In: Fructose ISBN: 978-1-62081-126-9
Editors: Brandon M. Johnston and Aaron B. Collins

Chapter 4

DETRIMENTAL EFFECTS OF EXCESSIVE FRUCTOSE INGESTION ON MEMORY AND OTHER BRAIN FUNCTIONS

E. C. Bruggeman[1], A. P. Ross[1], and M. B. Parent[1,2]
[1]Neuroscience Institute, Georgia State University,
Atlanta, Georgia, US
[2]Psychology Department, Georgia State University,
Atlanta, Georgia, US

ABSTRACT

Fructose is a monosaccharide found naturally in fruits, honey, and some vegetables. It also is added to foods in the form of sucrose, concentrated fruit juices, corn syrup, high fructose corn syrup, and crystalline fructose. The addition of fructose to a wide variety of foods and beverages has led to a significant increase in fructose consumption over the past three decades. This is a cause for concern, because excessive intake of fructose causes a variety of pathological effects, including hypertriglyceridemia, visceral adiposity, hyperinsulinemia, non-alcoholic fatty liver disease (NAFLD), elevated inflame-matory factors, insulin resistance, Type 2 diabetes, and hypertension/ cardio-vascular disease. These physiological effects of a high fructose diet are well-documented; in contrast, relatively little is known about the effects of excessive fructose consumption on the central nervous system. The purpose of this chapter is to review the effects of high fructose intake in rodents on the brain, with a particular focus on plasticity and memory. Evidence implicating elevated triglyceride levels, NAFLD, neuroinflammation, and oxidative stress in the pathological effects of a high fructose diet on brain function is presented. Sex-dependent effects of elevated fructose consumption and application of results from experimental models of fructose consumption to the human population also are discussed.

INTRODUCTION

Fructose is a monosaccharide found naturally in fruits, honey, and some vegetables. It also is added to foods in the form of sucrose (50% fructose), corn syrup, high fructose corn syrup (42 or 55% fructose), fruit juice concentrates (over 60% of calories in apple juice), and crystalline fructose (almost 100% fructose) [1]. In its various forms, fructose is added to countless foods, including carbonated beverages, fruit products (juices, jams, jellies, and canned fruit), baked goods, cereals, and dairy products [1]. Indeed, it is a challenge for the North American consumer to purchase processed foods that do not contain some form of added fructose.

The addition of fructose to such a wide variety of foods and beverages has led to a significant increase in fructose consumption [2, 3]. Between 1970 and 2005, the average annual intake of high fructose corn syrup increased in the United States from 0.5 pounds to 59 pounds, and the average intake of total sugars increased by 19% [4]. The average American's current fructose intake is estimated to be 10% of total daily energy and is over 17% in the 90th percentile [2]. Overall, men tend to consume more fructose than women, and adolescent boys are the highest consumers, ingesting an average of 75 grams of fructose per day [3]. When body weight is corrected for, however, children 1-10 years of age are the highest consumers, primarily due to consumption of fruits and fruit products [3]. The majority of fructose consumed by the other demographic groups is mostly from added sources [2], rather than from naturally-occurring sources, such as fruit. High fructose corn syrup is largely responsible for the increase in fructose consumption [5-7].

Fructose is metabolized differently than glucose, the other main dietary monosaccharide. Whereas glucose can be metabolized by all cells, fructose is metabolized primarily by the liver [8]. Upon ingestion, fructose is absorbed through the gastrointestinal tract via the GLUT5 transporter [9]. It is then transported to the liver via the hepatic portal vein and subsequently undergoes glycolysis within hepatocytes [8, 10, 11]. An important difference between glucose and fructose metabolism is that fructose metabolism is not regulated by the enzyme phosphofructokinase, which limits the production of triglycerides from glycolysis [11]. By bypassing this rate-limiting step, fructose ingestion results in larger elevations in plasma triglyceride concentrations than does glucose ingestion [12, 13]. Fructose-induced increases in plasma triglyceride concentrations are significant within 3 days [13] and persist as long as high fructose ingestion continues [13, 14]. Another key difference between fructose and glucose is that fructose does not stimulate the release of insulin from the pancreas [15, 16].

PERIPHERAL EFFECTS

When consumed in excessive amounts, a high fructose diet produces large increases in plasma triglyceride concentrations, liver mass [12, 17-20], liver lipid content [19, 21], and visceral adipose tissue [22-24]. Despite these increases, fructose consumption does not typically increase body mass [18, 19, 25], but see [26]. Excess fructose consumption can lead to numerous pathologies in both rodents and humans, including glucose intolerance [27, 28], insulin resistance [29-33], Type 2 diabetes [34, 35], non-alcoholic fatty liver disease

(NAFLD) [36, 37], hypertension [30, 33, 38], oxidative stress [35, 39], and cardiovascular disease [27, 40, 41].

CENTRAL EFFECTS

In contrast to the wealth of studies investigating the peripheral consequences of elevated fructose consumption, relatively few studies have focused on the effects of fructose on the central nervous system. One of the first studies to investigate the effects of excessive fructose consumption on brain function tested the effects of feeding hamsters pellets containing 60% fructose for 6 weeks [42]. Brain slices were maintained *ex vivo*, stimulated with insulin, and then several proteins in the insulin signaling cascade were quantified using Western blots. The results indicated that the high fructose diet produced central insulin resistance. Specifically, it reduced phosphorylation of the insulin receptor-β subunit (IR-β), which is the initial step that occurs when insulin binds to the insulin receptor (Figure 1). In addition, the high fructose diet significantly reduced phosphorylation of insulin receptor substrate-1 (IRS-1) and Akt/Protein kinase B (Akt/PKB), two downstream effector proteins in the insulin signaling cascade (Figures 1, 2). In the hippocampus, the high fructose diet decreased protein tyrosine phosphatase, an enzyme involved in regulating the phosphorylation of the insulin signaling proteins, and impaired insulin-induced long-term depression (LTD), a measure of synaptic plasticity.

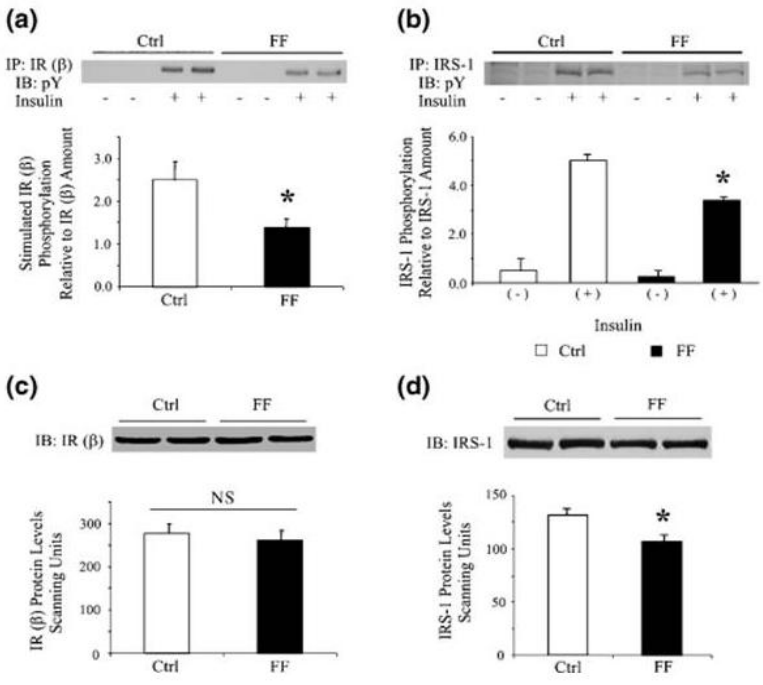

Figure 1. The effects of eating a control (Ctrl) or high fructose diet (60%; FF) on (a) insulin-mediated tyrosine phosphorylation of neural IR-β subunit, (b) insulin-mediated tyrosine phosphorylation of the substrate protein IRS-1, (c) total IR-β protein, and (d) total IRS-1 protein (*$p < 0.05$ vs. control hamsters). From [42] used with permission.

