopus, DOAJ and PubMed were searched for peer-reviewed articles. The search was conducted between January 20 2013 and July 31 2013. The first search was performed in PubMed to determine initial number of articles that met the aim of the study. Subsequent searches were conducted in Scopus, DOAJ and AJOL. At present, Scopus represent one of the most up-to-date databases for refereed publications. It contains all publications in Web of Science and Medline. DOAJ is one of the leading scientific databases of open access publications. Additional search was performed in AJOL (Africa’s most dense database for peer-reviewed articles), since most journals in this database were not indexed in Scopus and PubMed. The following keywords were used in the search process: Alcohol action on glycemia OR brain glucose OR cognitive functions; dynamics of glycemia, dynamics of glycemia during mental activities; dynamics of glycemia on fasting; dynamics of glycemia in non-alcohol users OR alcohol users; glycemic regulation during sobriety. For high quality articles, backward (references were searched to retrieve relevant data) and forward (reviewing additional articles that have cited the article, to locate follow-up studies or newer developments related to the phenomenon under study) searches were conducted. The search was terminated when no new information was found.

Literature selection process

We included studies (original communications and review articles in the original search processes; articles, books and book chapters – in the backward and forward searches) that report on the aim of this study. The articles were selected based on their relevance to the topic areas of study. The results of searches were filtered according to their relevance to the aim of this search. The titles that were logged in the various databases searched were analyzed against the key terms. Reports not wholly focused on the topic of this study were removed. This study included literatures that meant the following criteria:

1. Literatures that meant the parameters of the keyword search
2. We focus on studies that explicitly discuss effects of various alcohol doses on the blood and brain glucose levels and cognitive functions, dynamics of glycemia levels during mental activities on fasting in non-alcohol users and alcohol users with different periods of sobriety
3. We assess the quality of studies based on the clarity with which methodologies and results are described
4. The study includes a clear description of research background and context in which it was conducted.

Literatures that fulfilled the above criteria were stored in separate files. Electronic literatures were saved in their original formats as computer files. The reference list shows only a few peer-reviewed articles (out of the lots that meet the inclusion criteria) that were obtained in the search process [Figure 1].

Data analysis

Statistical calculations were performed using the statistical package for the social sciences 16.0 version (Chicago, IL, USA) for Windows and the Student’s t-test.[19] Statistical values are reported in Mean (standard error of the mean) as in table or in percentages (in text). The probability value for significance was set at $P < 0.05$. All quantities of alcohol are given in values of absolute ethanol.
Results and Discussion

The data of this review show that alcohol at large doses (over 40 g) has a negative effect on both the blood and brain glucose levels and also negatively affect cognitive functions. However, it is reported that moderate alcohol use might also negatively affect cognitive functions during complex task execution. Data on the effect of alcohol in small-doses on cognitive functions are contradictory. The differences on the effect of alcohol in small doses might be due to methodological issues, idiosyncrasy, type of tasks administered for analysis of cognitive functions, ethno-cultural peculiarities, socio-economic and educational status of the participants and between-participants’ differences. Several data show gradual decrease in the glycemic levels of humans on fasting (after the night’s rest). How the glycemic levels change during mental activities are poorly understood. There is a dearth of data on the pattern of change of blood glucose level during mental activities on fasting in non-alcohol users and alcohol users with different periods of sobriety.

Glycemic allostasis in alcohol users and non-alcohol users at rest and during mental activities on fasting

Glycemic levels in humans are tightly regulated within a narrow range between meals. The range for normal is approximately 4.44-6.66 mmol/L for capillary blood and 3.33-5.55 mmol/L for venous blood. Slight individual, gender, ethnic, age differences and disparities due to socio-economic status may exist.

Postprandially, glycemic levels increase. Thereafter (in the postabsorptive phase), a decrease in glycemia follows. In healthy humans, pancreatic glucose regulatory hormones and peptides (insulin, glucagon, amylin etc.) to a larger extent, hormones and peptides of other organs and tissues (intestine, liver, kidney, adrenals etc.) to a lesser extent, counterbalance the shifts in glycemia from the set point. A central processing system – the central nervous system – plays a key role in glycemic regulation. In pathology, these regulatory hormones or peptides might fail to adequately keep glycemia within the set point.

