Glycemia and Memory

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1. Introduction

One of the major functions of brain cells (neurons) is to receive, store, and participate in information retrieval – an important process for the successful daily activities of humans [1-3]. This function of neurons is termed ‘memory’ [1, 4, 5]. The present understanding of memory function is the product of the pioneering work of the German scientist Hermann Ebbinghaus [5]. Research suggests that many factors (both endogenous and exogenous) could affect memory function [6-8]. However, the effect of glucose on memory function remains extremely significant for the following reasons [9-12]. First, glucose is the vital energy substrate for neuronal functions [13, 14]. Second, inadequate level of glucose in the blood has been associated with a decrease in memory function [15]. Third, disorders in glucose metabolism have been related to various aspects of memory disorders [8, 16]. Furthermore, metabolic products of glucose in neurons themselves participate in one or more stages of memory formation [17-20]. Notwithstanding the significant accumulation of research data in last decades on the relationship between glycemia and neuronal functions [11, 12, 21], the mechanisms of how glucose affect memory functions remains entirely not understood. In this chapter, we shall examine the possible mechanisms and processes involved in the glucose regulation of memory function. We shall elaborate on the effect of glucose on the major processes of memory functions, precisely on the formation and retrieval of “neural data” – memory.

2. Memory as an integral function of neurons

More than 90% of human activities are dependent on higher integrative brain functions – a major subdivision, which is the topic of our discussion in the chapter. The higher integrative brain functions are the driving force during physical work. This is because the brain is the “chief” that directs resources for the successful completion of the task. Successful

activities of humans are largely dependent on memory function [22]. This function of neurons becomes vividly indispensable in situations involving its disorder. Memory is that function of neurons that involve storage and retrieval of information [22]. Some researchers have argued “forgetting” as an important aspect of memory function [23, 24]. This is partly because without forgetting, some new information might hardly go into storage. Hence, there are theories of forgetting – the most known ones are the single-trace fragility theory, decay theory, retrieval failure, interference theory, repression, consolidation theory [22]. Generally, several concepts/theories/models/hypotheses have been used to explain memory function of neurons [22, 25-27]. However, with steady scientific progress it is becoming clearer that none of these gives a complete, and precise definition of memory. In this regard, we shall also discuss briefly on the modern concepts of memory function of neurons in relation to cerebral glucose metabolism.

3. Factors that affect memory: Scanning for glucose’s role

Several factors affect memory functions, and they can either be endogenous or exogenous. Generally, the widely known substances/factors include narcotics, some prescription drugs, alcohol, some biomolecules (most notably glucose, fatty acids, amino acids), environmental factors, genetic and epigenetic factors [6-8, 21, 28]. Among the biomolecules that affect memory formation and retrieval, glucose is widely known and well-studied molecule. Glucose is the main substrate for memory formation and retrieval. Glucose not only provides the energy for memory formation and retrieval, but also, is involved in providing the necessary subunits or components for the formation of various neural components of the “neural data” – memory [9, 11, 12, 14, 21, 29, 30].

4. Glycemia: A key regulating factor for memory formation and retrieval

Decades of research have shown that a change in the glycemic level leads to a corresponding change in memory function of the brain [21, 29-41]. For example, decrease in blood glucose below the set point is reported to negatively affect memory function [9, 21, 29, 30]. Glycemia affect both memory formation and retrieval [9, 29].

Results of several studies have observed an inverted-U shaped dose-response relationship between glucose load and memory [31-34]. Recent study has shown that the optimum dose of glucose memory enhancement may differ under conditions of depleted glucose resources, and has other peculiarities [21].

Several controversies in the glucose memory facilitation effect remain. While some previous studies reported a “no effect relationship” between glucose and memory function [35, 36], others confirm this dose-response relationship [9, 31, 37, 38]. Researchers have suggested that this relationship is extremely dependent on the type of cognitive/memory task [39, 40].