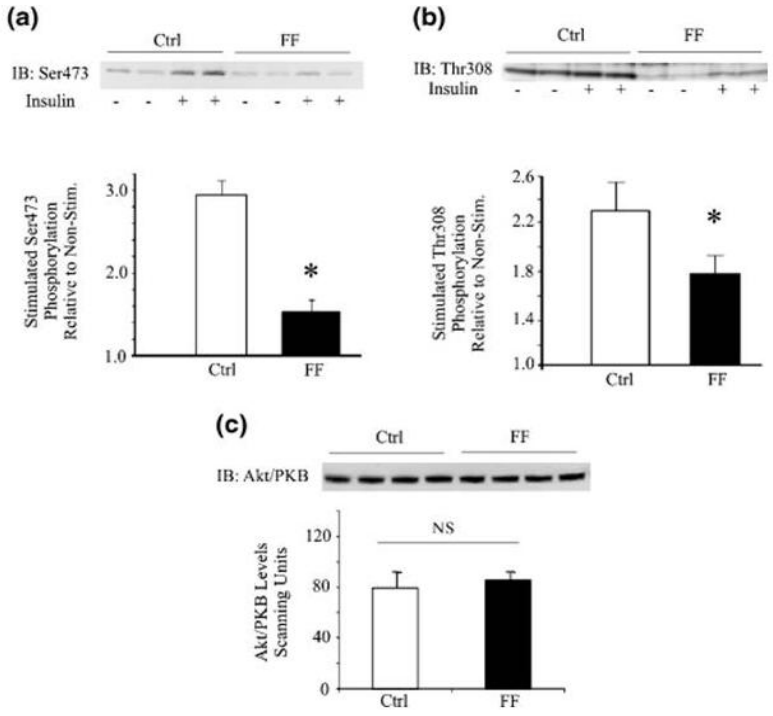

Figure 2. The effects of eating a control (Ctrl) or high fructose diet (60%; FF) on (a) insulin-mediated serine phosphorylation of Akt/PKB protein, (b) insulin-mediated threonine phosphorylation of Akt/PKB protein, and (c) total Akt/PKB protein (*$p < 0.05$ vs. control hamsters). From [42] used with permission.

Since then several other studies have been published indicating that elevated fructose consumption impairs normal brain function in a variety of ways. Rats that are fed a 60% fructose diet for 6 months demonstrate central leptin resistance as indicated by reduced basal phosphorylation levels of signal transducer and activator of transcription 3 (STAT3; a key protein in the leptin signaling cascade) in the hypothalamus [43]. Elevated fructose consumption also produces neuroinflammation. When rats are provided 10% fructose in the drinking water for 4 months, nuclear factor kappa B (NFκB) becomes activated in the cerebral cortex [44]. NF-κB is responsible for initiating the transcription of many different inflammatory factors, and the activation of this protein is a strong indicator of neuro-inflammation [45, 46]. Interleukin-1β and tumor necrosis factor-α, two primary inflammatory factors, also are significantly elevated in the cortices of fructose-drinking rats, as are levels of NADPH oxidase, which indicates oxidative stress [44]. Rats that are given a 23% fructose solution in their drinking water for 1 month have reduced neurogenesis in the dentate gyrus region of the hippocampus [47]. Finally, rats that are given a 10% fructose solution exhibit increased amyloid-β deposits in the cortex and hippocampus [48].

The fact that a high fructose diet disrupts the effects of insulin in hippocampal neurons led us to hypothesize that a high fructose diet would impair memory. This hypothesis is based on the fact that the hippocampus plays a pivotal role in memory [49] and converging lines of evidence indicate that neural insulin signaling facilitates hippocampal-dependent memory [50]. For instance, extensive evidence suggests that peripheral insulin resistance and Type 2 diabetes are associated with deficits in hippocampal-dependent declarative memory [51-55].

In addition, learning and memory of a spatial water maze experience are correlated with activation of the hippocampal insulin signaling pathway [55, 56]. Most importantly, direct infusions of insulin into the hippocampus enhance performance in a variety of memory tasks, and the memory-enhancing effects of hippocampal insulin administration are not observed in diabetic rats [57-59]. Moreover, direct infusion of an insulin antibody into the hippocampus, which blocks insulin signaling, impairs memory [57].

To test whether a high fructose diet would impair memory, we fed adult male rats either a control or 60% fructose diet for 19 weeks and then trained and tested them in the spatial water maze [18]. This is a commonly used behavioral measure of hippocampal function because hippocampal lesions impair memory in this task [60, 61]. Rats were trained to find a submerged platform using extra-maze cues. Learning was assessed by measuring the latency to swim to the platform across training trials. Memory was tested 48 h after training, with the platform absent. Memory measures included 1) time spent in the area of the pool where the platform was previously located (target quadrant), 2) latency to cross the platform location (target), and 3) number of target approaches. Swim speed also was measured to assess behavior not dependent on mnemonic performance.

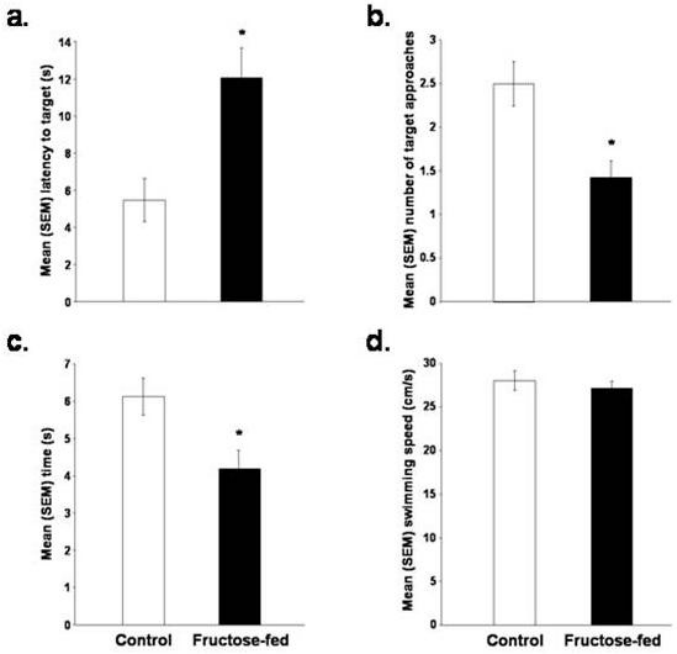

Figure 3. The effects of eating a control or high fructose (60%) diet for 138 days on the mean (+/-) SEM **(a)** latency to reach the target, **(b)** number of target approaches, **(c)** amount of time spent in the target quadrant and **(d)** swim speed during the spatial water maze retention test (*$p < 0.05$ vs. control rats). From [18] used with permission.

The results showed that the high fructose diet impaired memory. Fructose-fed rats exhibited decreased time spent in the target quadrant, an increased latency to reach the target, and fewer number of target approaches (Figures 3A-C). The diet did not impair acquisition performance during training (Figure 4), which suggests that the fructose diet did not influence navigational ability and that the rats were able to learn and retain the location of the platform

for short periods of time. The finding that the diet did not affect swim speed supports this interpretation (Figure 3D). Deficits were observed exclusively on the retention test given 48 h after training, which indicates that the diet specifically impaired long-term storage and/or retrieval. Given that postweaning human babies and adolescent males are the highest consumers of fructose [3], we conducted a subsequent study where we fed male rats a 60% fructose diet starting at weaning (postnatal day 21) and continuing into adulthood [62]. As in rats fed the diet starting in adulthood, rats fed the diet at weaning displayed hippocampal-dependent deficits in adulthood.

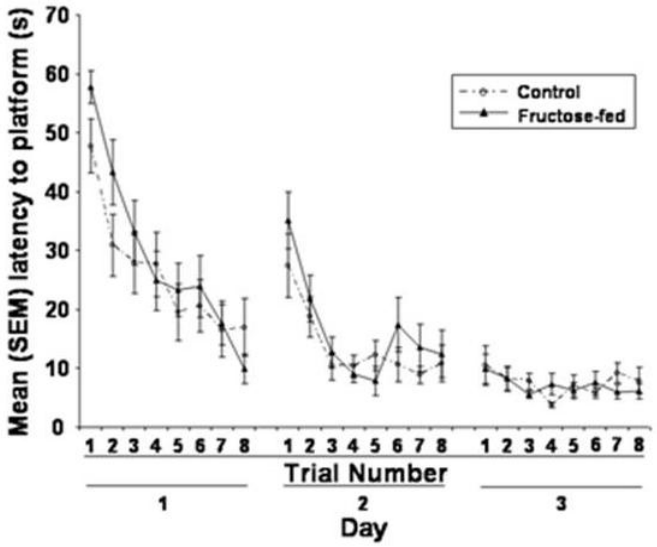

Figure 4. The effects of eating a control or high fructose (60%) diet for 138 days on the mean (+/-) SEM latency to reach the platform during spatial water maze training. From [18] used with permission.

