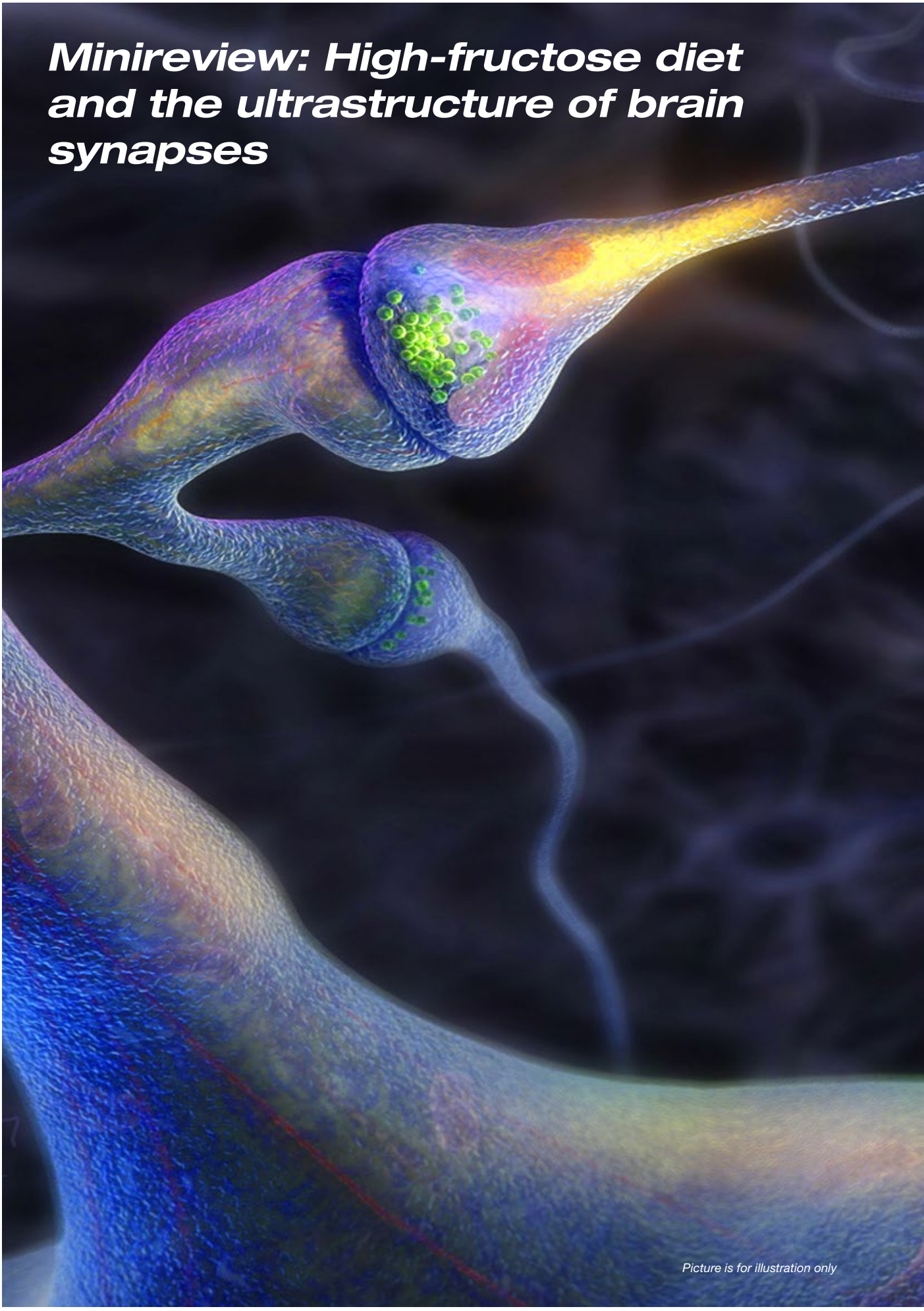
Minireview: High-fructose diet and the ultrastructure of brain synapses



Picture is for illustration only

G. Mark Marcello[1], Péter Sótonyi[1], Miklós Süth[1], Bence Rácz[1]*

Minireview: High-fructose diet and the ultrastructure of brain synapses

Keywords: fructose, sucrose, synaptic plasticity, ultrastructure, brain

1. SUMMARY

The brain is the hungriest organ. With this great energy demand, the brain's function may depend on what it is being fed to a greater extent than previously appreciated. Consumption of fructose and glucose in sustained high quantities in industrially processed foods and beverages in the modern Western diet raises complex questions of metabolic, and neurological well-being. Here, we review the effects of sugar on hippocampus associated short term memory. The following work on rodent models, and human clinical trials expound the influence of increased fructose versus glucose, or starch intake on the synaptic organization of a brain region extensively involved in cognitive functions. Through the well supported structure-function relationship of dendritic synapse profiles, synaptic functionality effects of increased fructose versus glucose consumption on hippocampal synapse ultrastructure may be seen. Together with behavioral, and functional findings, ultrastructural data demonstrate potential changes in hippocampal associated cognitive processes directly related to either elevated fructose or glucose intake.

