HIPPOCAMPUS 25:227–239 (2015)

Effects of Sucrose and High Fructose Corn Syrup Consumption on Spatial Memory Function and Hippocampal Neuroinflammation in Adolescent Rats

Ted M. Hsu,[1,2] Vaibhav R. Konanur,[2] Lilly Taing,[2] Ryan Usui,[2] Brandon D. Kayser,[2,3] Michael I. Goran,[3] and Scott E. Kanoski[1,2]*

ABSTRACT: Excessive consumption of added sugars negatively impacts metabolic systems; however, effects on cognitive function are poorly understood. Also unknown is whether negative outcomes associated with consumption of different sugars are exacerbated during critical periods of development (e.g., adolescence). Here we examined the effects of sucrose and high fructose corn syrup-55 (HFCS-55) intake during adolescence or adulthood on cognitive and metabolic outcomes. Adolescent or adult male rats were given 30-day access to chow, water, and either (1) 11% sucrose solution, (2) 11% HFCS-55 solution, or (3) an extra bottle of water (control). In adolescent rats, HFCS-55 intake impaired hippocampal-dependent spatial learning and memory in a Barne's maze, with moderate learning impairment also observed for the sucrose group. The learning and memory impairment is unlikely based on nonspecific behavioral effects as adolescent HFCS-55 consumption did not impact anxiety in the zero maze or performance in a non-spatial response learning task using the same mildly aversive stimuli as the Barne's maze. Protein expression of pro-inflammatory cytokines (interleukin 6, interleukin 1β) was increased in the dorsal hippocampus for the adolescent HFCS-55 group relative to controls with no significant effect in the sucrose group, whereas liver interleukin 1β and plasma insulin levels were elevated for both adolescent-exposed sugar groups. In contrast, intake of HFCS-55 or sucrose in adults did not impact spatial learning, glucose tolerance, anxiety, or neuroinflammatory markers. These data show that consumption of added sugars, particularly HFCS-55, negatively impacts hippocampal function, metabolic outcomes, and neuroinflammation when consumed in excess during the adolescent period of development. © **2014 Wiley Periodicals, Inc.**

KEY WORDS: carbohydrate; sugar; adolescence; hippocampus; obesity

INTRODUCTION

Consumption of a "Western diet" high in saturated fatty acids (SFA) and simple sugars (mono- and disaccharides) is associated with the development of obesity, Type 2 Diabetes, and cardiovascular disease (Hu et al., 2001; Landsberg et al., 2013). Emerging evidence derived from both humans and nonhuman animal models shows that in addition to these negative health outcomes, Western diet consumption is also associated with impairments in various cognitive domains, particularly learning and memory processes that rely on the integrity of the hippocampus (Molteni et al., 2002; Gunstad et al., 2006; Kanoski et al., 2007; Granholm et al., 2008; Stranahan et al., 2008; Murray et al., 2009; Kanoski and Davidson, 2010; Kanoski et al., 2010; Francis and Stevenson, 2011; Benito-Leon et al., 2013; Darling et al., 2013). In some cases, intake of a Western diet leads to hippocampal-dependent memory disruption following only very short periods of consumption [e.g., less than 2 weeks (Murray et al., 2009; Kanoski and Davidson, 2010)], suggesting that dietary factors can have negative impacts on cognitive function independent of (or prior to) the development of obesity and related metabolic derangements.

Consumption of added sugars can lead to hyperactivation of brain reward circuitry (Avena et al., 2008; Veldhuizen et al., 2011; Rudenga and Small, 2013; Stice et al., 2013) and, in some cases, increased overall kcal intake (Avena et al., 2012; la Fleur et al., 2014). Consumption of simple carbohydrates, particularly sugars present in soft drinks and other sugar-sweetened beverages (SSBs), has increased substantially in the past 30 years (Duffey and Popkin, 2007; Marriott et al., 2010; Bray, 2013). While the harmful metabolic outcomes of excessively consuming SSBs and other added sugars are coming to light (Bray et al., 2004; Johnson et al., 2009; Bocarsly et al., 2010; Bray, 2013; Goran et al., 2013; Te Morenga et al., 2013), the impact of consuming different sugars on cognitive function is poorly understood. Intake of Western diets high in SFAs and sugars can lead to substantial memory deficits in both humans and animal models [see (Kanoski and Davidson, 2011;

This article was published online on 3 October 2014. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected 15 October 2014.

[1] **Neuroscience Program, University of Southern California, Los Angeles, CA;** [2] **Department of Biological Sciences, Human and Evolutionary Biology Section, University of Southern California, Los Angeles, CA, USA;** [3] **Department of Preventive Medicine and Childhood Obesity Research Centre, University of Southern California, Los Angeles, CA.**

Grant sponsor: USC Institutional Support; Grant sponsor: USC Dornsife (SEK).