Ingesting excessive amounts of fructose for extensive periods of time does not always impair brain function or memory. For instance, feeding rats a 58% or 60% fructose diet protects them against ischemia reperfusion injury [63, 64]. In addition, elevated fructose consumption enhances learning of a bar-pressing task in mice [65]. We also have observed that female rats may be protected from the effects of a high fructose diet on cognitive function. In another study, we fed female rats a 60% fructose diet starting at weaning for a short (47 d), middle (88 d), or long (144 d) duration [66]. The short and middle durations were selected to test for possible developmental differences, and the long duration was selected because a high fructose diet impairs memory in male rats after 138 days [18]. After their respective diet durations, the rats were tested on an amphetamine self-administration task to test whether a high fructose diet impairs learning that occurs through drug reinforcement. The high fructose diet did not affect rates of acquisition of amphetamine self-administration, the number of infusions earned on either fixed-ratio or progressive-ratio schedules of reinforcement, nor the number of active lever presses during extinct-tion/reinstatement sessions. Follow-up experiments indicated that the 60% fructose diet also did not impair spatial water maze memory in these female rats nor in amphetamine-naïve female rats.

POSSIBLE MECHANISMS

It is likely that fructose acts through multiple processes to produce brain dysfunction, as summarized in Figure 5. As the evidence below will show, fructose could impair brain function by acting directly on brain cells and/or indirectly via one of its metabolic products.

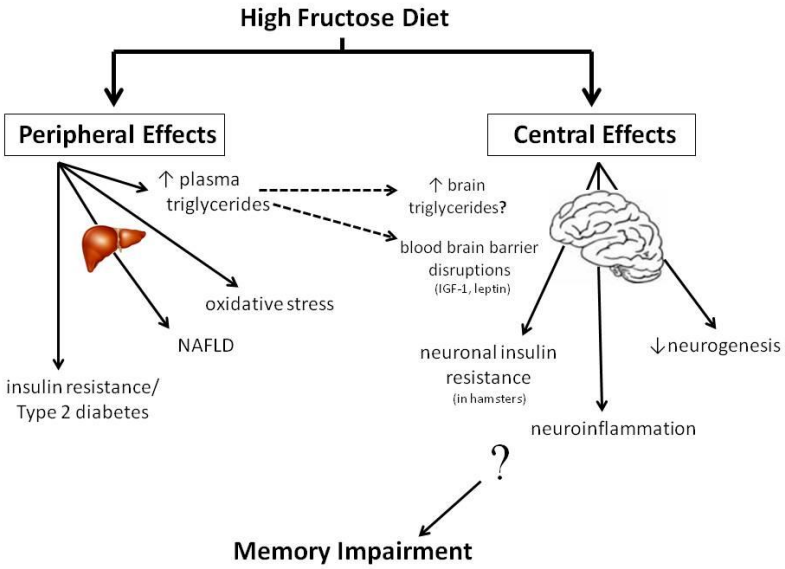

Figure 5. Possible mechanisms through which a high fructose diet may impair memory.

Whether peripheral increases in fructose can have a direct effect on brain function remains to be determined. Several older studies suggest that the transport of fructose across the blood brain barrier is extremely limited [67-69]. Recent evidence, however, suggests that the brain is responsive to fructose. For instance, cerebellar neurons are able to metabolize fructose [70], and fructose sensitive glucose transporters (GLUT5) are found on hippocampal and cortical microglia in both humans and rodents [71]. Importantly, drinking a 20% fructose solution increases expression of GLUT5 in the hippocampus [72]. A recent fMRI human study demonstrated that intravenous fructose infusions decrease cortical activity, whereas glucose infusions increase activity in the same brain regions [73].

Several lines of evidence support the hypothesis that elevated plasma triglyceride concentrations are involved in the memory-impairing effects of a high fructose diet. For instance, high fat diets impair hippocampal-dependent memory [74-76], and pharmacological manipulations that lower plasma triglyceride concentrations reverse the memory-impairing effects of a high fat diet [75]. We have found that the memory-impairing effects of a high fructose diet are slightly, but significantly correlated with the effects of the diet on postmortem plasma triglyceride concentrations (Figures 6A, B), but not with the effects of the diet on plasma free fatty acids, glucose, insulin, or leptin levels (Figures 7A-F) [18]. It also is worth noting that fructose-induced elevations in plasma triglyceride concentrations are less robust in females

than in males [66, 77, 78], which may explain, in part, why females are resistant to the memory-impairing effects of a high fructose diet.

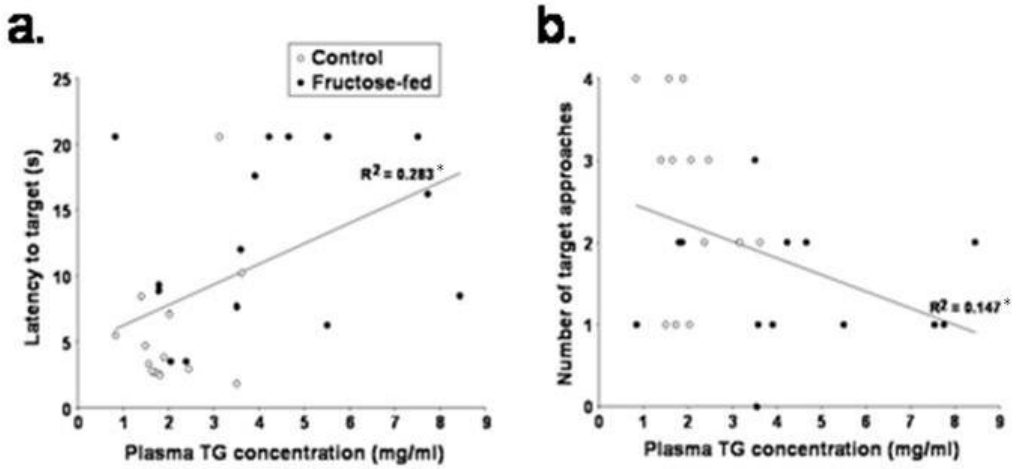

Figure 6. Scatterplots illustrating the association between **(a)** postmortem plasma TG concentrations and latency to reach the target and **(b)** the number of target approaches (*$p < 0.05$ vs. control rats). From [18] used with permission.

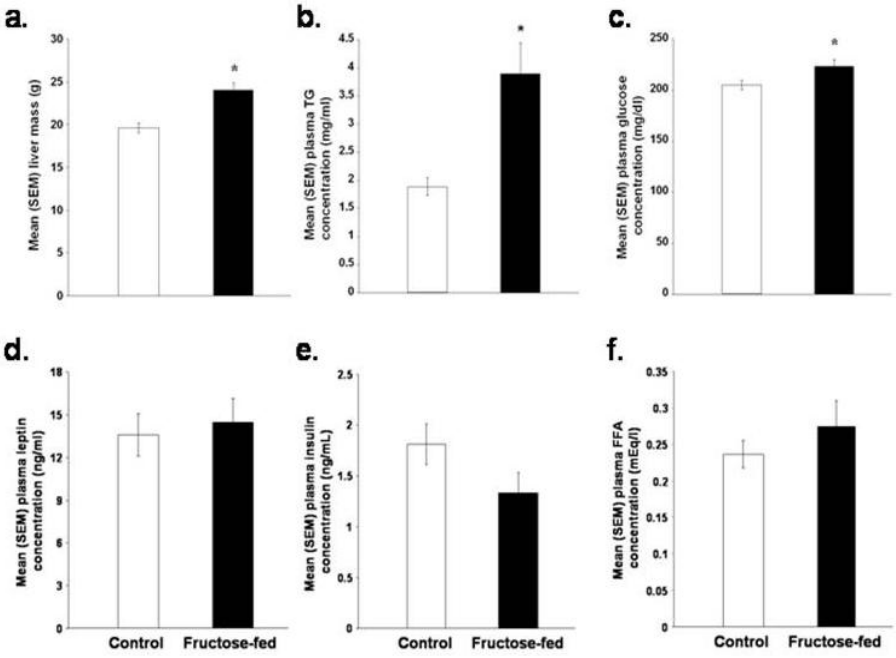

Figure 7. The effects of eating a control or high fructose (60%) diet for 138 days on the mean (+/-) SEM **(a)** liver mass, **(b)** plasma TG concentrations, **(c)** plasma glucose concentrations, **(d)** plasma leptin concentrations, **(e)** plasma insulin concentrations and **(f)** plasma FFA concentrations (*$p < 0.05$ vs. control rats). From [18] used with permission.

