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Mechanism of Alcohol Related Disruption of the Error Monitoring and Processing System

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***Abstract*—**The error monitoring and processing system, EMPS is the system located in the substantia nigra of the midbrain, basal ganglia and cortex of the forebrain, and plays a leading role in error detection and correction. The main components of EMPS are the dopaminergic system and anterior cingulate cortex. Although, recent studies show that alcohol disrupts the EMPS, the ways in which alcohol affects this system are poorly understood. Based on current literature data, here we suggest a hypothesis of alcohol-related glucose-dependent system of error monitoring and processing, which holds that the disruption of the EMPS is related to the competency of glucose homeostasis regulation, which in turn may determine the dopamine level as a major component of EMPS. Alcohol may indirectly disrupt the EMPS by affecting dopamine level through disorders in blood glucose homeostasis regulation.

***Keywords*—**Alcohol related disruption, Error monitoring and processing system, Mechanism.

I. INTRODUCTION

IT was reported that alcohol consumption disrupts the Error Monitoring and Processing System, EMPS [1], [2]. The effect of alcohol on the EMPS is reflected in the reduced amplitude of the Error Related Negativity, ERN, a negative deflection in the electroencephalogram with a maximum in the midline of the frontocentral region of the scalp having a latent period around 50-150ms [1], [3], [4]. Although, it has been suggested that alcohol may directly disrupt the system or indirectly by disrupting the stimulus processing system upon which the EMPS depends, the ways in which this disruption occurs are still poorly understood [2]. The EMPS is a monitoring response system located in the mediofrontal brain, basal ganglia and is responsible for error detection and correction [1] – [4]. Although, recently, precise brain regions like the substantia nigra, nucleus accumbens, amygdala, insula and hypothalamus have been implicated in modulating the functions of the EMPS [3], [5], its major components are the anterior cingulate cortex, ACC and dopaminergic system [1] – [3]. The functions of the EMPS are dependent on the degree of phasic dopamine activity on the ACC [2]. Considering the pivotal role of dopamine in regulating the activities of EMPS [1] – [3], it may be assumed that any change in the brain dopamine levels might necessarily affect error monitoring and processing [2]. Importantly, the levels of dopamine have been reported to change when subjects commit error, with subsequent effect on the ACC activeness [4], [6], [7].

How does alcohol disrupt the EMPS? Literature data suggest that there could be a link between error commission and glucose metabolism [8] – [18]. Coupled with the well known fact that alcohol consumption results in hypoglycemia [18], [19], it is therefore, necessary to assume that disorders in glucose homeostasis regulation might change the brain dopamine level [10] – [15], [17]. This change in dopamine levels may affect the activity of EMPS [1] – [3], [10] – [15], [16]. The possible effects of the changes in blood glucose level on the brain dopamine level (major factor that regulates EMPS) [10] – [15], [17], as well as the implication of the dopaminergic system in alcohol use [2] allows to assume that disorders in the competency of glucose homeostasis regulation (e.g. relative hypoglycemia) which might result after alcohol consumption [8], [18], [19] could be one major cause for the disruption of EMPS [1], [2], [10] – [15], [17] – [19]. In fact, current knowledge on brain metabolism, suggests that the degree of error monitoring and processing might depend on the concentration of glucose in extracellular fluid around neurons [9], [11]. Besides, current scientific data reveal that decrease in the competency of glucose metabolic regulation negatively affects neuronal functions through decreased dopaminergic activity [9] – [12], [17] which might in turn lead to increase in error commission [2], [9], [11].

Based on increasing evidence from a wide range of modern literature data [1] – [18], [20] – [27], here we proposed that the disruption of EMPS by alcohol might be indirect and realized through its effect on the competency of glucose homeostasis regulation. The indirect disruption of the EMPS is summed up in the hypothesis of alcohol-related glucose-dependent system of error monitoring and processing (Fig. 1). Included in this hypothesis are major concepts of [1], and [2], as well as the fishbone hypothesis of glucose metabolism [28]. The major concept of this hypothesis holds that the error processing capacity of the anterior cingulate depends on the blood-brain glucose proportionality level [9], [11], [28] which affects the dopaminergic system [9] – [18] as a major component of the EMPS [1] – [3].