Abbreviations used: ANOVA, analysis of variance; HFCS, high fructose corn syrup; IL, interleukin; IP, intraperitoneally; PN, postnatal day; SFA, saturated fatty acids; SSB, sugar-sweetened beverages

*Correspondence to: Scott E. Kanoski, University of Southern California, 3560 Watt Way, PED 107, Los Angeles, CA 90089-0652. E-mail: kanoski@usc.edu

Accepted for publication 16 September 2014.
DOI 10.1002/hipo.22368
Published online 20 September 2014 in Wiley Online Library (wileyonlinelibrary.com).

Kanoski, 2012; Francis and Stevenson, 2013; Freeman et al., 2013; Martin and Davidson, 2014) for reviews]. However, the relative impact of added sugars vs. SFA consumption on cognition is unclear given that intake of these dietary factors typically co-varies in human populations (Kant, 2003; Reedy and Krebs-Smith, 2010), and the majority of controlled animal model studies compare consumption of Western diets to low-fat, complex carbohydrate rodent diets. The present investigation specifically examines the impact of two different sugars [sucrose and high fructose corn syrup-55 (HFCS-55)], the most commonly used added sweeteners in the United States, on hippocampal-dependent spatial memory function, as well as metabolic and neuronal outcomes. These sugars differ primarily in the ratio of fructose to glucose, with 50:50 for sucrose and 55:42 for HFCS-55, and in the fact that fructose and glucose are "free" monosaccharides in HFCS-55 and are "bound" within the disaccharide sucrose. This latter distinction may contribute to differential metabolic impacts of the two sweeteners (Sanchez-Lozada et al., 2010; Sheludiakova et al., 2012).

Emerging evidence demonstrates that the negative impact of Western diet consumption on metabolic outcomes may be exacerbated during critical periods of development [see (Goran et al., 2013; Boersma et al., 2014) for review]. Several animal model experiments show that maternal sugar intake during gestation or lactation can have a negative impact on peripheral glucose regulation, body weight gain, and development of neuronal reward circuitry in offspring (Jen et al., 1991; Rawana et al., 1993; Vucetic et al., 2010; Vickers et al., 2011; Sun et al., 2012; Grissom et al., 2014). Adolescence, defined in rodents as beginning around postnatal day (PN) 28 and extending to PN60 (Tirelli et al., 2003; Brenhouse and Andersen, 2011) [or to PN42 by other accounts (Spear, 2000)], is another important critical period, as rapid maturation and remodeling of neurobiological systems make this period especially sensitive to perturbation (Spear, 2000; Chambers et al., 2003). Recent research has demonstrated that in addition to increased risk for developing metabolic disorders, intake of Western diets during adolescence also impairs learning and memory processes in both human and animal models (Privitera et al., 2011; Boitard et al., 2012; Valladolid-Acebes et al., 2013; Baym et al., 2014). However, the effect of consuming SSBs and other added sugars (independent of elevated fat intake) during adolescence on metabolic and cognitive outcomes is poorly understood. The present research uses a rat model to examine the effects of sucrose or HFCS-55 consumption during adolescence or adulthood on cognitive (spatial memory function, anxiety, response learning) and metabolic (blood glucose regulation, and hepatic inflammation) outcomes. To examine a potential neurobiological mechanism for cognitive deficits, we also investigated the effects of added sugar consumption on protein markers of inflammation in the dorsal subregion of the hippocampus, a brain region critically involved with spatial learning and memory (Fanselow and Dong, 2010). The concentrations of sucrose and HFCS-55 used in the present experiments (11%) are comparable to that of SSBs typically consumed by humans in modern Western cultures. Results provide novel information about the potential detrimental impact of added sugars/SSB consumption during critical periods of development on cognitive, metabolic, and neuronal outcomes.

MATERIALS AND METHODS

Animals and Diets

Thirty-eight adolescent male (50–70g; PN 30) and 38 adult male (250–270 g; PN 60) Sprague-Dawley rats (Charles River, Wilmington, MA) were housed individually in 12-h light/dark cycle. Animals had *ad libitum* access to chow (LabDiet 5001, St. Louis, MO) and water except where noted otherwise. All procedures received approval from the University of Southern California Animal Care and Use Committee.

Adult or adolescent rats ($n = 12$–13 per group) were given 30-days *ad libitum* access to water, low-fat chow, and either: (1) a 2nd water bottle (controls), (2) sucrose, or (3) HFCS-55 solution. Sucrose and HFCS-55 solutions were prepared to contain equal carbohydrate weight/volume (11%) as described in (Ackroff and Sclafani, 2011). Measurement of body weight, chow intake, water intake, and sugar solution intake was recorded every 2 or 3 days. Animals underwent behavioral training and testing (see below) following the 30-day sugar exposure period, during which lab chow and water were freely available. Access to the sugar solutions was given *ad libitum* for the HFCS-55 and sucrose groups throughout the behavioral procedures, however, intake levels were only monitored during the 30-day exposure period before behavioral training.