In the postprandial phase, a large part of absorbed glucose is stored in the liver as glycogen, while the rest is utilized for powering cells or is converted to other substrates. Following 5 h after food intake, ~¼-1/3 of glucose is deposited in the liver.

In the postabsorptive phase, under basal secretion of hormone, the liver of a 70 kg healthy person produces approximately 10 g of glucose/h. Out of the 10 g, ~6 g/h are used by the brain; 4 g/h by skeletal muscles, adipose tissues, erythrocytes, kidney medulla etc., During mental activities, the amount of glucose utilized by the brain increase by two fold or more. The contribution of glucose to the energy demands of brain cells at rest is ~40%. The results of our previous study also confirm this proportion by contribution of glycemia to brain functions (26.00% on fasting at rest; 30.00-36.70% on fasting during mental activities) among the factors that maintain adequate mental performance and cognitive functions in humans. Di Nuzzo et al. and Madsen et al. in their study have reported that during activation of brain functions, the peak level of glucose contribution to energy needs of neurons might exceed 90%.

The cerebral glucose level is proportional to the blood glucose level. Therefore, a change in blood glucose level will mean a corresponding change in the cerebral glucose content. This means that since glucose is the principal energy source for working neurons, if blood glucose decreases, mental performance will also decrease. Importantly, changes in

Figure 1: Flow chart of the methods of article selection. The chart gives a summary of works retrieved at each phase of analysis or search termination at the point when no new information was found. Duplicate copies are due to citation of the same document in two or more databases or similar study performed by different authors. Due to manuscript size limitation, the 79 full text documents out of the number that met the inclusion criteria were included for analysis, since the rest did not necessarily have substantial influence on discussion of the reviewed articles, most probably, because of the somewhat closely related discussion scope of the articles under analysis.
blood, cerebral glucose and mental activities had been reported in several studies.[29,54-58]

Alcohol may affect to different degrees, the peripheral and central glucoregulatory systems [Figure 2]. Minimal doses of alcohol consumption might actually be beneficial in lowering blood glucose levels, however, several meta-analyses and systemic reviews remain inconclusive on this issue.[59-65]

It is essential to note that the duration of alcohol’s effect on glycemic levels is not fully investigated. The dynamics of changes accompanied by glycemia in alcohol users and non-alcohol users at different physiological states are poorly understood. For instance, dynamics of changes in glycemic levels at rest and fasting in different categories of people with different attitudes to alcohol consumption is not fully researched. Since the time of Krebs, ethanol is known to cause hypoglycemia,[12,13] which might last up to 36 h after alcohol consumption.[43] The results of our study,[18] [Table 1] showed that blood glucose regulation in social drinkers during the period of sobriety (1-4 weeks after moderate drinking) could be impaired. Importantly, this impairment in glycemic regulation was observed only during intensive mental activities at an informational load of 2.65 bits/s on fasting. Since it takes approximately 3 weeks for de novo synthesis of proteins, we assumed that the inhibition of gluconeogenetic enzymes by ethanol even in social drinkers could take a much longer time, more than a week and might be identified in conditions of increased glucose requirement by the brain (during increased mental activities, especially on fasting). This becomes an issue for concern, especially when we consider the fact that one standard drink (8 g of ethanol) exceeds the concentration of endogenous ethanol[64] by almost 800 times.

We recently addressed the issue of differences in glycemic allostasis in people with different drinking behaviors. In the study,[18] based on the reported time of sobriety, all alcohol users were divided into two subgroups: 14 persons were alcohol users at 1-2 weeks of sobriety before the experiment; and 5 persons were alcohol users at 3-4 weeks of sobriety before the experiment. We showed disparities in glycemic allostasis regulation in male healthy subjects with different attitudes to alcohol use. The results of the study show increase in glycemic levels in all participants in the 1st 2 h of mental activities [Table 1]. Thereafter, a gradual fall in the glycemic levels was observed only among the alcohol. Increase in the blood glucose level in all phases of the experiment was noted among the non-alcohol users (abstainers) [Table 1].