2. Abbreviations used in this paper:

HFCS: High fructose corn syrup

HFHS: High fat high sugar

LTD: Long-term depression

LTP: Long-term potentiation

MSB: Multi-synaptic bouton

PSD: Postsynaptic density

3. Effect of fructose on the neural system

Function and structure must be considered concurrently to untangle the neurological effects of persistent increased sugar intake. In processed foods and drinks 'sugar' is added primarily as either sucrose (the disaccharide of covalently bonded fructose and glucose) or high fructose corn syrup (HFCS). HFCS may contain a higher percentage of glucose in certain applications but the commonly used HFCS-55 solution (55% fructose and 45% glucose) is most commonly used in rodent model studies. **[1]** Sugar supplemented industrially processed foods are a notable component of the Western diet.

An applicable simplification of the complex Western diet is the high fat high sugar (HFHS) diet. The sugar half of the HFHS diet is practically represented by sucrose or HFCS-55; in turn, roughly half of these sugars are fructose. **[2]**

To get a more precise understanding of what fructose does to the brain, studies focus on either pure fructose compared to glucose or look at the two sugars together in the form of sucrose or HFCS. In adult, and in young rats it was shown that short term pure fructose feeding may induce metabolic perturbations with markers of neuroinflammation in the hippocampus. **[3,4]** In an adult mouse model of metabolic syndrome, pure fructose supplementation in water was found to decrease adult neurogenesis alongside decreased performance in a paradigm of hippocampus-associated learning and memory **[5]**, showing decreased long-term potentiation (LTP), and decreased long-term depression (LTD) - both forms of memory-related synaptic plasticity. **[6]**

[1] University of Veterinary Medicine, Budapest, Department of Anatomy and Histology
* corresponding author

Another mouse model study found that while high fructose diet decreases physical activity, it does not affect neurogenesis, and learning. **[7]**

Such contradicting findings may be seen throughout the current literature of neuroscience focused on fructose. It is clear that more studies are warranted in order to gain a more exact understanding of the impact of fructose on multiple aspects of brain function. Pairing functional with structural findings therefore seems essential. More precise quantification of synaptic ultrastructure is required to support findings of decreased functional synaptic plasticity, and decreased cognitive performance on hippocampus-associated spatial learning, and memory tasks. Most studies use biochemical methods with a molecular approach on brain homogenates to reveal potential effects of fructose on hippocampal cognitive function. Extrapolation of the effect of fructose supplementation on the fine structure of neuropil from hippocampal homogenates lends itself to questionable conclusions of synaptic structural plasticity.

The dendritic spine-synapses of hippocampal CA1 – the hippocampus' region of primary excitatory input **[8]** - fluctuate in size with different morphological characteristics in response to input from Schaffer collaterals of CA3 as well as afferent input from outside the hippocampus. The ultrastructural changes of dendritic spines in response to axonal input may be considered neuroanatomical indicators of synaptic efficacy. **[9]** The CA1 is the brain region with the most quantitative data available. **[10]** Dendritic spines enlarge following LTP, and decrease in size following LTD. **[10]** As such, LTP and LTD associated functional synaptic plasticity may be neuroanatomically quantified through measuring ultrastructural parameters of structural synaptic plasticity. In addition to ultrastructural measurements of dendritic spines, the neuropil may be investigated for specific markers of structural synaptic plasticity. A multi-synaptic bouton (MSB), a structure represented by one terminal bouton forming a synapse with two or more dendritic spines, and a perforated post-synaptic density (pPSD) are both structures indicating a robust synaptic connection. MSBs are markers of late phase LTP and indicate naturally forming complexity with maintained information specificity in a neural network. **[11,12]** MSBs indicate presynaptic functional strength while pPSDs are markers of powerful postsynaptic strength/excitability **[13,14]**. Therefore, finding MSBs, and pPSDs may be taken as indicators of structural synaptic plasticity as well as robust network functionality. As the flow of information transfer in neuronal circuitry dynamically changes so the underlying synaptic ultrastructure changes with it. A change in functionality in this case may be supported by observable, and quantifiable structural change.