Behavioral Procedures

Barnes maze

The Barnes maze is an elevated white circular platform (Diameter: 122 cm Height: 140 cm) with 18 uniform holes (9.5 cm diameter) spaced every twenty degrees around the outside edge (Med Associates; St Albans, VT). A hidden black escape box [38.73-cm long × 11.43-cm wide × 7.62-cm depth (5.08-cm to step)] is placed underneath one hole. Four distinguishable spatial cues (Black and white stripes, a white circle, a red triangle, and an assortment of irregular shapes) are present on each wall of the room surrounding the maze and were readily visible to the animal. An upside-down opaque black start box is attached to a pulley system, allowing the experimenter (from a separate room) to initiate a trial and release the animal for training and testing with minimal experimenter interaction. Each rat was assigned a specific escape hole according to the position of the spatial cues with the location counterbalanced across groups. Animals were transported from the home cage in plastic bins with wood chip bedding to the Barnes maze room. Each animal first underwent a habituation session that consisted of 1 min inside the transport bin placed under the maze, 2 min underneath the start box in the center

of the maze, and 3 min inside the escape box. One day after the habituation session, animals underwent 6 days of Barnes maze training. Training consisted of 2 trials per day, during which the rat is required to locate the assigned designated escape hole according to the spatial cues on the walls. Mildly aversive stimuli (120W bright overhead light and 75db white noise) are utilized to provide motivation to locate the escape hole (Rosenfeld and Ferguson, 2014). At the start of each video-recorded trial, the animal is placed within the start box at the center of the maze. After 30 sec, the start box is raised by an experimenter in a separate room, and the animal is free to traverse the maze. Once the animal finds the escape hole (which is free from overhead illumination), the white noise is shut off by an experimenter in a separate room monitoring via live video feed and the animal is allowed to remain in the escape box for 1 min. The animal is then removed and placed in a separate room for 2 min, and the maze surface and escape box are cleaned with 10% ETOH and the maze is rotated 180 degrees (to eliminate olfactory strategies). The procedure is then repeated for the 2nd trial. If the animal failed to find the escape hole in 2 min, the experimenter places the animal inside the escape hole for 1 min. Latency (time to reach the escape hole) was calculated by an experimenter (in a separate room; monitoring live video feed) blind to experimental groups.

To assess spatial memory retention, a probe test was conducted two days after the last Barnes maze training session. Procedures were as described above, except over the two trials, no escape box is present. In each trial, the animal is allowed to explore the maze for 2 min. The dependent variable is the % of correct hole investigations (calculated by the experimenter blind to experimental groups). Correct hole investigations were defined a priori as investigations of the correct hole, or the holes immediately adjacent to it. The percentage of correct hole investigations was then calculated by dividing the number of correct investigations by the total number of hole investigations.

Zero maze

To test for potential anxiety effects associated with SSB consumption, the same rats underwent testing in a zero maze (63.5-cm fall height, 116.8-cm outside diameter) two days after Barnes maze memory probe test. The zero maze is an elevated circular track, divided into four equal length sections. Two sections were open with 3-cm high curbs, whereas the two other closed sections contained 17.5-cm high walls. Animals were placed in the maze for 5 min while the experimenter records the total time spent in open sections (defined as the head and front two paws in open arms).

Response task (Y-maze)