Positive dynamics of the increase in the glycemic level among the non-alcohol users in a condition of active use of glucose by the brain points to the high reserve of gluconeogenesis amongst them and the pronounced stimulation of this process during mental activities. Steady increase in glycemia among the non-alcohol users under mental activities could be considered as “functional, relative hyperglycemia”, which is necessary to maintain a high energy demand of neurons of the working brain and the quality of task execution (with a small range of error commission or performance error), especially during prolonged mental work.

After 6 h of mental work, three participants developed symptoms of neuroglycopenia (glycemic level was lower than 3.00 mmol/L). This means that the reserve of gluconeogenesis in alcohol users during the periods of sobriety during prolonged mental work on fasting is not adequate to maintain euglycemia.

The estimated proportion by contribution of the negative impact of ethanol on the dynamics of blood glucose levels during mental work on fasting in the alcohol users ranged from 18.1% ($r = -0.425; P = 0.03$ to 64.8% ($r = -0.81; P < 0.00$). Thus, for the 1st time, the results of this study revealed a long-term (within 1-4 weeks after alcohol use) impairment of glycemic allostasis in the form – failure in maintaining proper glycemic level in alcohol users and the development of functional relative hypoglycemia.[18]

**Figure 2:** General scheme of the effect of alcohol on glycemic regulation. Alcohol affects glycemic levels through mechanisms regulating the glycemia—central nervous system and peripheral organs and tissues. Alcohol may decrease the rate of protein turnover or the synthesis of cellular subunits/components involved in peripheral and central glucoregulatory systems.

**Contribution of gluconeogenesis and glycogenolysis to maintaining glycemic levels on fasting during mental activities**

Research data suggest that during fasting, glycemic level is regulated primarily by gluconeogenesis and glycogenolysis. Reports[14,15,25-28,37,66-70] show a wide disparity in the percentage by contribution of gluconeogenesis and glycogenolysis on fasting. This might be due to the different methodological approaches, ethno-cultural peculiarities in glycemic regulation, gender and between-participants’ differences, gluconeogenetic substrate(s) that were determined.[166] For instance, alanine and glutamate have the greatest contribution to endogenous production of glucose. It is our opinion that these differences might be due to other physiological indices (e.g., body mass index), psycho-emotional status, as well as other behavioral indices (e.g., smoking, alcohol use). van Thien et al.[25] and Landau et al.[19] in their study have reported that in a healthy person, starting from 12 h of fast, the percentage by contribution of gluconeogenesis and glycogenolysis is approximately the same ~50/50%. Aronoff et al.[37] reported that after night fast (8-12 h of fasting), liver glycogenolysis remains the main process that maintains glycemia. Hellerstein et al.[24] report that immediately after the night’s fast in
Table 1: Values (mean [standard error of the mean]) healthy males (20-29 years) at rest (before mental work) and during long-term intensive mental work\[16\]