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II. METHODS

A search of the databases of Pubmed, African Journals OnLine, and Embase from 1940 to April 2010, using such terms as 'error monitoring', 'error processing', 'error system' and 'alcohol and error processing', as well as information obtained from libraries, were used to analyze data of the processes and mechanisms of alcohol related disruption of the error monitoring and processing system. Relevant references from these publications were also obtained. All the retrieved publications were reviewed with emphasis on the effect of various alcohol doses on the blood and brain glucose levels, and cognitive functions, and their possible role in the EMPS, including associated theories and hypothesis were critically examined.

III. RESULTS AND DISCUSSION

There are at least four hypotheses and/or theories that could explain how alcohol consumption affects the error monitoring and processing system by reducing ERN amplitude. They are hypothesis of error detection of the ERN [3], [29]; reinforcement-learning theory of the ERN [2], [30]; conflict-monitoring theory of the ERN [2], [3], [30], [31]; and the integrated conflict-monitoring and reinforcement-learning theory of the ERN [2], [3], [29] – [31].

A. Alcohol and the Error Detection Theory of the ERN

Alcohol disrupts response monitoring and the effectiveness of cognitive capacity [1], [2], [25]. It is known that alcohol reduces the amplitude of ERN and activeness of the dorsal ACC [1], [2]. Amplitude of ERN reduces with reduction in response correctness [1], [3], [4], [6]. Alcohol acts on dopamine receptors by interfering with the activity of dopaminergic system which subsequently leads to the decrease in ERN amplitude [1], [2]. Thereby, alcohol may lower the activity of the error detection system, by decreasing the error detection capacity which is associated with the quality of information upon which the error monitoring system depends [2], [3], [32]. The resultant effect is lowering of response correctness and effectiveness of cognitive capacity [1] – [3], [30]. Alcohol intoxication disrupts normal execution of stimulus related activation of the ACC, cerebellum and the prefrontal cortex which in turn leads to cognitive deficit [2], [25], [30].

B. Alcohol and the Reinforcement Learning Theory of the ERN

This theory is based on recent findings which suggest that the basal ganglia monitor and steadily predict the result of ongoing events (ability to determine whether the end-result of events will be favorable or not) [3], [4], [16], [30], [31]. The theory explains how ACC controls and increases the effectiveness of action and modulates commands with the help of dopamine signals. ACC receives command information from several neuronal origins, called controllers (basal ganglia, dorsolateral prefrontal and orbitofrontal cortices, amygdala etc) [2], [3], [31]. In conditions, when incoming commands are conflicted, ACC acts as a signal selector and transfers information which may be more adequate for a successful completion of a set target to the motor systems and controllers. This is why ACC is regarded as a control filter [2], [3], [29] - [32]. Effect of dopamine signal on the apical dendrites of motor neurons of ACC modulates the amplitude of ERN, so that the phasic decrease in dopamine activity (meant that the result of the present action is worse than expected) is associated with a high ERN and vice versa [3], [31].

Nucleus accumbens may play significant role in the realization of the action of dopamine on the ACC [3], [5]. Reference [5] shows that nucleus accumbens is greatly implicated in error monitoring and processing. Nucleus accumbens is a limbic motor interface, which receives information from the prefrontal cortex, hypothalamus, amygdala under which its actions are modulated by dopamine. Besides, the nucleus accumbens can receive information preceding ERN in the ACC [3], [4], [20].

One of the acute effects of alcohol which is the activation of dopaminergic neurons in the ventral tegmentum is associated with increased nucleus accumbens dopamine level [4], [5]. The reinforcing properties of alcohol are realized through dopamine D1 and D2 receptors [2]. According to the reinforcement learning theory of the ERN, alcohol related disruption of the mesencephalic dopamine system may decrease the amplitude of ERN by increasing the "tonic" activity of mesencephalic dopamine system and subsequently leading to inhibition of ACC activity, the result of which is the reduction of ERN amplitude [2], [5].