Modulating factors of the glucose memory facilitation effect include physiological state (body mass index etc.), glucose dose, types of cognitive tasks used and cognitive demand [9, 39]. These factors are the possible sources of variance in the glucose facilitation of memory. Owen and colleagues (2008) investigated the dose response relationship of the glucose memory facilitation effect at glucose dosages of 0, 15, 25, 50 and 60 g [9]. They also examined the interactions between length of fasting interval (2 hours versus 12 hours) and the optimum dose of glucose. Their results revealed glucose facilitation of spatial working memory and verbal declarative memory following 25 g glucose. Furthermore, they observed that glucose memory facilitation effect is dependent on the following: the greater the length of fasting, the greater the glucose dose needed to facilitate memory [9]. So, at overnight fast (approximately 12 hours) the higher dose of glucose (i.e. 60 g) was needed to facilitate memory, whereas the lower dose (25 g) enhanced working memory performance following a 2 hour fast [9].

Figure 1. Comprehensive model of glucose memory facilitation

The mechanisms responsible for memory formation and retrieval are in constant perturbations of several factors (which might be competing factors, endogenous or exogenous in nature). The processes and mechanisms that ensure memory formation are the synthesis and activity of neurotransmitters (dopamine, d-serine, glutamate, acetylcholine etc), and

receptor subunit systems; metabolic signaling pathways; LTP/LTD (long-term potentiation/long-term depression); genetic and epigenetic modifications. (Memory retrieval might involve the same systems and processes, but with different mechanisms). Both memory formation and retrieval involve other brain functions, including attention. The systems and processes earlier stated are affected by cerebral glucose, which can serve as a substrate or produce intermediate substrates for some stages of their syntheses. The cerebral glucose content is dependent on the plasma glucose, both of which are under constant regulation by the brain (hypothalamus), some internal organs (liver, kidney). The blood glucose is constantly regulated, also by the effect of the neuro-endocrine control on the gastrointestinal tract, organs (such as the liver and kidney), as well as the effect of the hypothalamus on these organs. The processes that are regulated in these organs by the higher regulatory centres (e.g. hypothalamus) are food intake, gluconeogenesis, glycogenolysis, glucose cycling – to ensure normal glycemic allostasis. These higher control centres, and the memory function are under constant pressure from modulating factors such as exogenous (e.g. environmental, ethanol), endogenous (ethanol, some physiological indices) – might affect the resultant effect of glucose on memory function. Alcohol actions [42-45] as represented on the model are one of a bi-directional effect of summation, meaning that alcohol affects memory, as well as glucose regulatory systems. The receptor systems of the brain could be modulated by both alcohol and glucose [46, 47]. Alcohol is a psychotic substance in widespread usage in the world. Importantly, this substance is also produced *in vivo* during biochemical reactions in an organism (including humans). In certain circumstances (varying physiological state, for instance during pregnancy, disease states), the level of endogenous ethanol produced significantly increases. This increase might have a protective effect, but the reason or mechanism on the general role of the increase in endogenous concentration ethanol is not fully known. Ethanol affects some neurotransmitters and receptor systems. Ethanol acts on ionotropic, metabotropic G-protein receptor, potassium ion channels [48-50]. Ethanol acts on metabotropic receptors of mGluR5, mGluR2/3, mGluR1 [51-53]. These metabotropic receptors (mGluR3 of the prefrontal cortex) have been also implicated in cognitive disorders in especially alcoholics [54]. mGluR5 and mGluR1 receptors have been recently implicated in cognition [53]. Ethanol causes hypoglycemia [43, 55]. Besides, it is reported that alcohol causes disorders in the expression of several genes, although the mechanisms remain not quite clear [56].

Glucose plays a pivotal role in memory and might enhance LTP/LTD [57] as hypoglycemia is associated with deficits in memory, and learning [58, 59]. Apart from producing ATP for neural energy, other substances may be synthesized from glucose that affects neuronal activity and functions (including memory) [60-62]. For example, it is known that d-serine (maybe synthesized from glucose molecule) affects LTP, synaptic plasticity, enhance information retrieval [60-64]. Hypoglycemia is associated with both d-serine and NO release aimed at enhancing LTP [58]. These substances can also regulate neuronal transcription factors [65]. A vast number of these signaling pathways, neurotransmitter and receptor systems, and are dependent on the activity level of neurons, and activity dependent transcriptions – activators and suppressor [66, 67]. Other brain cells (especially astrocytes) can modulate neuronal activity through

various mechanisms, involving NMDA, d-serine, Ca²⁺, ATP, glutamate. Hence, these brain cells, which are affected by ethanol, might exert their resultant effect on neurons through astroglial linkages [68, 69].