Fructose-induced increases in plasma triglyceride concentrations could lead to increases in brain triglyceride concentrations. A high fat diet supplemented with 20% high fructose corn syrup in the drinking water increases cholesterol and disrupts lipid metabolism in the hippocampus [79]. Rats with Type 2 diabetes have significantly higher brain triglyceride concentrations than do control or Type 1 diabetic rats [80]. The involvement of triglycerides in the fructose-induced memory impairment is further supported by evidence showing that direct infusions of the triglyceride triolein into the brain ventricles [81], or the free fatty acid palmitate into the hippocampus [75], impair memory. In addition, application of triolein to hippocampal slices impairs long term potentiation (LTP) [75], the leading candidate synaptic mechanism underlying memory [82].

Fructose-induced elevations in plasma triglyceride concentrations also might impair brain function indirectly, by affecting the transport of substances across the blood brain barrier. For instance, high fat diet-induced elevations in plasma triglyceride concentrations interfere with leptin transport across the blood brain barrier [83]. This is important because peripheral [84] and central [85, 86] administration of leptin enhances memory, including hippocampal-dependent memory. Elevated plasma triglyceride concentrations also prevent insulin-like growth factor (IGF-1) from crossing the blood brain barrier [87]. Peripheral administration of IGF-1 improves memory in diabetic rats [88] and is associated with better cognitive skills in aging humans [89].

Our initial hypothesis was that elevated fructose consumption could impair hippocampal function by producing hippocampal insulin resistance. Although feeding hamsters a 60% fructose diet produces central insulin resistance (Figures 1, 2) [42], research from our laboratory indicates that fructose does not have a similar effect in the hippocampi of rats. Specifically, we found that feeding rats a 60% fructose diet for 19 weeks did not affect total IR-β subunit or total Akt/PKB protein, nor the degree of insulin-stimulated phosphorylation of these proteins in the hippocampus [90, 91]. Although we did not measure hippocampal insulin concentrations, it is not likely that the fructose diet reduced hippocampal insulin concentrations. This is because previous studies indicate that a high fructose diet does not reduce peripheral insulin concentrations [62, 92, 93] and the majority of brain insulin concentrations is believed to come from the periphery (reviewed in [94]). One possible reason why we may not have replicated the finding that a 60% fructose diet decreases insulin-stimulated phosphorylation of IR-β and Akt/PKB proteins [42] is that we used hippocampal slices rather than whole brain slices. That possibility does not seem likely, however, given that Mielke and colleagues also found that the high fructose diet impairs other measures of insulin function specifically in hippocampal neurons (decreased protein tyrosine phosphatase and decreased insulin-stimulated LTD). The fact that we studied rats rather than hamsters may account for why we did not replicate these findings. Although both are rodents, rats and hamsters do have differences in energy metabolism and regulation. For instance, hamsters absorb fructose more rapidly than rats [95]. Also, intra-hypothalamic injections of cholecystokinin reduce food intake in rats, but not in hamsters [96, 97]. Rats and hamsters differ in a variety of other ways as well, such as in the concentrations of hypothalamic catecholamines [98], the inflammatory response to a pulmonary toxic insult [99, 100], and cholesterol metabolism in cultured hepatic cells [101]. Regardless of the exact reasons for these differences, our findings suggest that hippocampal insulin resistance does not mediate the memory-impairing effects of a high-fructose diet in rats.

A high fructose diet also may impair memory by disrupting liver function. Feeding rats a 60% fructose diet is a model of NAFLD, which includes hepatomegaly [18], hypertriglyceridemia [18, 37], and increased hepatic lipids [37]. NAFLD encompasses conditions ranging from simple hepatic lipid accumulation to severe hepatic cirrhosis [102]. Humans with NAFLD consume significantly more fructose than do humans without NAFLD [63, 103]. Approximately 50% of people with NAFLD also have cognitive impairments, ranging from mild to severe [104]. Furthermore, patients suffering from liver cirrhosis experience enhanced cognitive performance following a liver transplant [105]. Interesting to note, however, is that in our study a high fructose diet produced NAFLD in female rats [90], but did not impair their memory [66]. This may indicate that NAFLD may not be the mechanism through which a high fructose diet impairs memory, or that females have a mechanism (e.g., estrogen) that protects them from the memory-impairing effects of NAFLD.

Another possibility is that fructose impairs memory by interfering with hippocampal neurogenesis. The dentate gyrus region of the hippocampus is one of only two brain areas in which new neurons are created throughout the lifespan [106-108]. Interestingly, high fructose diets decrease cell proliferation in the hippocampus [47]. In addition, when hippocampal neurogenesis is pharmacologically prevented [109], spatial learning is not affected, but memory is impaired in the water maze task, which suggests that new neurons are essential for the storage and/or retrieval of spatial memories. This pattern of effects (i.e., spared acquisition; impaired retention) parallels the effects of fructose in our studies [18].

Finally, fructose could impair brain function through a process that involves neuroinflammation. It is well documented that neuroinflammation impairs cognition [110-114]. Also, high fat diets may impair memory, at least in part, via neuroinflammation [115, 116]. Elevated fructose consumption activates NFκB and elevates interleukin-1β and tumor necrosis factor-α in the cerebral cortex of rats [44]. Preliminary evidence from our lab suggests that a high fructose diet impairs memory in rats that have the highest levels of hippocampal glial fibrillary acidic protein, a neuroinflammatory marker [90]. In addition to neuroinflammation, oxidative stress is another possible mechanism through which fructose impairs memory. Oxidative stress and inflammatory processes often occur in tandem during cellular dysfunction [117, 118]. Elevated levels of oxidative stress are associated with impaired cognition [119-121], and antioxidant treatment attenuates cognitive impairments [122-124]. High fat diets and high fat/high fructose diets increase hippocampal oxidative stress [79, 125].

PHYSIOLOGICAL RELEVANCE

One question is whether the high fructose concentrations employed in rodent studies are relevant to humans [126, 127], given that the concentrations are much higher than those typically consumed by humans [2, 3]. The differences between rats and humans make it impossible to determine what concentrations are directly comparable between rats and humans based on intake. Although rats are similar to humans, they are not identical in their processing of fructose and lipids [93, 95, 128, 129]. Rats often require much higher doses of substances (e.g. analgesics, antidepressants, anxiolytics) than do humans. For instance, approximately 0.3 mg/kg of fluoxetine alleviates anxiety symptoms in a full-grown human,

but it takes approximately 10 mg/kg of fluoxetine to alleviate anxiety symptoms in a rat [130, 131]. We can examine relevance to humans by focusing on endpoints rather than on dietary component concentrations. A significant amount of correlational evidence implicates high fructose consumption in the growing rates of insulin resistance, Type 2 diabetes, and heart disease in humans [6, 40, 132-134], all pathologies that a high fructose diet produces in rats. Moreover, comparisons of other endpoints suggest that fructose concentrations used in rodent studies are not extreme. For instance, in humans, only excessive fructose intake increases body weight [135]; whereas, a 60% fructose concentration does not in rats [18, 136]. Similarly, high fructose concentrations produce diarrhea in humans [137]; in contrast, we observe no such changes in rats. A recent study in rhesus monkeys demonstrates that a high fructose diet produces peripheral pathologies (e.g., insulin resistance, metabolic syndrome) similar to those seen in rodent studies [138]. This provides strong evidence to support the physiological relevance to humans of studies that have employed high fructose concentrations.