A separate group of rats underwent a non-spatial response task in a Y-maze (each arm width = 14 cm; 29-cm high walls, 54.6-cm arm length) after 30-day adolescent (beginning PN30, as above) access to either 11% HFCS solution or water (control) ($n = 10$/group). The purpose of this task was to determine whether learning and memory impairments associated with adolescent SSB consumption are specific to hippocampal-dependent spatial tasks, or rather, extend to other behavioral tasks that utilize the same mildly aversive stimuli, and involve learning and memory processes (response learning) that are not impacted by hippocampal lesions (Chang and Gold, 2003). Procedures are modified from (Chang and Gold, 2003; Kanoski et al., 2011). Briefly, animals placed in the Y-maze (which is stationed on top of the Barnes maze in the same room as Barnes maze training) are required to find an escape box that is consistently located at the end of the right arm relative to the starting position. During each trial, animals are subjected to the same mildly aversive stimuli presented in the Barnes Maze (bright overhead light and white noise). Following a habituation session (1-min underneath the maze, 3-min confined in the escape box, no aversive stimuli presentation), animals underwent 1 day of training and 1 day of testing. In training, trials ended when one of the following occurred: (1) the rat located the escape box by entering the right (correct) arm and traversing to the escape box; or (2) the rat entered the incorrect (left) arm. Animals were required to complete five consecutive correct trials before ending the session. After making a correct response, the animal is allowed to remain in the escape box for 1 min (free from overhead light and white noise), and is then removed and placed in a separate room for 2 min. Before the beginning of the next trial, the starting arm and escape box location are changed randomly (with escape box always to the right of starting arm) to minimize the effect of extra-maze cues, and the maze, platform, and escape box are cleansed with 10% ETOH. After each incorrect response, the animal is placed in a bin next to the maze and exposed to the overhead light and white noise for 30 sec, and the trial is repeated until a correct response is made. Memory retention testing occurred under the same conditions two days after the training session. The dependent variables were the number of trials required to reach criterion (Trials to criterion), and latency to find the escape box during correct trials. This latter dependent variable served as a control for potential groups differences in sensitivity to the stimuli and/or motivation to escape the stimuli. Latency and accuracy were scored by an experimenter (blind to the experimental groups) watching live video feed in a separate room. Consistent with the first cohort, body weights did not significantly differ between the adolescent HFCS-exposed and control groups at the time of testing or at any point during the 30-day exposure period.

IP Glucose Tolerance Test (IPGTT)

Animals were food deprived 24 h before a glucose tolerance test that occurred two days after zero maze testing. Immediately before the test, baseline blood glucose readings were obtained from tail tip and recorded by a blood glucose meter (One touch Ultra2, LifeScan, Milpitas, CA). Each animal was then intraperitoneally (IP) injected with dextrose solution (0.923 g/kg body weight, 1 mL/kg) and blood glucose readings were obtained at 30, 60, 90, and 120 min after IP injections.

Tissue Collection

Following a 6-hour fast, brains were rapidly removed from the skull after decapitation and placed on a brain matrix (Kopf Instruments, Tujunga, CA) for coronal sectioning (2-mm sections). Tissue from the dorsal hippocampus was extracted bilaterally from one 2-mm thick section using a 2-mm inner diameter tissue punch (Ted Pella, Redding, CA). The brain tissue was immediately flash frozen in cooled isopentane and stored in −80°C until further processing. Immediately after decapitation trunk blood was collected and centrifuged at 15,000g for 10 min to collect serum. Plasma was extracted and stored in −80°C. Liver tissue was collected by cutting off an approximate volume of 0.5cm^3 from the tip of the largest lobe, and stored at −80°C.

Immunoblotting

Proteins in the brain tissue lysates were separated using sodium dodecyl sulfate polyacrylamide gel electrophoresis. The proteins were transferred onto poly-vinylidene difluouride membranes and subjected to immunodetection analysis using enhanced chemiluminescence (Chemidoc XRS, BioRad, Hercules, CA). An anti-Interleukin-1β antibody (1:500, Catalog #ab9787, Abcam, Cambridge, MA) was used to evaluate the concentration of interleukin-1β (IL-1β) relative to a loading control signal detected by an anti-β tubulin antibody (1:5000, Catalog #2128S, Cell Signaling, Danvers, MA). An anti-interleukin-6 antibody (1:500, Catalog # ab6672, Abcam, Cambridge, MA) was used to evaluate the concentration of interleukin-6 (IL-6) relative to a loading control signal detected by an anti-β actin antibody (1:5000, Catalog # NB600-503, Novus biological, Littleton, CO). Blots were quantified with densitometry analysis using National Institutes of Health software (Image J).

Enzyme-Linked Immunosorbent Assay (ELISA)

Concentrations of IL-1β and IL-6 in liver tissue lysates were evaluated using IL-1β (Catalog #ab100768, Abcam, Cambridge, MA) and IL-6 (Catalog #ab100713, Abcam, Cambridge, MA) ELISA kits, respectively. Concentration of insulin in plasma was evaluated using an Insulin ELISA kit (Catalog #10–1250-01, Mercodia, Winston-Salem, NC). Procedures were conducted as per the manufacturer's instructions.

Data Analyses

Barne's Maze training was analyzed using repeated-measures analysis of variance (ANOVA), with Group as a between-subjects variable and Trial as a within-subjects variable. Individual trials were analyzed separately via one-way ANOVA using Newman Keuls posthoc analyses to compare individual groups when overall Group effects were significant. Overall ANOVAs were conducted across the 1st half of training (1st six trials; before asymptote performance), and separately across the 2nd half of training. Chow intake, SSB intake, total kcal intake, body weight, IPGTT were also analyzed using a similar repeated-measures ANOVA strategy with Time Period as a within-subjects variable. Plasma insulin, hippocampal and liver cytokine levels, zero maze performance, and response task performance were analyzed with one-way ANVOA; Newman Keuls posthoc analyses compared individual groups when overall Group effects were significant. Statistical significance was declared at $P < 0.05$.

