How Fructose Affects the Hippocampus

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Abstract: This review explores the effects of fructose on the hippocampus: hippocampal function and structure, hippocampal neurogenesis, and hippocampal cognitive function. First, this result confirms that excess fructose intake affects the microstructure of pathways connecting the hippocampus to other brain areas. Fructose has the potential to affect neurogenesis in the hippocampus, and a diet high in fructose can impair learning and memory, leading to cognitive impairment. However, further research is needed to apply animal experiments to humans in the future. The literature review focused on the effects of fructose, but a balanced intake of other nutrients also needed to be considered.

Keywords: fructose, hippocampus, memory

1. Introduction

High fructose corn syrup generally replaced sucrose in beverages in the late 20th century. Reassessing the connection between fructose and health is necessary.

Adequate fructose intake of 50 g/day or 10% of energy is thought to have no negative effect on lipid and glucose control, while 100 g/day has no effect on body weight (Rizkalla, 2010) [7].

The effect of fructose on the hippocampus has also attracted some attention. In the early 20th century, scientists recognized that the hippocampus plays a fundamental role in certain types of memory and learning (Scoville and Milner, 1957) [9]. The hippocampus is primarily in charge of long-term memory storage conversion, spatial memory and positioning, and other functions, which are equivalent to the GPS in the brain. Humans may have Alzheimer's disease or dementia if the hippocampus is dysfunctional. Studies have shown that excessive sugar intake is a significant cause of hippocampal damage.

This chapter reviews the critical literature on the effects of a high fructose diet on the hippocampus in the human body. This topic mainly focuses on three aspects: the function and structure of the hippocampus, neurogenesis, and cognitive function. This chapter begins with the discovery of the hippocampus: what is the hippocampus, and its importance to the human body. This analysis is followed by fructose: what are fructose, its metabolism, and its damage to the human body. Finally, three effects of fructose on the hippocampus are discussed. This review critically evaluates the effect of fructose on the hippocampus.

2. Results and discussion

2.1 Discovery of the hippocampus

The hippocampus is the part of the brain in the central nervous system of mammals that has been most studied in detail. Its general anatomical resemblance to the hippocampus inspired its name for the sea creature, the hippocampus (Knierim, 2015) [5]. Hippocampus is a group of structures in the limbic system that includes the dentate gyrus (DG), the hippocampus, the subiculum, presubiculum, and parasubiculum, as well as the entorhinal cortex. These structural bands make up the hippocampal structure. The limbic system is considered a "primitive brain" deep within the brain. It involves hunger, motivation, sexual drive, emotions, pain, pleasure, appetite, and memory. The hippocampus is the back of the limbic lobe of the brain. The hippocampus sends the output through the output lobe of the receiving part of the entorhinal cortex in the frontal hippocampus of the brain. The brain is given a spatiotemporal framework by the hippocampus in which the cognitive aspects of many senses, emotions, and experiences are closely connected (Knierim, 2015) [5]. Rafael Lorente de Nó [6], however, discovered that it was necessary to give each little subregion its name in 1934 since they were sufficiently diverse in their cellular organisation and connections. Thus, he gave the three CA areas that include pyramidal neurons the names CA1, CA2, and CA3, as well as the terminal portion of the DG lobe that contains polymorphic cells like CA4.

The hippocampus has been understood to be important for some types of memory and learning since the early 1950s. The ability to permanently encode new information into long-term memory was permanently lost in a patient who underwent bilateral hippocampus resection for refractory epilepsy, according to Scoville and Milner's seminal research (Scoville and
pathways connecting the hippocampus and other brain regions. High-fructose diets have particularly negative effects on changes in human hippocampal volume and connectivity, unravelling the mystery of fructose's pair of microstructural effects on brain function.

2.3.1 Structure and function of the hippocampus

The hippocampus is essential for learning, memory, and spatial navigation. The hippocampus is responsible for primary human memory in the recent past, holding memories vividly over weeks for quick access. In addition, the hippocampus acts as a switching station in the memory process. When neurons in the cerebral cortex receive various sensory or perceptual messages, they pass those messages to the hippocampus. Storing or discarding information is also processed by the hippocampus in the human brain.

2.2 Fructose and its metabolism

Fructose provides rich nutrients in natural fruits, and it is a monosaccharide. However, in sweets and beverages, fructose tends to provide only "calories" and no other nutrients in sweets and drinks (Bray, 2007) [2]. Honey, dates, molasses and figs contain 10% fructose, while grapes, raw apples, persimmons and blueberries contain 5-10% fructose. Most vegetables and meats also do not contain fructose (Bray, 2007) [2]. In addition, the taste and sweetness of fructose are better than that of traditional sugar. Commercially pure fructose is a crystalline form produced from corn or sucrose and used as an ingredient in food and beverages.