CONCLUSION

A high fructose diet produces a variety of peripheral metabolic disruptions, leading to detrimental effects on the brain (e.g., insulin resistance, inflammation, oxidative stress). A high fructose diet impairs hippocampal-dependent memory in male rats but does not do so in female rats. Although the mechanisms through which elevated fructose ingestion impairs memory are not entirely elucidated, possible intermediates include elevated plasma triglyceride concentrations, NAFLD, decreased neurogenesis, neuroinflammation, and oxidative stress. It is important to consider that humans generally do not eat *just* a high fructose diet. Most imbalanced diets contain an excess of both fat and sugar [4]. A more relevant model of diet-induced pathologies may be a high fat/high sucrose diet [139]. Although it is imperative to understand the combined effects of all dietary components on human pathologies, it also is important that we identify the effects of each dietary component individually. Research on high fructose diets has begun to provide some clarity on the role that fructose alone plays in the development of diet-related brain dysfunctions.

REFERENCES

[1] Hanover, L.M. and J.S. White, Manufacturing, composition, and applications of fructose. *Am J Clin Nutr*, 1993. 58(5 Suppl):724S-732S.

[2] Vos, M.B., J.E. Kimmons, C. Gillespie, J. Welsh, and H.M. Blanck, Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. *Medscape J. Med.*, 2008. 10(7):160.

[3] Marriott, B.P., N. Cole, and E. Lee, National estimates of dietary fructose intake increased from 1977 to 2004 in the United States. *J. Nutr.*, 2009. 139(6):1228S-1235S.

[4] Wells, H.F. and J.C. Buzby, *Dietary Assessment of Major Trends in U.S. Food Consumption, 1970-2005*, in *Economic Research Bulletin No. 33*, E.R. Service, Editor. 2008, United States Department of Agriculture.

[5] Havel, P.J., Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr. Rev.*, 2005. 63(5):133-57.

[6] Bray, G.A., S.J. Nielsen, and B.M. Popkin, Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am. J. Clin. Nutr.*, 2004. 79(4):537-43.

[7] Putnam, J.J. and J.E. Allshouse, *Food Consumption, Prices, and Expenditures, 1970-1997*. 1999, U.S.D.A., Economic Research Service.

[8] Topping, D.L. and P.A. Mayes, The concentration of fructose, glucose and lactate in the splanchnic blood vessels of rats absorbing fructose. *Nutr. Metab.*, 1971. 13(6):331-8.

[9] Douard, V. and R.P. Ferraris, Regulation of the fructose transporter GLUT5 in health and disease. *Am. J. Physiol. Endocrinol. Metab.*, 2008. 295(2):E227-37.

[10] Basciano, H., L. Federico, and K. Adeli, Fructose, insulin resistance, and metabolic dyslipidemia. *Nutr. Metab. (Lond)*, 2005. 2(1):5.

[11] Mayes, P.A., Intermediary metabolism of fructose. *Am. J. Clin. Nutr.*, 1993. 58(5 Suppl):754S-765S.

[12] Bruckdorfer, K.R., I.H. Khan, and J. Yudkin, Fatty acid synthetase activity in the liver and adipose tissue of rats fed with various carbohydrates. *Biochem. J.*, 1972. 129(2):439-46.

[13] Zavaroni, I., Y.D. Chen, and G.M. Reaven, Studies of the mechanism of fructose-induced hypertriglyceridemia in the rat. *Metabolism*, 1982. 31(11):1077-83.

[14] Vrana, A., P. Fabry, and L. Kazdova, Effect of dietary fructose on fatty acid synthesis in adipose tissue and on triglyceride concentration in blood in the rat. *Nutr. Metab.*, 1973. 15(4):305-13.

[15] Curry, D.L., Effects of mannose and fructose on the synthesis and secretion of insulin. *Pancreas*, 1989. 4(1):2-9.

[16] Grant, A.M., M.R. Christie, and S.J. Ashcroft, Insulin release from human pancreatic islets in vitro. *Diabetologia*, 1980. 19(2):114-7.

[17] Michaelis, O.E.t. and B. Szepesi, Effect of various sugars on hepatic glucose-6-phosphate dehydrogenase, malic enzyme and total liver lipid of the rat. *J. Nutr.*, 1973. 103(5):697-705.

[18] Ross, A.P., T.J. Bartness, J.G. Mielke, and M.B. Parent, A high fructose diet impairs spatial memory in male rats. *Neurobiol. Learn Mem.*, 2009. 92(3):410-6.

[19] Kawasaki, T., K. Igarashi, T. Koeda, K. Sugimoto, K. Nakagawa, S. Hayashi, R. Yamaji, H. Inui, T. Fukusato, and T. Yamanouchi, Rats fed fructose-enriched diets have characteristics of nonalcoholic hepatic steatosis. *J. Nutr.*, 2009. 139(11):2067-71.

[20] Stanhope, K.L., A.A. Bremer, V. Medici, K. Nakajima, Y. Ito, T. Nakano, G. Chen, T.H. Fong, V. Lee, R.I. Menorca, N.L. Keim, and P.J. Havel, Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. *J. Clin. Endocrinol. Metab.*, 2011. 96(10):E1596-605.

[21] Bergheim, I., S. Weber, M. Vos, S. Kramer, V. Volynets, S. Kaserouni, C.J. McClain, and S.C. Bischoff, Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. *J. Hepatol.*, 2008. 48(6):983-92.

[22] Alzamendi, A., D. Castrogiovanni, H.H. Ortega, R.C. Gaillard, A. Giovambattista, and E. Spinedi, Parametrial adipose tissue and metabolic dysfunctions induced by fructose-rich diet in normal and neonatal-androgenized adult female rats. *Obesity (Silver Spring)*, 2010. 18(3):441-8.

[23] Alzamendi, A., A. Giovambattista, A. Raschia, V. Madrid, R.C. Gaillard, O. Rebolledo, J.J. Gagliardino, and E. Spinedi, Fructose-rich diet-induced abdominal adipose tissue endocrine dysfunction in normal male rats. *Endocrine*, 2009. 35(2):227-32.

[24] Zakula, Z., G. Koricanac, S. Tepavcevic, M. Stojiljkovic, T. Milosavljevic, and E.R. Isenovic, Impairment of cardiac insulin signaling in fructose-fed ovariectomized female Wistar rats. *Eur. J. Nutr.*, 2011.

[25] Lee, W.C., C.T. Chien, H.J. Yu, and S.W. Lee, Bladder dysfunction in rats with metabolic syndrome induced by long-term fructose feeding. *J. Urol.*, 2008. 179(6):2470-6.

[26] Kanarek, R.B. and N. Orthen-Gambill, Differential effects of sucrose, fructose and glucose on carbohydrate-induced obesity in rats. *J. Nutr.*, 1982. 112(8):1546-54.

[27] Zavaroni, I., S. Sander, S. Scott, and G.M. Reaven, Effect of fructose feeding on insulin secretion and insulin action in the rat. *Metabolism*, 1980. 29(10):970-3.

[28] Hill, R., N. Baker, and I.L. Chaikoff, Altered metabolic patterns induced in the normal rat by feeding an adequate diet containing fructose as sole carbohydrate. *J. Biol. Chem.*, 1954. 209(2):705-16.

[29] Beck-Nielsen, H., O. Pedersen, and H.O. Lindskov, Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. *Am. J. Clin. Nutr.*, 1980. 33(2):273-8.

[30] Hwang, I.S., H. Ho, B.B. Hoffman, and G.M. Reaven, Fructose-induced insulin resistance and hypertension in rats. *Hypertension*, 1987. 10(5):512-6.

[31] Thorburn, A.W., L.H. Storlien, A.B. Jenkins, S. Khouri, and E.W. Kraegen, Fructose-induced in vivo insulin resistance and elevated plasma triglyceride levels in rats. *Am. J. Clin. Nutr.*, 1989. 49(6):1155-63.

[32] D'Angelo, G., A.A. Elmarakby, D.M. Pollock, and D.W. Stepp, Fructose feeding increases insulin resistance but not blood pressure in Sprague-Dawley rats. *Hypertension*, 2005. 46(4):806-11.

[33] Perez-Pozo, S.E., J. Schold, T. Nakagawa, L.G. Sanchez-Lozada, R.J. Johnson, and J.L. Lillo, Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int. J. Obes. (Lond)*, 2010. 34(3):454-61.

[34] Cohen, A.M., A. Teitelbaum, and E. Rosenman, Diabetes induced by a high fructose diet. *Metabolism*, 1977. 26(1):17-24.