RESULTS

Spatial Learning and Memory (Barnes Maze)

The adolescent-exposed HFCS-55 group was impaired in acquisition of the spatial Barnes Maze task relative to controls (Fig. 1a). A significant Group main effect was observed across the first six trials ($P < 0.05$); posthoc analyses confirmed that the group effect was based on a significant difference between the HFCS-55 and the control group ($P < 0.05$). Individual trial analyses showed that the sucrose group demonstrated increased latency on the 3rd trial compared to controls, whereas significant differences were observed between the HFCS-55 and control groups on trials, 3, 4, and 6. The HFCS-55 group was also impaired in the memory probe test relative to controls [Fig. 1b; Significant Group main effect ($P < 0.05$) and posthoc HFCS-55 vs. control effect ($P < 0.05$)].

There were no significant differences between the adult-exposed sucrose or HFCS-55 groups and controls for Barnes maze acquisition performance (Fig. 1c), nor for memory probe test performance (Fig. 1d).

Anxiety (Zero Maze)

No significant differences were obtained between adolescent- (Fig. 2a) or adult- (Fig. 2b) exposed SSB and control groups for Zero maze test of anxiety.

Non-Spatial Response Task (Y-maze)

For both training and testing, no significant differences were found between adolescent-exposed HFCS-55 and control groups for either of the dependent variables (trials to criterion, average correct trial latency) (Figs. 2c,d). Both HFCS-55 and control groups demonstrated improvement in this task in the memory retention test, reflected by significant decreases in both dependent variables during the testing phase compared to the training phase (Figs. 2c,d; ps < 0.05).

Added Sugar kcals, Chow kcals, Total kcals, and Body Weight

Added sugar kcal consumption was comparable between the adolescent-exposed HFCS-55 and sucrose groups across the 30-day exposure period (Fig. 3a). The sucrose group consumed slightly more than the HFCS-55 group across later Time Periods (significant Group difference on the 8th and 14th Time Period, ps < 0.05); however, there were no overall significant