5. Mechanisms of glucose effect on memory

While several studies have noted that glucose is a critical factor for memory function, what is not exactly clear is whether the effect is a direct or indirect one. In this section, we shall be mainly concerned with the mechanisms and processes of how glucose affects memory. Pertinent literature and latest developments in the field will be reviewed. It will be necessary to have in mind that memory function (formation and retrieval of neural data) is overlapped or is connected with other brain functions such as perception, attention etc. Therefore, glucose is a vital regulating factor for other brain functions. We shall consider the various views, concepts and models of how glucose affects memory function, and provide a comprehensive model of glucose memory facilitation effect (Figure 1).

5.1. Conceptual model of glucose memory facilitation

Smith and colleagues (2011) suggested a conceptual model of glucose facilitation of memory. Their neurocognitive model stipulates that glucose or acute stress/emotional arousal increases the concentration of circulating glucose in the periphery, and subsequently, the central nervous system. This increase in glucose exerts its effects on insulin, acetylcholine (ACh) synthesis and/or K_{ATP} channel function which subsequently leads to memory enhancement. Research has confirmed that there is specific cognitive domain that is most amenable to the glucose memory facilitation effect. The domain is episodic memory [41].

5.2. Comprehensive model of glucose memory facilitation

Memory formation or retrieval involves the synthesis of many biomolecules related to glucose metabolism [41, 70-73]. Glucose memory facilitation effect is a complex phenomenon comprising of several players including organs/systems of glucose metabolism, several competing factors, both genetic and epigenetic [42, 46, 72, 74]. Based on available data, here we propose a comprehensive model of glucose memory facilitation.

5.2.1. Neurotransmitter systems

Several neurotransmitter systems have been implicated in memory function. Here, we shall briefly consider a few of the principal neurotransmitter systems involved in memory function. The literatures report significant role of dopaminergic, glutamatergic, serotonergic, cholinergic, and noradrenergic systems in memory function [75-78]. We shall consider d-serine involvement in memory formation owing to the fact that its main receptor – the NMDA receptor is one of the key receptors involved in long-term memory formation (as a result of its long-term potentiation effect). Long-term potentiation, as opposed to long-term depression is

an integral process necessary for memory formation (especially long-term memory) [68, 69]. In fact, the NMDA receptor itself is implicated as one of the “alcohol receptors” [79]. Therefore, bi-directional effect of summation might occur through alcohol effect on neurotransmitter receptor systems, and glucose metabolism. The resultant effect is aggravation of memory dysfunction.

5.2.2. *Metabolic signaling pathways*

Since glucose is a metabolic product or must be involved in the cell’s metabolic pathways before its usefulness is realized; therefore, it is necessary to assume that metabolic pathways, involving glucose molecule are those pathways crucial for memory formation or retrieval. Unfortunately, research in this aspect is scanty. A number of signaling pathways are involved in glucose metabolism, but there is no sufficient evidence on how they are associated with memory function [80]. The widely studied signaling pathways that have a relationship between glucose metabolism and memory functions [81, 82] include CREB pathway [83, 84], AMPK [85, 86], Notch signaling [87], mTOR pathway [88] etc. The mTOR pathway has been majorly implicated in both glucose and memory function. Importantly, it was reported that glucose specifically affects memory through this pathway [84, 88, 89].

5.2.3. *Genetic and epigenetic regulation (activity dependent genes and epigenetic factors)*

The enhancement of memory by glucose might be related partly to the functions of activity dependent genes [90, 91], as well as epigenetic modifications (DNA methylation and histone modifications) by glucose or its metabolites [10, 91-94].