[35] Patel, J., A. Iyer, and L. Brown, Evaluation of the chronic complications of diabetes in a high fructose diet in rats. *Indian J. Biochem. Biophys.*, 2009. 46(1):66-72.

[36] Castro, G.S., J.F. Cardoso, H. Vannucchi, S. Zucoloto, and A.A. Jordao, Fructose and NAFLD: metabolic implications and models of induction in rats. *Acta Cir. Bras.*, 2011. 26 Suppl 2:45-50.

[37] Ackerman, Z., M. Oron-Herman, M. Grozovski, T. Rosenthal, O. Pappo, G. Link, and B.A. Sela, Fructose-induced fatty liver disease: hepatic effects of blood pressure and plasma triglyceride reduction. *Hypertension*, 2005. 45(5):1012-8.

[38] Catena, C., G. Giacchetti, M. Novello, G. Colussi, A. Cavarape, and L.A. Sechi, Cellular mechanisms of insulin resistance in rats with fructose-induced hypertension. *Am. J. Hypertens,* 2003. 16(11 Pt 1):973-8.

[39] Hininger-Favier, I., R. Benaraba, S. Coves, R.A. Anderson, and A.M. Roussel, Green tea extract decreases oxidative stress and improves insulin sensitivity in an animal model of insulin resistance, the fructose-fed rat. *J. Am. Coll. Nutr.,* 2009. 28(4):355-61.

[40] Elliott, S.S., N.L. Keim, J.S. Stern, K. Teff, and P.J. Havel, Fructose, weight gain, and the insulin resistance syndrome. *Am. J. Clin. Nutr.,* 2002. 76(5):911-22.

[41] Nandhini, A.T., V. Thirunavukkarasu, M.K. Ravichandran, and C.V. Anuradha, Effect of taurine on biomarkers of oxidative stress in tissues of fructose-fed insulin-resistant rats. *Singapore Med. J.*, 2005. 46(2):82-7.

[42] Mielke, J.G., C. Taghibiglou, L. Liu, Y. Zhang, Z. Jia, K. Adeli, and Y.T. Wang, A biochemical and functional characterization of diet-induced brain insulin resistance. *J. Neurochem.,* 2005. 93(6):1568-78.

[43] Shapiro, A., W. Mu, C. Roncal, K.Y. Cheng, R.J. Johnson, and P.J. Scarpace, Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* 2008. 295(5):R1370-5.

[44] Liu, X., D. Luo, M. Zheng, Y. Hao, L. Hou, and S. Zhang, Effect of pioglitazone on insulin resistance in fructose-drinking rats correlates with AGEs/RAGE inhibition and block of NADPH oxidase and NF kappa B activation. *Eur. J. Pharmacol.,* 2010. 629(1-3):153-8.

[45] O'Neill, L.A. and C. Kaltschmidt, NF-kappa B: a crucial transcription factor for glial and neuronal cell function. *Trends Neurosci.,* 1997. 20(6):252-8.

[46] Lawrence, T., The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb. Perspect. Biol.,* 2009. 1(6):a001651.

[47] van der Borght, K., R. Kohnke, N. Goransson, T. Deierborg, P. Brundin, C. Erlanson-Albertsson, and A. Lindqvist, Reduced neurogenesis in the rat hippocampus following high fructose consumption. *Regul. Pept.,* 2011. 167(1):26-30.

[48] Luo, D., X. Hou, L. Hou, M. Wang, S. Xu, C. Dong, and X. Liu, Effect of pioglitazone on altered expression of Abeta metabolism-associated molecules in the brain of fructose-drinking rats, a rodent model of insulin resistance. *Eur. J. Pharmacol.,* 2011. 664(1-3):14-9.

[49] Ergorul, C. and H. Eichenbaum, The hippocampus and memory for "what," "where," and "when". *Learn Mem.,* 2004. 11(4):397-405.

[50] Park, C.R., Cognitive effects of insulin in the central nervous system. *Neurosci. Biobehav. Rev.,* 2001. 25(4):311-23.

[51] Convit, A., Links between cognitive impairment in insulin resistance: an explanatory model. *Neurobiol. Aging,* 2005. 26 Suppl 1:31-5.

[52] Messier, C., Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. *Neurobiol. Aging,* 2005. 26 Suppl 1:26-30.

[53] Stewart, R. and D. Liolitsa, Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabet Med.,* 1999. 16(2):93-112.

[54] Strachan, M.W., I.J. Deary, F.M. Ewing, and B.M. Frier, Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care,* 1997. 20(3):438-45.

[55] Zhao, W., H. Chen, H. Xu, E. Moore, N. Meiri, M.J. Quon, and D.L. Alkon, Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J. Biol. Chem.,* 1999. 274(49):34893-902.

[56] Dou, J.T., M. Chen, F. Dufour, D.L. Alkon, and W.Q. Zhao, Insulin receptor signaling in long-term memory consolidation following spatial learning. *Learn Mem.,* 2005. 12(6):646-55.

[57] McNay, E.C., C.T. Ong, R.J. McCrimmon, J. Cresswell, J.S. Bogan, and R.S. Sherwin, Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. *Neurobiology of Learning and Memory*, 2010. In Press, Uncorrected Proof.

[58] Moosavi, M., N. Naghdi, N. Maghsoudi, and S. Zahedi Asl, The effect of intrahippocampal insulin microinjection on spatial learning and memory. *Horm. Behav.,* 2006. 50(5):748-52.

[59] Babri, S., H. Gholamipour, S.N. Rad, and S. Khameneh. *Evaluation of insulin intrahippocampal injection on memory consolidation in normal and diabetic male rats.* in *Long-Term Potentiation: Forty Unforgettable Years.* 2006. Atlanta, GA.

[60] Moser, E., M.B. Moser, and P. Andersen, Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *J. Neurosci.,* 1993. 13(9):3916-25.

[61] Morris, R.G., F. Schenk, F. Tweedie, and L.E. Jarrard, Ibotenate Lesions of Hippocampus and/or Subiculum: Dissociating Components of Allocentric Spatial Learning. *Eur. J. Neurosci.,* 1990. 2(12):1016-1028.

[62] Ross, A.P., E.C. Bruggeman, A.Kasumu, J.G. Mielke, and M.B. Parent, Non-alcoholic fatty liver disease impairs hippocampal-dependent memory in male rats. *Physiol Behav*, 2012. In Press.

[63] Jordan, J.E., S.A. Simandle, C.D. Tulbert, D.W. Busija, and A.W. Miller, Fructose-fed rats are protected against ischemia/reperfusion injury. *J. Pharmacol. Exp. Ther.,* 2003. 307(3):1007-11.

[64] Joyeux-Faure, M., E. Rossini, C. Ribuot, and P. Faure, Fructose-fed rat hearts are protected against ischemia-reperfusion injury. *Exp. Biol. Med. (Maywood),* 2006. 231(4):456-62.

[65] Messier, C., K. Whately, J. Liang, L. Du, and D. Puissant, The effects of a high-fat, high-fructose, and combination diet on learning, weight, and glucose regulation in C57BL/6 mice. *Behav. Brain Res.,* 2007. 178(1):139-45.

[66] Bruggeman, E.C., C. Li, A.P. Ross, J.M. Doherty, B.F. Williams, K.J. Frantz, and M.B. Parent, A high fructose diet does not affect amphetamine self-administration or spatial water maze learning and memory in female rats. *Pharmacol. Biochem. Behav.,* 2011. 99(3):356-64.

[67] Klein, J.R., R. Hurwitz, and N.S. Olsen, Distribution of intravenously injected fructose and glucose between blood and brain. *J. Biol. Chem.,* 1946. 164(2):509-12.

[68] Thurston, J.H., C.A. Levy, S.K. Warren, and E.M. Jones, Permeability of the blood-brain barrier to fructose and the anaerobic use of fructose in the brains of young mice. *J. Neurochem.,* 1972. 19(7):1685-96.

[69] Oldendorf, W.H., Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. *Am. J. Physiol.,* 1971. 221(6):1629-39.