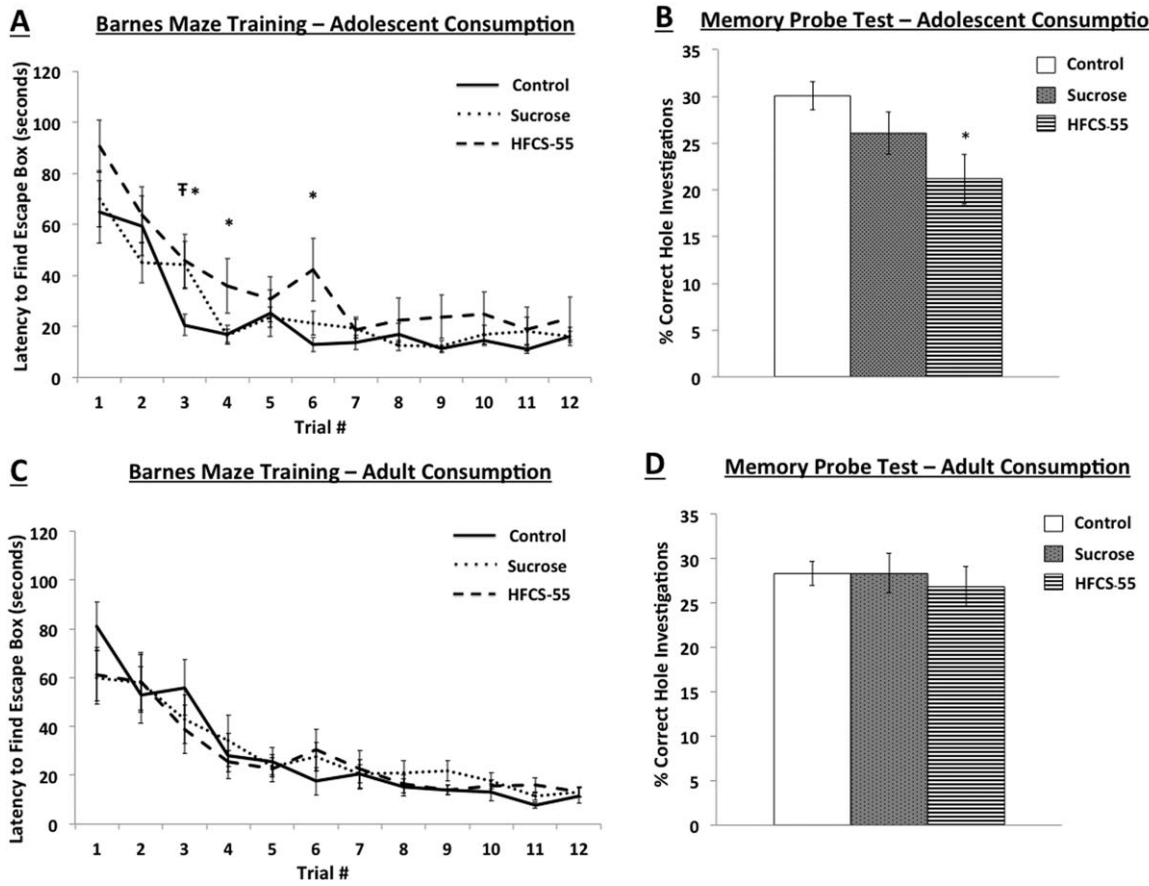

FIGURE 1. Latency to find the escape box (seconds) during 6-day Barnes maze training and the percentage of correct hole investigations during a non-reinforced memory probe test following 30-day adolescent (A,B) or adult (C,D) exposure to SSBs (HFCS-55 or sucrose) or control. Data are mean ± SEM; ∓$P < 0.05$ Sucrose vs. Control, *$P < 0.05$ HFCS-55 vs. Control.

Group, or Group × Time Period effects. Both added sugar groups compensated for sugar kcal intake by consuming less chow than the control group (Fig. 3b), such that total kcal consumption was not different among the three groups (Fig. 4a), nor was the rate of body weight gain or terminal body weight (Fig. 4b). Carbohydrate intake broken down by monosaccharide showed that fructose consumption did not differ between the adolescent SSB groups, whereas glucose intake was significantly lower in the HFCS-55 vs. the sucrose group ($P < 0.01$; data not shown).

The adult sucrose group consumed more sugar kcals across earlier Time Points compared to the HFCS-55 group (Fig. 3c). While a significant difference was only obtained on the 2nd Time Period, the overall pattern led to a Group × Time Period significant interaction ($P < 0.01$). Adult-exposed added sugar groups also compensated by consuming less chow than the controls (Fig. 3d); however, this caloric compensation was less accurate than for adolescent-exposed rats, leading to significantly higher total kcal consumption for both added sugar groups vs. controls [Fig. 4c; significant overall Group effect ($P < 0.01$) and significant HFCS-55 vs. control ($P < 0.01$) and Sucrose vs. control ($P < 0.01$) posthoc effects]. While terminal body weights did not significantly differ between the adult SSB groups and controls, the rate of body weight gain was higher for the SSB groups vs. the control group [Fig. 4d; significant Group × Time Period interaction ($P < 0.01$)]. Similar to adolescent-exposed rats, fructose consumption for adults did not differ between the SSB groups, whereas glucose intake was significantly lower in the HFCS-55 vs. the sucrose group ($P < 0.01$; data not shown).

Glucose Regulation (IPGTT and Plasma Insulin)

The adolescent-exposed SSB groups had higher plasma insulin levels compared to controls [Fig. 5b; significant Group main effect ($P < 0.05$); significant posthoc comparisons for both groups vs. controls, ps < 0.05)]. Glucose tolerance was also altered for the HFCS-55 group vs. controls [Fig. 5a; significant Group × Time Period interaction; significant Group main effect at 30min ($P < 0.05$); posthoc HFCS-55 vs. control comparison at 30min $P < 0.05$]. A trend was also observed for higher blood glucose levels at 30 min for the Sucrose group vs. controls (posthoc comparison, $P < 0.08$).