C. Alcohol and the Conflict-Monitoring Theory of the ERN

This theory suggests that ACC trace for response conflict by simultaneous activation of descending response channels and sends this information to cognitive control brain regions like the lateral prefrontal cortex [30], [31]. Conflict occurs as a result of simultaneous activation of different regions, controlling the activation of different levels of competing motor control units in the motor cortex [2], [3], [29] – [31]. Processing of stimulus is characterized by constant flow of activity in the pathways that send stimulus related information to the cortex of the hindbrain, and subsequently results in the corresponding response in the motor cortex [2], [22], [30] – [32]. Distractive stimulus may activate incorrect response in this system [2], [31]. As opposed to the reinforcement learning theory, the conflict monitoring theory supports the fact that ACC produces an additional excitability phasic response, N2 (N2 is produced by the neurons of ACC as a conflict monitor, while ERN is produced also by ACC as the control monitor), when it detects a pre-response conflict [2], [31]. According to the conflict monitoring theory, ERN is formed when a constant processing stimulus after error commission results in the activation of correct responses, subsequently producing a post-error conflict [2], [3], [30],

[31]. Alcohol selectively acts on the ERN, while the N2 amplitude is not affected [2]. Alcohol related disruption of stimulus processing decreases the activation of correct responses, immediately after when subjects commit an error which in turn decreases the post-error conflict and so decreases the ERN amplitude [2], [3], [6], [31].

D. Integrated Conflict Monitoring and Reinforcement Learning Theory of the ERN

This model considers the integration of electrophysiological signals during monitoring of action and reinforcement learning at the biological and cognitive levels [5]. The model considers ERN as part of the constant process of ongoing monitoring [3] – [5], [30], [31]. According to this integrated view of the ERN, ACC filters sensory impulses and sends error signals to other brain regions [3], [5]. Although not fully understood, it is suggested that these error signals are generated by the basal ganglia (the adaptive critics), which undertake processing of input signals, and are also predictor of event related results [3], [5], [20], [29]. Discrepancy between these processes produces a phasic shift in dopamine signal, leading to "temporal difference error". These errors are sent through the mesencephalic dopamine system to three brain regions – 1) motor control systems (i.e. amygdala, dorsolateral prefrontal and orbitofrontal cortices); 2) control filter – ACC; 3) and again to the adaptive critics – basal ganglia. Phasic shift in dopamine signal (may be caused by alcohol) in these regions disinhibits ACC and modulates the magnitude of ERN-signal [3] – [5], [20], [30], [31].

E. Hypothesis of Alcohol-Related Glucose-Dependent System of Error Monitoring and Processing (ARGD-EMPS Hypothesis)

The ways in which alcohol affects the EMPS are still poorly understood [1], [2]. Recent studies suggest the possibility that alcohol's effect on the EMPS is related to its action on glucose homeostasis regulation, especially in tasks requiring high cognitive control [8], [11] – [22], [26]. The number of errors committed in an experiment is inversely correlated with the glycemic levels, especially among alcohol users [8]. Our analysis [8], [10] – [22], [25] – [27], [32] suggests the possibility that hypoglycemia might be necessary for the disruption of the activity of EMPS among alcohol users.

The ARGD-EMPS hypothesis (Fig. 1) is based on the notion that the effects of alcohol consumption on the system are the result of disorders in glucose homeostasis regulation [10] – [22], [25], [26], which in turn is associated with decrease in cognitive functions (may be manifested as increased error commission) [1] – [3], [6], [9], [16].