[70] Funari, V.A., J.E. Crandall, and D.R. Tolan, Fructose metabolism in the cerebellum. *Cerebellum*, 2007. 6(2):130-40.
[71] Payne, J., F. Maher, I. Simpson, L. Mattice, and P. Davies, Glucose transporter Glut 5 expression in microglial cells. *Glia*, 1997. 21(3):327-31.
[72] Shu, H.J., K. Isenberg, R.J. Cormier, A. Benz, and C.F. Zorumski, Expression of fructose sensitive glucose transporter in the brains of fructose-fed rats. *Neuroscience*, 2006. 140(3):889-95.
[73] Purnell, J.Q., B.A. Klopfenstein, A.A. Stevens, P.J. Havel, S.H. Adams, T.N. Dunn, C. Krisky, and W.D. Rooney, Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans. *Diabetes Obes. Metab.*, 2011. 13(3):229-34.
[74] Winocur, G. and C.E. Greenwood, The effects of high fat diets and environmental influences on cognitive performance in rats. *Behav. Brain Res.*, 1999. 101(2):153-61.
[75] Farr, S.A., K.A. Yamada, D.A. Butterfield, H.M. Abdul, L. Xu, N.E. Miller, W.A. Banks, and J.E. Morley, Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology*, 2008. 149(5):2628-36.
[76] Granholm, A.C., H.A. Bimonte-Nelson, A.B. Moore, M.E. Nelson, L.R. Freeman, and K. Sambamurti, Effects of a saturated fat and high cholesterol diet on memory and hippocampal morphology in the middle-aged rat. *J. Alzheimers Dis.*, 2008. 14(2):133-45.
[77] Couchepin, C., K.A. Le, M. Bortolotti, J.A. da Encarnacao, J.B. Oboni, C. Tran, P. Schneiter, and L. Tappy, Markedly blunted metabolic effects of fructose in healthy young female subjects compared with male subjects. *Diabetes Care*, 2008. 31(6):1254-6.
[78] Galipeau, D., S. Verma, and J.H. McNeill, Female rats are protected against fructose-induced changes in metabolism and blood pressure. *Am. J. Physiol. Heart Circ. Physiol.*, 2002. 283(6):H2478-84.
[79] Stranahan, A.M., R.G. Cutler, C. Button, R. Telljohann, and M.P. Mattson, Diet-induced elevations in serum cholesterol are associated with alterations in hippocampal lipid metabolism and increased oxidative stress. *J. Neurochem.*, 2011. 118(4):611-5.
[80] Malaisse, W.J., Y. Zhang, K. Louchami, A. Sener, L. Portois, and Y.A. Carpentier, Brain phospholipid and triglyceride fatty acid content and pattern in Type 1 and Type 2 diabetic rats. *Neurosci. Lett.*, 2006. 409(1):75-9.
[81] Cotera, V.E., E. Jorge, and E.C. Mcnay, *Saturated fatty acids impair, while unsaturated fatty acids enhance, hippocampal memory and metabolic processes*. 2010, Society for Neuroscience: San Diego.
[82] Lynch, M.A., Long-term potentiation and memory. *Physiol. Rev.*, 2004. 84(1):87-136.
[83] Banks, W.A., A.B. Coon, S.M. Robinson, A. Moinuddin, J.M. Shultz, R. Nakaoke, and J.E. Morley, Triglycerides induce leptin resistance at the blood-brain barrier. *Diabetes*, 2004. 53(5):1253-60.
[84] Paz-Filho, G.J., T. Babikian, R. Asarnow, T. Delibasi, K. Esposito, H.K. Erol, M.L. Wong, and J. Licinio, Leptin replacement improves cognitive development. *PLoS One*, 2008. 3(8):e3098.
[85] Farr, S.A., W.A. Banks, and J.E. Morley, Effects of leptin on memory processing. *Peptides*, 2006. 27(6):1420-5.

[86] Oomura, Y., N. Hori, T. Shiraishi, K. Fukunaga, H. Takeda, M. Tsuji, T. Matsumiya, M. Ishibashi, S. Aou, X.L. Li, D. Kohno, K. Uramura, H. Sougawa, T. Yada, M.J. Wayner, and K. Sasaki, Leptin facilitates learning and memory performance and enhances hippocampal CA1 long-term potentiation and CaMK II phosphorylation in rats. *Peptides*, 2006. 27(11):2738-49.

[87] Dietrich, M.O., A. Muller, M. Bolos, E. Carro, M.L. Perry, L.V. Portela, D.O. Souza, and I. Torres-Aleman, Western style diet impairs entrance of blood-borne insulin-like growth factor-1 into the brain. *Neuromolecular Med.*, 2007. 9(4):324-30.

[88] Lupien, S.B., E.J. Bluhm, and D.N. Ishii, Systemic insulin-like growth factor-I administration prevents cognitive impairment in diabetic rats, and brain IGF regulates learning/memory in normal adult rats. *J. Neurosci. Res.*, 2003. 74(4):512-23.

[89] Aleman, A., W.R. de Vries, E.H. de Haan, H.J. Verhaar, M.M. Samson, and H.P. Koppeschaar, Age-sensitive cognitive function, growth hormone and insulin-like growth factor 1 plasma levels in healthy older men. *Neuropsychobiology*, 2000. 41(2):73-8.

[90] Bruggeman, E.C. Unpublished.

[91] Ross, A.P. Unpublished.

[92] Zaman, M.Q., V. Leray, J. Le Bloc'h, C. Thorin, K. Ouguerram, and P. Nguyen, Lipid profile and insulin sensitivity in rats fed with high-fat or high-fructose diets. *Br. J. Nutr.*, 2011. 106 Suppl 1:S206-10.

[93] Taghibiglou, C., A. Carpentier, S.C. Van Iderstine, B. Chen, D. Rudy, A. Aiton, G.F. Lewis, and K. Adeli, Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. *J. Biol. Chem.*, 2000. 275(12):8416-25.

[94] Mielke, J.G. and Y.T. Wang, Insulin, synaptic function, and opportunities for neuroprotection. *Prog. Mol. Biol. Transl. Sci.*, 2011. 98:133-86.

[95] Thomson, A.B., C.A. Hotke, and W.M. Weinstein, Comparison of kinetic constants of hexose uptake in four animal species and man. *Comp. Biochem. Physiol. A Comp. Physiol.*, 1982. 72(1):225-36.

[96] Miceli, M.O. and C.W. Malsbury, Feeding and drinking responses in the golden hamster following treatment with cholecystokinin and angiotensin II. *Peptides*, 1983. 4(1):103-6.

[97] Chen, J., K.A. Scott, Z. Zhao, T.H. Moran, and S. Bi, Characterization of the feeding inhibition and neural activation produced by dorsomedial hypothalamic cholecystokinin administration. *Neuroscience*, 2008. 152(1):178-88.

[98] Fuller, R.W. and S.K. Hemrick-Luecke, Species differences in epinephrine concentration and norepinephrine N-methyltransferase activity in hypothalamus and brain stem. *Comp. Biochem. Physiol. C*, 1983. 74(1):47-9.

[99] Carter, J.M. and K.E. Driscoll, The role of inflammation, oxidative stress, and proliferation in silica-induced lung disease: a species comparison. *J. Environ. Pathol. Toxicol. Oncol.*, 2001. 20 Suppl 1:33-43.

[100] Dorger, M., A.M. Allmeling, R. Kiefmann, S. Munzing, K. Messmer, and F. Krombach, Early inflammatory response to asbestos exposure in rat and hamster lungs: role of inducible nitric oxide synthase. *Toxicol. Appl. Pharmacol.*, 2002. 181(2):93-105.

[101] Botham, K.M., V.Q. Hoang, A.K. Jones, M.J. Martinez, B. Ochoa, and K.E. Suckling, Comparison of the effects of cyclic AMP analogues on cholesterol metabolism in cultured rat and hamster hepatocytes. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.*, 1996. 113(1):185-91.

[102] Kopec, K.L. and D. Burns, Nonalcoholic fatty liver disease: a review of the spectrum of disease, diagnosis, and therapy. *Nutr. Clin. Pract.*, 2011. 26(5):565-76.

[103] Thuy, S., R. Ladurner, V. Volynets, S. Wagner, S. Strahl, A. Konigsrainer, K.P. Maier, S.C. Bischoff, and I. Bergheim, Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1 concentrations and with fructose intake. *J. Nutr.*, 2008. 138(8):1452-5.

[104] Newton, J.L., Systemic symptoms in non-alcoholic fatty liver disease. *Dig. Dis.*, 2010. 28(1):214-9.