The body similarly metabolises most sugars. However, fructose is handled a little differently than other sugars. Whether it is natural fructose in fruit or fructose as an added component, their metabolism is mainly from the liver. It is difficult to absorb from the gastrointestinal tract after fructose is digested, and it does not stimulate the release of insulin from the isolated pancreas like glucose. It cannot enter most cells because they lack glutamate-5 (Bray, 2007) [2]. Fructose produces fructose-1-phosphate in the liver, kidney and small intestine under the action of specific fructokinase. After that, dihydroxyacetone phosphate and glyceraldehyde are generated under the catalysis of 1-phosphate fructose aldolase. The latter is phosphorylated by glyceraldehyde kinase to generate glyceraldehyde-3-phosphate. Finally, the product and dihydroxyacetone phosphate are oxidatively decomposed through the glycolysis pathway or synthesised glycogen through gluconeogenesis (Sun and Empie, 2012) [10].

The main organ that can metabolise fructose is the liver, fructose does not require the participation of insulin, so it has less impact on blood sugar, but this does not mean that people can eat many fructose-rich foods. Because fructose does not depend on insulin to directly enter the cell for metabolism, its intake also increases human hepatic gluconeogenesis and de novo lipogenesis (DNL), and raised triglyceride levels, it is more likely to cause fat deposition in human organs.

Fructose is widely used in food processing and other fields. It is the sweetest natural sugar with good taste and a low glycemic index. Fructose does not induce the body to secrete insulin and leptin-like glucose, making it easier to feel full and reducing eating. However, excessive intake of fructose can have adverse effects on human health.

2.3 The effect of fructose on the hippocampus

2.3.1 Structure and function of the hippocampus

In 2020, a study by Clark et al. [3] investigated whether dietary fructose intake in 103 children aged 7-11 was associated with changes in human hippocampal volume and connectivity, unravelling the mystery of fructose's pair of microstructural pathways connecting the hippocampus and other brain regions. High-fructose diets have particularly negative effects on
hippocampal function during sensitive periods of neurocognitive development, such as childhood and adolescence. To investigate the effects of fructose intake on the neuroanatomy of the hippocampus in children, including grey and white matter, we employed an in vivo magnetic resonance imaging (MRI) method that provides a non-invasive way to observe neurodevelopment in the human brain. T1-weighted acquisitions can quantify grey matter volume in specific brain regions, and diffusion tensor imaging (DTI) is a sensitive imaging method for determining the microstructure of white matter tracts that connect different brain regions. They used structural MRI and diffusion MRI to look at the relationship between dietary fructose and added sugar intake and hippocampal development in healthy children aged 7 to 11.

Increased consumption of fructose, monosaccharides, glucose and added sugars was discovered to be connected with increased volume of the CA2/3 subregion of the right hippocampus. On the other hand, greater intake of fructose-related substances was the only factor associated with increased MD of the normal cingulate-prefrontal brain connection. Furthermore, they found an association in the right but not the left hemisphere, broadly consistent with previous studies showing the effects of environmental damage on the hippocampus. Notably, the increase in hippocampal CA2/3 subfield volume may be due to inflammation and synaptic pruning delays triggered by sugar intake, which typically occurs in early adolescence. This view is supported by Cisternas et al. (2015) [4], who investigated fructose's effect on synaptic plasticity in the hippocampus to elucidate the underlying mechanisms behind behavioural outcomes. Using electrophysiological recordings of input-output analysis, synaptic integrity was evaluated. The effect of fructose on the synaptic structure was also determined by examining hippocampal synaptic fragments using electron microscopy. The number of synaptic contacts was found to decrease from 27±3 per 100 μm2 in the control group to 17±4 per 100 μm2 in the treated group. During adolescence, hippocampal volume peaks, and synaptic pruning begins. In general, greater habitual glucose or added sugar consumption was linked to an increase in right CA2/3 volume but not hippocampal connectivity. Additionally, it was discovered that the CA3 subfield exhibited preferential sensitivity, and they could not decipher the boundary between the CA2 and CA3 subfields due to FreeSurfer's pre-defined limitations. Future research should take into account manual tracking to confirm whether consuming too much-added sugar has a preference for the CA3 subregion of the hippocampus. These results confirm animal studies demonstrating a larger consumption of added sugars, particularly fructose, throughout childhood is linked to alterations in hippocampus structure and connectivity.