Since epigenetic profile of the cells play crucial role in glucose metabolism and neuronal cell functions, here, we would suggest that the initial epigenetic data (program) of the involved cells responsible for glucose memory facilitation are partly important for the differences reported in the literature. Epigenetic mechanisms of glucose metabolism and memory functions are regulated by the activity of transcription factors [10, 95]. Due to the importance of glucose in the functioning of the CNS [96], this regulation may be modulated by glucose molecule itself. For example, the data of Li et al. (2010) indicate that glucose regulates gene transcription in the liver by increasing the level of ATP, hence inhibiting AMP-activated protein kinase and inducing hepatocyte nuclear factor 4 α to stimulate cytochrome P450 7A1 gene transcription. Glucose also increases histone acetylation and decreases H3K9 methylation in the cytochrome P450 7A1 chromatin [97].

Recent experiments show that glucose is involved in the regulation of functions even at the progenitor cell level. Metabolism-sensing factors have recently been implicated in the regulation of neural stem cell fate through epigenetics modification [92, 98]. Hayakawa et al. (2013) reported that in embryonic stem cell population, glucose metabolite induces switching from the inactive state by Ogt-Sirt1 to the active state by Mgea5, p300, and CBP at the Hcrt gene locus [92]. The many pathways of glucose metabolism allows for the inclusion of its metabolic products into numerous cellular activities. For example, substrates of glucose metabolic pathways (acetyl-CoA, ATP, NAD⁺, glutamine, UDP-N-acetyl-glucosamine, N-acetyl-D-

mannosamine etc.) are candidates of epigenetic modifications. Acetyl-CoA is a donor of histone acetylation. NAD⁺ regulates Sirt1, a member of the sirtuin family, which functions as histone deacetylase and is also a metabolic sensor [92] (for review see Hayakawa et al. 2013). Epigenetic regulation by glucose or its metabolites affects memory functions and glucose metabolism itself through a shift in the cellular concentrations of critical metabolites implicated in higher integrative brain functions and metabolism.

A key mechanism for this epigenetic regulation is executed by the peripheral circadian oscillation [99]. However, importantly the peripheral clock and the central one could have some kind of metabolic associations. The concentration of NAD⁺/NADH plays critical link between metabolism and circadian rhythm [99]. Glucose and other metabolic substances may modulate the circadian rhythm by fluctuations in NAD⁺/NADH ratio. Compelling evidences now indicate that circadian misalignment could cause serious metabolic problems. In fact, transgenerational inheritance in metabolic alterations could be related to some mechanisms of epigenetic origin modulated by circadian clocks. Methylation of the leptin gene is associated with impaired glucose tolerance in the period of gestation [100]. This and many other discoveries on transgenerational inheritance represent substantial contribution to understanding the pathogenesis of diabetes, obesity in children [100-102].

Epigenetic regulations are not only affected by metabolites, but also body mass index, intrauterine environment, exercise, and other environmental factors [101].

It might be possible that epigenetic dysregulation of cerebral glucose metabolism is the result of cognitive impairment since glucose metabolism is controlled by epigenetic mechanisms and is also associated with cognition. Emerging evidences indicate that metabolic regulation (through epigenetic mechanisms) might be involved in memory function disorders. Reports show that a major pathogenesis of the CNS disorder such as Alzheimer's disease involves metabolic alterations, especially in glucose metabolism and associated hormonal or peptide signaling. Metabolic disorders in CNS pathologies are associated with brain insulin signaling. For example, a substantial quantity of insulin receptors is located in the hippocampus (a brain region which is basically concerned with the acquisition, consolidation and recall of new information) [103]. Impaired brain insulin signaling is implicated in cognitive impairment. Moreover, cognitive impairment is associated with diabetes and obesity, which are metabolic disorders [104]. De la Monte (2009) reported that in the initial stage of Alzheimer's disease, cerebral glucose metabolism is reduced by 45% and cerebral blood flow approximately by 18% [104]. Earlier, Arnáiz et al. (2001) reported that among twenty patients with mild cognitive impairment, impaired cerebral glucose metabolism and cognitive functioning were able to predict deterioration in mild cognitive impairment [105]. Mild cognitive impairment is an important indicator of the development of Alzheimer's disease. Notably, impairment in cerebral glucose metabolism was even a better predictor (75%) compared to neuropsychological tests (65%) widely used in the assessment of cognitive impairment [105]. The authors further concluded that measures of temporoparietal cerebral metabolism and visuospatial function may aid in predicting the evolution to Alzheimer's disease for patients with mild cognitive impairment [105].