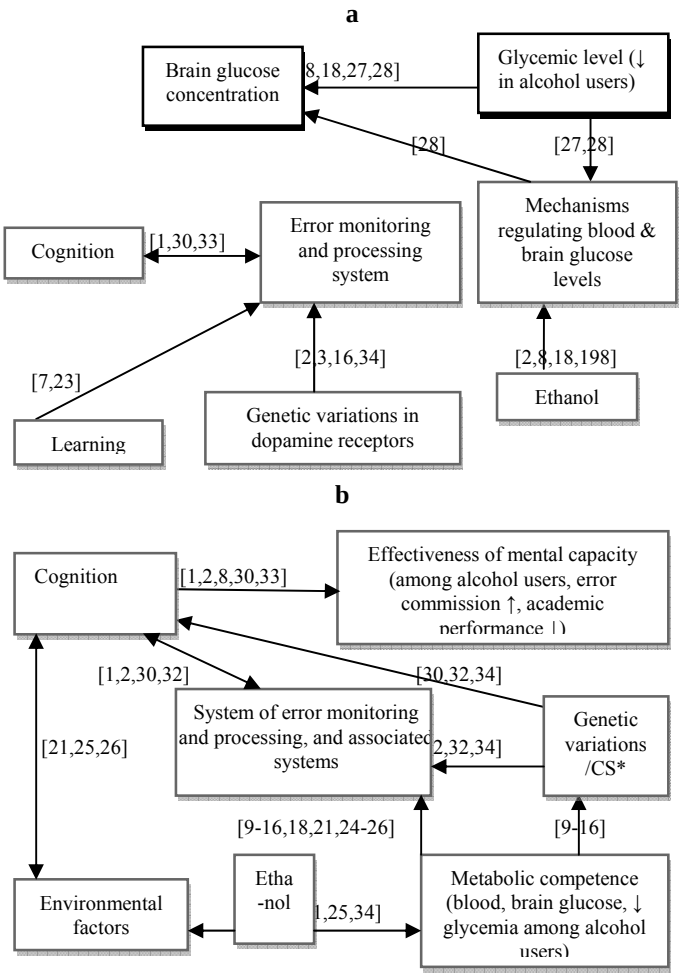

Fig. 1 Hypothesis of the indirect disruption of the error monitoring and processing system by ethanol through its action on the glycemic level

***Note**: The sign, ↓ = decrease, ↑ = increase, *CS = Change in Sensitivity of dopamine receptors.*

Fig. 1(a): Ethanol affects the functions of the EMPS by altering the brain and blood glucose levels through its action on the mechanisms that regulate the blood-brain glucose concentration. Genetic variations in dopamine receptors can also affect the activities of the EMPS. Learning affects this system by decreasing the degree of error commission. The resultant effect of all these components on EMPS indirectly affect cognition, at the same time as the level of cognition can affect the activity level of EMPS.

Fig. 1(b): Ethanol as a component of environmental factors can affect cognition, as the level of cognition may affect the level of alcohol use. Ethanol reduces the glycemic level of alcohol users, especially in tasks requiring high cognitive control, and subsequently affecting EMPS by (i) its action on the system (ii) and may cause genetic variations or may change the sensitivity of dopamine receptors, thereby, affecting the degree of gene expression. Genetic variations (e.g. in dopamine receptors) could affect the level of cognition. Also, the level of cognition may determine (or reflected in) the effectiveness of cognitive activities.

The number of errors committed in a cognitive task by alcohol users correlates with academic performance (a factor of cognitive functions) [33]. In accordance with the ARGD-EMPS hypothesis, it is envisaged that alcohol consumption during tasks requiring high cognitive control might result in glucose homeostasis disregulation [1] – [3], [10] – [22], [25] – [27], [31] which might lower the activity of the dopaminergic

system [10] – [17], with subsequent effect on the ACC activeness [20] – [22], leading to low ERN amplitude [1] – [3], [20] – [22]. The brain glucose level may determine the degree of error processing [21], [10] – [17]. In fact, decreased glucose metabolism in ACC closely correlates with the results of neurophysiological tests [21].