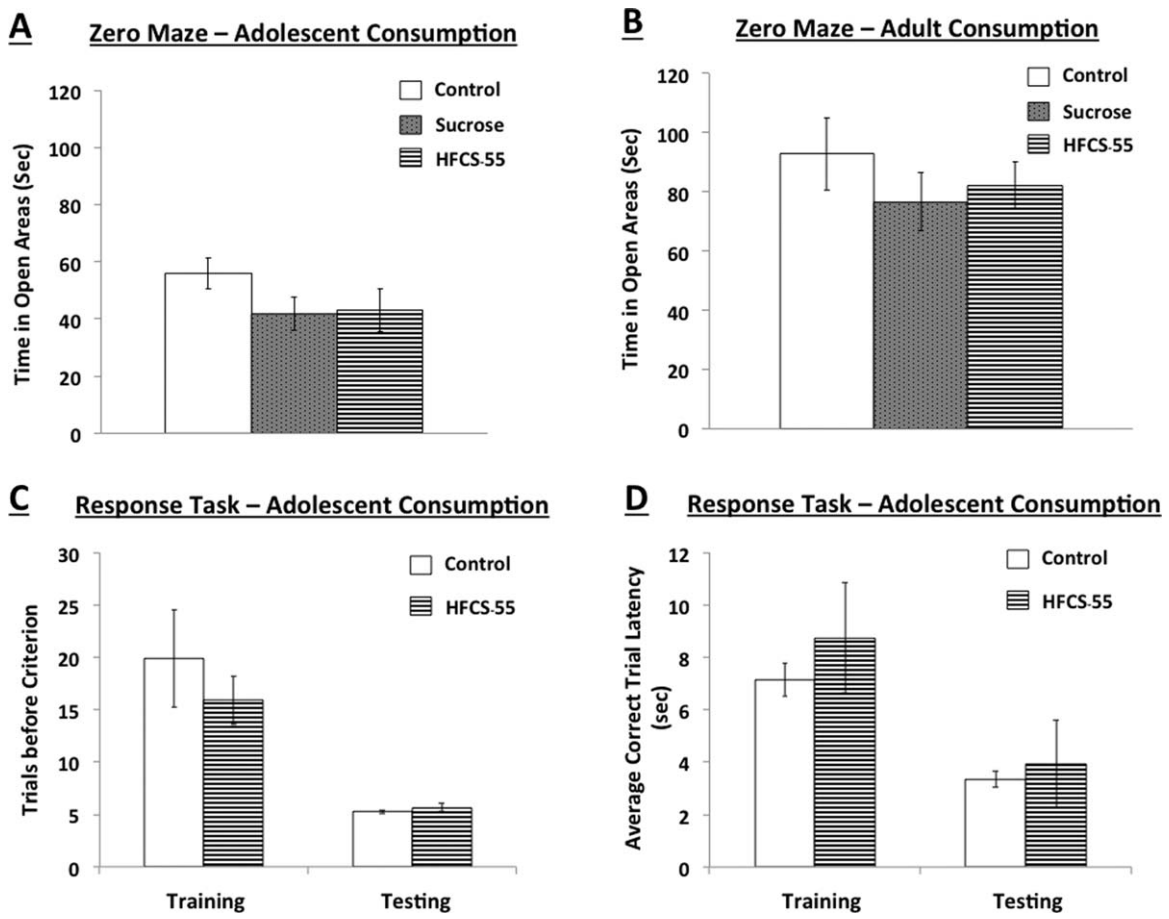

FIGURE 2. Time spent in open arms during a Zero maze anxiety test following 30-day, (A) adolescents or (B) adult SSB access period. Trials before criterion (C) and average correct trial latency (D) during non-spatial response task training and testing following 30-day adolescent exposure to HFCS-55 or control. Data are mean ± SEM.

No group differences were obtained in the adult-exposed groups for the IPGTT (Fig. 5c). However, a significant main effect was obtained for plasma insulin levels [Fig. 5d; significant Group main effect ($P < 0.05$)], which was based on a difference between the Sucrose and control group (posthoc comparison, $P < 0.05$).

Liver Cytokines

IL-1β protein levels were increased in the liver for both adolescent-exposed SSB groups vs. controls [Fig. 6a; significant Group main effect; significant posthoc comparisons to controls for both groups ($P < 0.05$)]. No differences were observed for liver IL-6 protein levels for the adolescent-exposed SSB groups (Fig. 6b), nor were any differences observed for the adult groups for either cytokine (Fig. 6c,d).

Hippocampus Cytokine Levels

A significant main effect of Group was observed in adolescent-exposed groups for both IL-1β and IL-6 levels in hippocampus (Fig. 7a,b). In both cases the effect was based on elevated protein levels for the HFCS-55 vs. the controls group (posthoc comparisons, ps < 0.05) with no difference between sucrose and control groups. No group differences were obtained for the adult groups for either cytokine (Fig. 7c,d).

DISCUSSION

This study demonstrates that consumption of added sugars during adolescence impairs hippocampal-dependent spatial learning and memory in rats. A 30-day period of *ad libitum* access to 11% solutions of sucrose or HFCS-55 during adolescence impaired spatial learning rate in a Barnes maze task relative to controls. Moreover, during a non-reinforced memory retention probe test, the adolescent-exposed HFCS-55 group showed evidence of memory impairment relative to controls. These learning and memory deficits were not accompanied by differences in anxiety based on performance in the Zero maze