Studying the effect of fructose supplementation on the extensively studied hippocampus is relevant in beginning to unravel how increased fructose intake may influence the brain's function, and structure. The hippocampus is more directly relevant however; it has been shown to have a significant higher order functional role in the complex circuitry of feed intake regulation. **[15]** The hippocampus is responsive to both leptin, and insulin; fascinatingly, double meal eating has been observed in amnesic people with hippocampal damage. **[15]** Studying the hippocampus may not only clarify the effect of fructose supplementation on spatial learning, and memory but may show changes in the feed intake regulation of fructose itself. To determine what effect increased fructose supplementation may have on memory it is important to clarify what question is being asked, and then tested. In rodent models: species, age, form and concentration of sugar, length of treatment, presence of body weight gain, and supplementation in water or in food are all factors which provide a specific trial environment which may only be accurately compared to analogous studies. Such likeness is essential for appropriate comparability between rodent model trials before we may begin to tease apart findings of fructose' cognitive influence in human clinical trials, and what true cognitive impact fructose may have epidemiologically in sustained lifelong Western diet.

4. Acknowledgement

The Project is supported by the European Union and co-financed by the European Social Fund (grant agreement no. EFOP-3.6.2- 16-2017- 00012). BR were supported by the János Bolyai Research Fellowship of the Hungarian Academy of Sciences.

5. References

[1] Rippe JM, Angelopoulos TJ (2013) Sucrose, high-fructose corn syrup, and fructose, their metabolism and potential health effects: what do we really know? *Adv Nutr* 4: 236-245.

[2] Moeller SM, Fryhofer SA, Osbahr AJ, 3rd, Robinowitz CB, Council on S, et al. (2009) The effects of high fructose syrup. *J Am Coll Nutr* 28: 619-626.

[3] Cigliano L, Spagnuolo MS, Crescenzo R, Cancelliere R, Iannotta L, et al. (2018) Short-Term Fructose Feeding Induces Inflammation and Oxidative Stress in the Hippocampus of Young and Adult Rats. *Mol Neurobiol* 55: 2869-2883.

[4] Djordjevic A, Bursac B, Velickovic N, Vasiljevic A, Matic G (2015) The impact of different fructose loads on insulin sensitivity, inflammation, and PSA-NCAM-mediated plasticity in the hippocampus of fructose-fed male rats. *Nutr Neurosci* 18: 66-75.

[5] Cisternas P, Salazar P, Serrano FG, Montecinos-Oliva C, Arredondo SB, et al. (2015) Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance. *Biochim Biophys Acta* 1852: 2379-2390.

[6] van der Borght K, Kohnke R, Goransson N, Deierborg T, Brundin P, et al. (2011) Reduced neurogenesis in the rat hippocampus following high fructose consumption. *Regul Pept* 167: 26-30.

[7] Rendeiro C, Masnik AM, Mun JG, Du K, Clark D, et al. (2015) Fructose decreases physical activity and increases body fat without affecting hippocampal neurogenesis and learning relative to an isocaloric glucose diet. *Sci Rep* 5: 9589.

[8] Niciu MJ, Kelmendi B, Sanacora G (2012) Overview of glutamatergic neurotransmission in the nervous system. *Pharmacol Biochem Behav* 100: 656-664.

[9] Harris KM, Stevens JK (1989) Dendritic spines of CA 1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. *J Neurosci* 9: 2982-2997.

[10] Harris KM, Weinberg RJ (2012) Ultrastructure of synapses in the mammalian brain. *Cold Spring Harb Perspect Biol* 4.

[11] Toni N, Buchs PA, Nikonenko I, Bron CR, Muller D (1999) LTP promotes formation of multiple spine synapses between a single axon terminal and a dendrite. *Nature* 402: 421-425.

[12] Toni N, Buchs PA, Nikonenko I, Povilaitite P, Parisi L, et al. (2001) Remodeling of synaptic membranes after induction of long-term potentiation. *J Neurosci* 21: 6245-6251.

[13] Sorra KE, Harris KM (1993) Occurrence and three-dimensional structure of multiple synapses between individual radiatum axons and their target pyramidal cells in hippocampal area CA1. *J Neurosci* 13: 3736-3748.

[14] Bourne JN, Harris KM (2008) Balancing structure and function at hippocampal dendritic spines. *Annu Rev Neurosci* 31: 47-67.

[15] Davidson TL, Kanoski SE, Schier LA, Clegg DJ, Benoit SC (2007) A potential role for the hippocampus in energy intake and body weight regulation. *Curr Opin Pharmacol* 7: 613-616.