It is established that the brain glucose level is proportional to the blood glucose level [27], [28]. That is why a decrease in blood glucose concentration leads to a decrease in brain glucose concentration, and subsequently a decrease in cognitive functions, which may be marked by increased error commission [3], [21], [27]. The fact that decrease in blood glucose level, caused by alcohol consumption in a cognitive task might affect the activities of the EMPS by increasing the number of error commission [1] – [3], [10] – [22], [25] – [27], [32] is evident in the hypothalamic control of blood and brain glucose levels by dopaminergic system [15], [17]. The blood glucose level increases with increase in homovanillic acid (metabolite of dopamine) on fasting [17]. Effect of glucose on dopamine is realized through the activities of GLUT-2 receptor (also similar to the pancreatic β cell) located in hypothalamic neurons [13], [15], [17].

In case of unsuccessful response (i.e. error), the basal ganglia and hypothalamus is actively engaged with the working system of cognitive control formed by the interaction between dopaminergic system and ACC [3], [16], [20]. The increased error commission associated with alcohol consumption might be related to decrease in dopaminergic functions [2], which is likely caused by decreased competence of glucose homeostasis regulation (i.e. decrease in blood glucose level) [12], [13], [15], [17]. Several studies have shown a link between the dopaminergic system and glucose homeostasis regulation [9] – [17]. In fact the link between the dopaminergic system and the blood glucose level is manifested in Parkinson disease, schizophrenia, and tardive dyskinesia in which disorders in dopaminergic functions are associated with disorders in peripheral glucose metabolism [9], [11], [14]. Also, administration of dopamine agonist like bromocripton may lead to hyperglycemia [25]. The mechanism of these processes is presently not fully understood, although it is known that antipsychotics act not only on dopamine receptors, but also on other neurotransmitter systems [25]. Putting into consideration the role of blood glucose level in the dopaminergic system and maintenance of brain functions [9] – [15], [26], as well as the vital role of dopamine as a major component of the error monitoring and processing system [1] – [3], [9], [11], it may be suggested that disorders in glucose homeostasis regulation may lead to disruption of the EMPS [9], [11], [21], [23] (Fig. 1). This is the main concept of the hypothesis of alcohol-related glucose-dependent system of error monitoring and processing (Fig. 1). This hypothesis explains a general view of the processes and mechanism involved in error commission under alcohol consumption. The central components of this hypothesis which determine the degree of error commission are the blood and brain glucose concentrations, as well as the brain dopamine level.

The difference in the amplitude of ERN (including individual differences) that is reflected in the magnitude of phasic dopamine response in the process of error processing [32], [34], may be related to genetic variations in dopamine receptors, especially DRD2 and DRD4, as well as other genes coding for enzymes and transporters of dopamine like cathehol-O-methyltransferase and dopamine transporter, DAT [17], [32], [34] (Fig. 1). Glucose receptors, including the insulin-like growth factor (IGF-1 and IGF-2) are located in significant numbers in DAT-expressing dopamine neurons of the midbrain [10], [13], [15], [17]. Glucose, insulin, IGF-1 and IGF-2 play a unique role in modulating the functions of the dopaminergic system [10], [13] – [15], [17]. In fact, the amygdala dopamine level increases immediately after injection of glucose [3], [12], [13].

IV. CONCLUSION

1) Blood and brain glucose levels play a vital role in error commission, and are related to the activeness of the error monitoring and processing system, EMPS through the modulation of the activity of the dopaminergic system.

2) The hypothesis of alcohol-related glucose-dependent system of error monitoring and processing, in which some concepts of [1], [2], including the fishbone hypothesis of glucose metabolism are incorporated [28] explains the general processes and mechanism of alcohol related disruption of the EMPS.

3) The major concept of this hypothesis holds that the disruption of the EMPS is related to the competency of glucose homeostasis regulation, which in turn may determine the dopamine level as a major component of EMPS.

4) Alcohol may indirectly disrupt the EMPS by affecting dopamine level through disorders in blood glucose homeostasis regulation. The effect of alcohol consumption on EMPS may be realized through its action on the blood and brain glucose levels.

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