These data are very important especially when we consider the increasing prevalence of cognitive disorders. For instance, it is estimated that in 2030 years, the cases of Alzheimer's disease in relation to 2012 will double (35.6 million). No doubts, research in this direction is exceedingly necessary [106]. Previously other authors have also reported that impairment in cerebral glucose metabolism is associated with decline in cognition and memory functions. Schapiro et al (1988) studied the rate of cerebral metabolism for glucose with positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose in a 47 year-old man with trisomy 21 Down's syndrome and Alzheimer related dementia, and reported poorer general intelligence, visuospatial ability, language, and memory function compared with younger (19-33 years) patients with Down's syndrome [107]. Cerebral metabolism for glucose in the older patient was 28% less than in the younger patients. Besides, hypometabolism was reported in the parietal and temporal lobes of the brain cortices. Importantly, the study of Schapiro et al (1988) was probably one of the most comprehensive investigations to show the association between different diseases involving CNS disorder and their relationship with cerebral glucose metabolism [107]. Approximately a decade after Schapiro et al.'s (1988) work [107], Pietrini et al. (1997) reported another predictor method for Alzheimer's disease risk prior to dementia in patients with Down's syndrome who were above 40 years (mean of 50 years) of age [108]. Pietrini, et al. (1997) confirmed their hypothesis that despite normal cerebral glucose metabolism at rest, an audiovisual stimulation (was used as a stress test) revealed abnormalities in cerebral glucose metabolism before the development of dementia in the parietal and temporal cortices which represent most vulnerable regions to Alzheimer's disease [108].

These CNS pathologies are now believed to be regulated by epigenetic mechanisms [109] and could have pretty good correlations with epigenetic mechanisms of cerebral glucose metabolism. Other CNS pathologies involving cognitive impairments such as epilepsy [110], schizophrenia [111, 112], Parkinson's disease [113], multiple sclerosis [114] had been associated with disturbances in glucose metabolism.

Figure 2. Interacting system (comprising of memory function, error monitoring and processing system, and modulators) of the reciprocability of neural systems of memory and the error monitoring and processing system. The modulators between the two reciprocals are glucose, other endogenous and exogenous substances/factors. N/B: Glucose can be an endogenous, as well as an exogenous factor; exogenous sources include per os administration of glucose, etc.; endogenous sources include gluconeogenetic production of glucose molecules, etc.

6. Glucose error commission depression effect: Cue to an overlapping bridge of neural error systems, memory and glucose metabolism?

Our data and those of other authors show strong negative relations between glycemia and error commission. Whether this is due to the effect of glucose on memory or neural systems of error commission, is what is not exactly clear (see figure 2). There are no precise borders between the brain regions responsible for memory and error commission. Therefore, it is possible that the effect of glucose on error commission could be the resultant effect on the chief brain regions for memory function. Neural systems (or regions) of memory implicated in error commission have been linked to brain regions also involved in some aspects of memory function [115-117]. The brain systems concerned with error commission are referred to the error monitoring and processing system. The major regions of the brain concerned with error commission are the anterior cingulate cortex, basal ganglia, prefrontal cortex. These brain regions (especially the prefrontal cortex) are also implicated in memory function [45, 115, 117].

7. Effect of alcohol on glycemia and memory: More than just a bi-directional modulating effect

Alcohol is the most prevalent psychotic substance in the world. While alcohol affects glucose metabolism, memory also remains one of the most vulnerable functions of the brain that suffers from the negative effect of alcohol use [15, 16, 29, 30, 44, 45, 118]. Hence, there is the need to examine its effect on memory function and glucose regulatory mechanisms. Here, we view alcohol as a positive modulating factor for memory (especially at endogenous concentration), and as a psychopathological substance at blood concentrations higher than the normal physiological level.

8. Conclusion

Glucose is the foremost energy substrate for neuronal functions (memory). It provides the energy bonds needed for the formation of memory and takes part in information retrieval from neural stores. Both glucose and its metabolites are involved in different stages of memory formation and retrieval. Several factors such as ethanol, some physiological indices, and other competing factors modulate the effect of glucose on memory function.

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