<table>
<thead>
<tr>
<th>Time of blood sampling</th>
<th>Glycemic levels, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstainers, n=8</td>
</tr>
<tr>
<td>Initial, before mental work</td>
<td>4.24 (0.19)</td>
</tr>
<tr>
<td>After 2 h of mental work</td>
<td>4.91 (0.15)*</td>
</tr>
<tr>
<td>$t$=2.79; $P$$&lt;$0.05*</td>
<td></td>
</tr>
<tr>
<td>After 4 h of mental work</td>
<td>5.40 (0.18)</td>
</tr>
<tr>
<td>$t$=4.46; $P$$&lt;$0.005*</td>
<td>$t$=4.19; $P$$&lt;$0.005</td>
</tr>
<tr>
<td>After 6 h of mental work</td>
<td>5.78 (0.13)*</td>
</tr>
<tr>
<td>$t$=6.70; $P$$&lt;$0.001*</td>
<td>$t$=2.35; $P$$&lt;$0.05*</td>
</tr>
<tr>
<td>$t$=8.06; $P$$&lt;$0.001</td>
<td>$t$=9.04; $P$$&lt;$0.001*</td>
</tr>
</tbody>
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Only significant values are shown: *Differences are significant in relation to the initial level of glycemia in its own group. Differences are significant in relation to the level of glycemia in abstainers in the corresponding phase of blood sampling. Differences are significant between the values of alcohol users 1-2 weeks before the study and alcohol users 3-4 weeks before the study, in the same phase of blood sampling. Statistical significance was calculated using the Student’s t test.
of gluconeogenesis was parallel to concentration-dependent inhibition alcohol dehydrogenase.\textsuperscript{[12,13]} Alcohol inhibits gluconeogenesis (to a different extent) from lactate, glycerol, dihydroxyacetone-acetone, proline, serine, alanine, fructose, galactose, etc., Krebs et al. identified 66% inhibition of gluconeogenesis from lactate.\textsuperscript{[13]} Ethanol decreases alanine uptake (for gluconeogenesis) by 35%.\textsuperscript{[9]} Alcohol inhibits pyruvate roughly by 5 fold. The concentration and type of other substrates in the medium can significantly change the degree of inhibition by alcohol. This inhibition is the result of the metabolic action of alcohol dehydrogenase – reduction of (free nicotinamide adenine dinucleotide [NAD]+)/(free NADH) ratio.\textsuperscript{[13]} Maximum inhibition of gluconeogenesis by alcohol is achieved after ~30 min following alcohol exposure.\textsuperscript{[40]} Whether or not the inhibitory effect of alcohol on gluconeogenesis vary with age is what is not exactly clear. Some years back, however, Sumida et al.\textsuperscript{[72]} showed that the \textit{in vitro} inhibitory effect of gluconeogenesis by alcohol was especially noted in matured hepatocytes, than in young ones.\textsuperscript{[72]} Hence, it would be expected that the effect of alcohol consumption on gluconeogenesis would be more pronounced for the older humans, compared to young adults. This issue of the age differences in alcohol action on liver gluconeogenesis needs further attention. In this direction, earlier study by Rikans et al.\textsuperscript{[73]} showed that acetaldehyde dehydrogenase (the enzyme that, in part, determines alcohol toxicity) in the liver of adults is lower by 15-20%.\textsuperscript{[73]} Nevertheless, it was also reported that variations in this range do not increase the hepatotoxicity of ethanol.\textsuperscript{[73]} Rikans et al.\textsuperscript{[73]} also reported that there was no significant difference in the gluconeogenesis in matured and young hepatocytes. It would be necessary for objective-driven research to approach some of these contradictions in data reporting. From the results of this review suggest that the higher negative impact of alcohol use observed among adolescents and young adults, is due to the vulnerability of the nervous system. Nevertheless, some peculiarities in the enzymatic composition might play a role.

From the discussion above, it could be deduced that early studies on the effect of alcohol on glucose metabolism were focused mostly on gluconeogenesis. Recent studies considering the effect of alcohol on the breakdown of glycogen in the liver unravel relevant facts. The results of van de Wiel\textsuperscript{[74]} showed that alcohol not only inhibits gluconeogenesis, but also impairs glycolygetic process, resulting in a further worsening of hypoglycemia.\textsuperscript{[74]} Mokuda et al.\textsuperscript{[75]} studied the effect of alcohol on the oxidation of glucose, gluconeogenesis, glycogenesis and glycogenolysis in the liver and identified the following. Ethanol improved short-term oxidation of glucose by 1.3 times ($P < 0.05$); gluconeogenesis from lactate was reduced by 5.3 times ($P < 0.01$); glycogenolysis increased by 2 times ($P < 0.01$); glycogen content of the liver was significantly reduced ($P < 0.05$); gluconeogenesis was reduced by 1.70-2.30 times ($P < 0.01$). Mokuda et al.\textsuperscript{[75]} argue that the effect of alcohol on glucose metabolism might have significant differences between fasting state and non-fasting state. This view is in agreement with our opinion on the disparities in the proportion by contribution of various processes to glycemic levels observed in many studies.