2.3.2 Hippocampus neurogenesis

The hippocampus is involved in learning and spatial memory, and neurogenesis in the hippocampus is required to form new memories. It is predicted that fructose blocks neurogenesis in the hippocampus. In 2011, Van der Borght et al. [11] studied the effect of ingesting three different sugar solutions (sucrose, glucose and fructose) on hippocampal neurogenesis over four weeks. In a study limited to 24 male Sprague-Dawley rats, the rats were divided into four groups.

Hippocampal neurogenesis was reduced by about 40% after four weeks of ingesting fructose or sucrose solutions. It is sucrose and fructose that are impaired in hippocampal neurogenesis, suggesting that fructose is the component that affects neurogenesis since sucrose is a disaccharide composed of glucose and fructose. The reduction in hippocampal neurogenesis was accompanied by an increase in hippocampal apoptosis and increased circulating TNF-α levels. Therefore, they speculate that the decrease in hippocampal neurogenesis may be due to increased apoptosis induced by TNF-α.

Similarly, in 2015, Cisternas et al. [4] found that MetS decreases adult hippocampal neurogenesis. They examined the effects of MetS on hippocampal neurogenesis as the generation of new neurons contributes to neural plasticity and memory.

With a high intake of fructose, hippocampal neurogenesis is reduced. The studies by Van der Borght et al. and Cisternas et al. have some limitations. In their studies, fructose-fed animals also frequently reduced their food intake to compensate for the caloric intake from the monosaccharide solution. In these cases, there is no additional caloric expenditure, but there is a considerable reduction in other nutrient intakes.

2.3.3 Cognitive function of the hippocampus

Subsequently, high fructose intake also affected cognitive function in the hippocampus, which was irreversible. Finally, in 2015, Wu et al. [12] found that an eight-month high-fructose diet impairs learning and memory in male rats, leading to cognitive impairment.

The insulin signalling system in the hippocampus, which is essential for hippocampal-dependent memory processing, was severely impaired by a high-fructose diet. One of the potential mechanisms of fructose's impact on the hippocampus may be T2DM (insulin resistance). Numerous studies have shown that T2DM is associated with cognitive impairment and that T2DM mainly affects hippocampus-based declarative memory performance. Insulin resistance is caused by ingesting high-fructose foods and decreased insulin receptor-mediated signalling in the brain and learning. Poor memory is associated with Insulin resistance (HOMA-IR) and mean escape latency in this experiment.
A high-fructose diet can cause peripheral insulin resistance, which can affect hippocampal-dependent cognitive function. Recent studies have shown that fructose intake-induced cognitive impairment is related to impaired insulin signalling and increased oxidative stress and mitochondrial motility associated with changes in the study, especially in the frontal cortex. In 2018, Sangüesa et al. [8] found fructose-drinking mice exhibited abnormal glucose tolerance tests and impaired insulin signalling in the frontal cortex, manifested by markedly reduced insulin receptor substrate two protein levels and phosphorylation of protein kinases, and increased levels of degrading enzymes. These findings are consistent with studies demonstrating comparable outcomes in the cerebral cortex and hippocampus and demonstrate that the fructose-induced Mets-like state influences numerous oxidative stress processes in the brain, causing lipid peroxidation and protein nitrosylation. Acute fructose treatment results in memory impairment, altered enzymatic antioxidant defences, and oxidative damage to lipids and proteins. These problems are irreversible after returning to a regular diet.

The current study shows that the cognitive impairment caused by fructose intake is related to impaired insulin signalling, oxidative stress, and increased mitochondrial motility. However, whether this trend also occurs in humans requires further research. In addition, further studies are needed to understand whether protective mechanisms are associated with youth in these animal models or sex differences.

3. Conclusion

In conclusion, the storage and processing of spatial information involve the hippocampus, one of the essential organs in the human brain. This literature review highlights the damage of fructose to the hippocampus in the brain. Overall, these studies emphasise that excessive fructose intake can affect the hippocampal structure and reduce overall hippocampal connectivity in the brain, especially in childhood. Subsequent, fructose may affect hippocampal neurogenesis. Last, a high fructose diet can lead to cognitive impairment by impairing learning and memory, and these problems can be lifelong. However, such studies remain narrow in focus on animal studies of the effects of fructose on hippocampal function in rats. Its impact on hippocampal function in the human brain requires further study in the future. In addition, most studies looking at fructose brain effects on hippocampal function focus only on ingested fructose, ignoring other nutrients. One of the tough challenges for all researchers in this domain is to study the effect of excessive fructose intake on hippocampal function in people of different ages and genders, and to ensure a balanced intake of other nutrients, as these effects are irreversible.

References