[105] Garcia-Martinez, R. and J. Cordoba, Acute-on-chronic liver failure: the brain. *Curr. Opin. Crit. Care*, 2011. 17(2):177-83.

[106] Eriksson, P.S., E. Perfilieva, T. Bjork-Eriksson, A.M. Alborn, C. Nordborg, D.A. Peterson, and F.H. Gage, Neurogenesis in the adult human hippocampus. *Nat. Med.*, 1998. 4(11):1313-7.

[107] Lledo, P.M., M. Alonso, and M.S. Grubb, Adult neurogenesis and functional plasticity in neuronal circuits. *Nat. Rev. Neurosci.*, 2006. 7(3):179-93.

[108] Gould, E., A. Beylin, P. Tanapat, A. Reeves, and T.J. Shors, Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.*, 1999. 2(3):260-5.

[109] Shors, T.J., D.A. Townsend, M. Zhao, Y. Kozorovitskiy, and E. Gould, Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus*, 2002. 12(5):578-84.

[110] Oitzl, M.S., H. van Oers, B. Schobitz, and E.R. de Kloet, Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. *Brain Res.*, 1993. 613(1):160-3.

[111] Lee, J.W., Y.K. Lee, D.Y. Yuk, D.Y. Choi, S.B. Ban, K.W. Oh, and J.T. Hong, Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. *J. Neuroinflammation*, 2008. 5:37.

[112] Tanaka, S., M. Ide, T. Shibutani, H. Ohtaki, S. Numazawa, S. Shioda, and T. Yoshida, Lipopolysaccharide-induced microglial activation induces learning and memory deficits without neuronal cell death in rats. *J. Neurosci. Res.*, 2006. 83(4):557-66.

[113] Hauss-Wegrzyniak, B., M.G. Vannucchi, and G.L. Wenk, Behavioral and ultrastructural changes induced by chronic neuroinflammation in young rats. *Brain Res.*, 2000. 859(1):157-66.

[114] Hauss-Wegrzyniak, B., P. Dobrzanski, J.D. Stoehr, and G.L. Wenk, Chronic neuro-inflammation in rats reproduces components of the neurobiology of Alzheimer's disease. *Brain Res.*, 1998. 780(2):294-303.

[115] Lu, J., D.M. Wu, Y.L. Zheng, B. Hu, W. Cheng, Z.F. Zhang, and Q. Shan, Ursolic acid improves high fat diet-induced cognitive impairments by blocking endoplasmic reticulum stress and IkappaB kinase beta/nuclear factor-kappaB-mediated inflammatory pathways in mice. *Brain Behav. Immun*, 2011. 25(8):1658-67.

[116] Pistell, P.J., C.D. Morrison, S. Gupta, A.G. Knight, J.N. Keller, D.K. Ingram, and A.J. Bruce-Keller, Cognitive impairment following high fat diet consumption is associated with brain inflammation. *Journal of Neuroimmunology*, 2010. 219(1-2):25-32.

[117] Zhang, K., Integration of ER stress, oxidative stress and the inflammatory response in health and disease. *Int. J. Clin. Exp. Med.,* 2010. 3(1):33-40.
[118] Flohe, L., R. Brigelius-Flohe, C. Saliou, M.G. Traber, and L. Packer, Redox regulation of NF-kappa B activation. *Free Radic. Biol. Med.,* 1997. 22(6):1115-26.
[119] Massaad, C.A. and E. Klann, Reactive oxygen species in the regulation of synaptic plasticity and memory. *Antioxid. Redox. Signal,* 2011. 14(10):2013-54.
[120] Sultana, R., M. Perluigi, and D.A. Butterfield, Oxidatively modified proteins in Alzheimer's disease (AD), mild cognitive impairment and animal models of AD: role of Abeta in pathogenesis. *Acta Neuropathol.,* 2009. 118(1):131-50.
[121] Lovell, M.A. and W.R. Markesbery, Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. *Nucleic Acids Res.,* 2007. 35(22):7497-504.
[122] Head, E., Oxidative damage and cognitive dysfunction: antioxidant treatments to promote healthy brain aging. *Neurochem. Res.,* 2009. 34(4):670-8.
[123] Mecocci, P., Oxidative stress in mild cognitive impairment and Alzheimer disease: a continuum. *J. Alzheimers Dis.,* 2004. 6(2):159-63.
[124] Alzoubi, K.H., O.F. Khabour, B.A. Rashid, I.M. Damaj, and H.A. Salah, The neuroprotective effect of vitamin E on chronic sleep deprivation-induced memory impairment: the role of oxidative stress. *Behav. Brain Res.,* 2012. 226(1):205-10.
[125] Morrison, C.D., P.J. Pistell, D.K. Ingram, W.D. Johnson, Y. Liu, S.O. Fernandez-Kim, C.L. White, M.N. Purpera, R.M. Uranga, A.J. Bruce-Keller, and J.N. Keller, High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. *J. Neurochem.,* 2010. 114(6):1581-9.
[126] Dolan, L.C., S.M. Potter, and G.A. Burdock, Evidence-based review on the effect of normal dietary consumption of fructose on blood lipids and body weight of overweight and obese individuals. *Crit. Rev. Food Sci. Nutr.,* 2010. 50(10):889-918.
[127] Rizkalla, S.W., Health implications of fructose consumption: A review of recent data. *Nutr. Metab. (Lond),* 2010. 7:82.
[128] Adams, S.H., K.L. Stanhope, R.W. Grant, B.P. Cummings, and P.J. Havel, Metabolic and endocrine profiles in response to systemic infusion of fructose and glucose in rhesus macaques. *Endocrinology,* 2008. 149(6):3002-8.
[129] Masson, S., O. Henriksen, A. Stengaard, C. Thomsen, and B. Quistorff, Hepatic metabolism during constant infusion of fructose; comparative studies with 31P-magnetic resonance spectroscopy in man and rats. *Biochim. Biophys. Acta,* 1994. 1199(2):166-74.
[130] Eli-Lilly. *PROZAC Prescribing Information*. 1987 revised March 19, 2009 June 17, 2009]; Available from: http://pi.lilly.com/us/prozac. pdf?reqNacId=undefined.
[131] Borsini, F., J. Podhorna, and D. Marazziti, Do animal models of anxiety predict anxiolytic-like effects of antidepressants? *Psychopharmacology (Berl),* 2002. 163(2):121-41.
[132] Gross, L.S., L. Li, E.S. Ford, and S. Liu, Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am. J. Clin. Nutr.,* 2004. 79(5):774-9.
[133] Hu, F.B. and V.S. Malik, Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. *Physiol. Behav.,* 2010. 100(1):47-54.

[134] Montonen, J., R. Jarvinen, P. Knekt, M. Heliovaara, and A. Reunanen, Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *Journal of Nutrition,* 2007. 137(6):1447-1454.

[135] Livesey, G. and R. Taylor, Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. *Am. J. Clin. Nutr.,* 2008. 88(5):1419-37.

[136] Abdullah, M.M., N.N. Riediger, Q. Chen, Z. Zhao, N. Azordegan, Z. Xu, G. Fischer, R.A. Othman, G.N. Pierce, P.S. Tappia, J. Zou, and M.H. Moghadasian, Effects of long-term consumption of a high-fructose diet on conventional cardiovascular risk factors in Sprague-Dawley rats. *Mol. Cell Biochem.,* 2009. 327(1-2):247-56.

[137] Skoog, S.M. and A.E. Bharucha, Dietary fructose and gastrointestinal symptoms: a review. *Am. J. Gastroenterol.,* 2004. 99(10):2046-50.

[138] Bremer, A.A., K.L. Stanhope, J.L. Graham, B.P. Cummings, W. Wang, B.R. Saville, and P.J. Havel, Fructose-fed rhesus monkeys: a nonhuman primate model of insulin resistance, metabolic syndrome, and type 2 diabetes. *Clin. Transl. Sci.,* 2011. 4(4):243-52.

[139] Sampey, B.P., A.M. Vanhoose, H.M. Winfield, A.J. Freemerman, M.J. Muehlbauer, P.T. Fueger, C.B. Newgard, and L. Makowski, Cafeteria diet is a robust model of human metabolic syndrome with liver and adipose inflammation: comparison to high-fat diet. *Obesity (Silver Spring),* 2011. 19(6):1109-17.