Putting into consideration all these findings reported by the different authors, in a condition of fasting (and during mental work), inhibition of gluconeogenesis is the leading cause of hypoglycemia in alcohol users.\textsuperscript{[12,13]} This inhibition occurs as a result of the interaction between ethanol and alcohol dehydrogenase, a shift in the (NAD)/(NADH) ratio in the direction of reduction which is also reflected in the (lactate)/(pyruvate) ratio.\textsuperscript{[12,13]} The principal organ responsible for hypoglycemic effect of ethanol is the liver, due to the high activity of liver alcohol dehydrogenase.

There is a need for further research into the regulatory mechanisms of glucose allostasis in different population groups (while controlling for gender, psycho-emotional status, etc.) at varying physiological states. It is crucial, to consider the duration in which a person started alcohol consumption in life (i.e. the time of exposure to alcohol in the process of growth might be a valuable indication of glycemic allostasis in the later part of life). For instance, prenatal exposure to ethanol results in increased expression of gluconeogenic genes. This results in increased gluconeogenesis after birth and with an increase in the age, which might lead to type 2 diabetes.\textsuperscript{[76]}

In general, disorders caused by alcohol on glucose metabolism may represent only a smaller percentage of the effect of alcohol on the polypeptides of an organism. The results of Karinch et al.\textsuperscript{[77]} confirm this. Karinch et al.\textsuperscript{[77]} had demonstrated that alcohol intoxication induce defect in global protein synthesis (including liver proteins).

**Limitations of the study**

A major limitation in this review is that our search was based on English literatures, hence we cannot claim to have completed a comprehensive and international review. This limitation may be mitigated by the reality that English has been the lingua franca of the majority of the web. The articles for this review were searched in only four out of the hundreds of scientific databases in the world (i.e., <1% of the world databases). Therefore, articles not indexed in these databases where the search was conducted that might necessarily be useful for the review had been ignored. This might have resulted to a bias in the discussion of research data. In addition, content of databases and web of literatures increase daily.

**Conclusion**

Glycemic allostasis during mental activities on fasting is poorly regulated in alcohol users even after a long duration of sobriety, compared to non-alcohol users. The major contributor to the maintenance of euglycemia during mental activities after the night’s rest (during continuing fast) is gluconeogenesis. Ethanol is a classical factor not only for gluconeogenesis
inhibition, but also for increased glycogenolysis rate. Increased activity of alcohol dehydrogenase (especially under decreased activity of acetaldehyde dehydrogenase) is the prime cause of gluconeogenesis inhibition by alcohol. Gluconeogenesis inhibition by alcohol is mostly expressed in the liver because of the higher activity of alcohol dehydrogenase in this organ. In the 1st h of fasting, possibly the hypoglycemic effect of alcohol is due to the faster glycogenolysis. Therefore, a higher level of glycemia during the 1st h of fast, subsequently followed by a decrease might be noted in alcohol users. Under continued hours of fasting, the hypoglycemic effect of ethanol is due mainly to its inhibitory effect on gluconeogenesis. Glycemic allostasis in a working person depends, at least, on his attitude to alcohol consumption, the duration of mental work and the period of sobriety. A shift in glycemic allostasis to the direction of working functional hyperglycemia to maintain euglycemia is a fundamental regulatory mechanism in young healthy non-alcohol users during prolonged mental activities on fasting.

**Future directions**

Since glycemic allostasis during mental activities on fasting is differently regulated in alcohol users even after a long duration of sobriety, compared to non-alcohol users, it will be necessary to investigate the dynamics of the respective hormones responses (and related neuropeptides) to the changing glycemic levels during mental activities on fasting. At present, the results of numerous studies investigating the effect of alcohol use in hormone (insulin) resistance indicate substantial role of other hormones/factors. Importantly, not only insulin resistance, but also leptin resistance, other hormones such as ghrelin, IGF, neuropeptides play important role in the resultant effect of alcohol on glucose allostasis. Moreover, some of these hormones or peptides exhibit synergism on insulin sensitivity, which will subsequently affect glucose metabolism. Therefore, there is need to examine the effect of other hormones and neuropeptides (related to insulin sensitivity) on insulin resistance and their resultant effect on glucose metabolism in alcohol users and non-alcohol users.

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