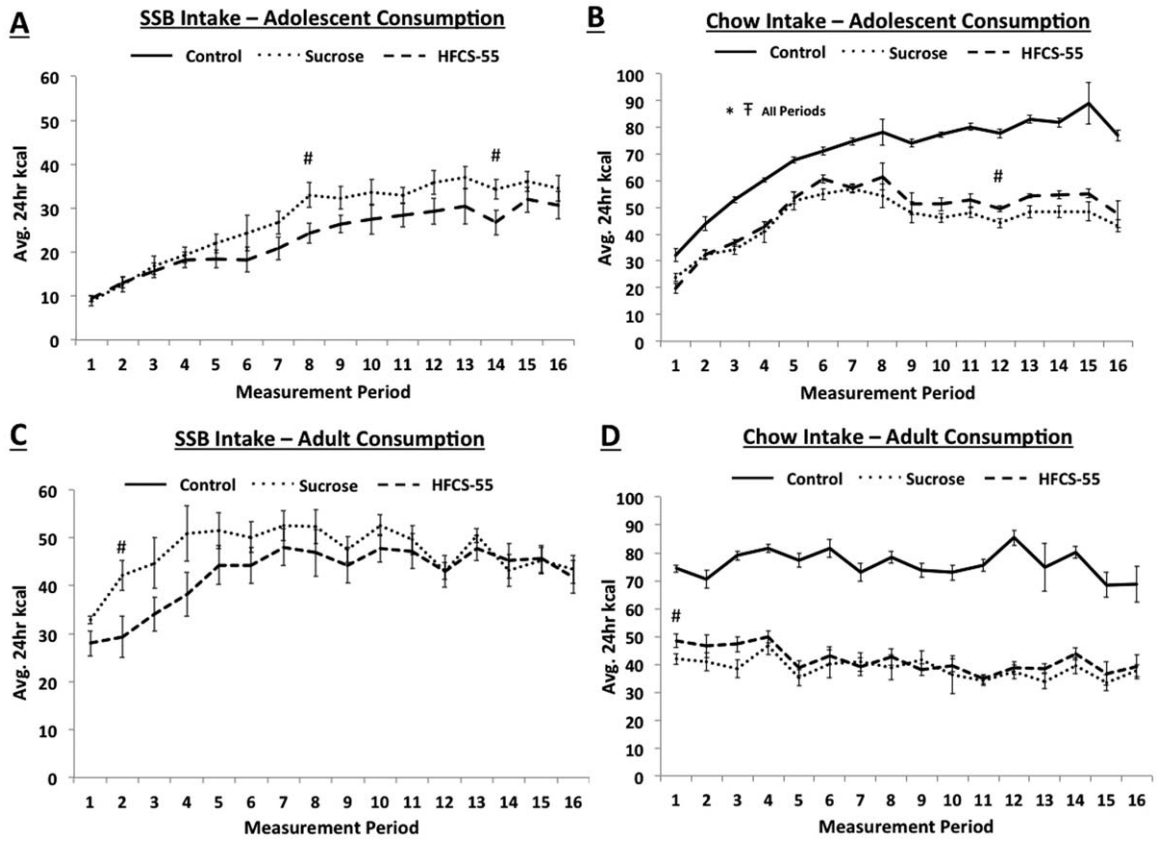

FIGURE 3. Average 24 h kcal intake for adolescent groups of, (A) sucrose or HFCS-55 solution, (B) solid food (chow), and average 24 h kcal intake for adult groups of, (C) sucrose or HFCS-55 solution, and (D) chow. Data are mean ± SEM; ∓$P < 0.05$ Sucrose vs. Control, *$P < 0.05$ HFCS-55 vs. Control, #$P < 0.05$ Sucrose vs. HFCS-55.

test. Further, no learning and memory differences were observed in a non-spatial response task using the same mildly aversive stimuli and escape parameters as the Barnes maze, suggesting that memory deficits were specific to hippocampal-dependent processes and were not based on nonspecific motivational or performance differences. Interestingly, adult rats given 30-day access to the same added sugar solutions showed no significant impairment in spatial learning and memory, nor did they display anxiety differences relative to controls. These findings indicate that (1) consumption of added sugars, independent of elevated fat intake, can produce detrimental effects on hippocampal function, and (2) adolescence is a critical period of development during which learning and memory processes are particularly susceptible to the effects of added sugars.

The learning and memory deficits associated with adolescent sugar consumption are unlikely to be secondary to increased overall kcal consumption, nor to increased overall adiposity and obesity. The adolescent experimental groups consumed approximately 35% of their total kcals from the added sugars; however, they efficiently compensated by reducing their total chow consumption such that total kcal intake matched the control group. Similarly, the adolescent experimental groups did not differ from controls in terms of body weight gain across the 30-day exposure period. On the other hand, caloric compensation in the adult sugar-exposed groups was less accurate. While chow intake was reduced in adult experimental groups compared to controls, total daily kcal intake for both the adult HFCS-55 and sucrose groups was significantly higher than controls throughout most of the 30-day exposure period. This pattern led to an increased rate of body weight gain for adult SSB groups compared to controls; however, terminal body weights did not differ by group. Overall, these data strongly suggest that the cognitive impairment induced by SSB consumption during adolescence occurs independently of excessive total kcal intake and obesity. A related possibility is that the memory impairment in rats exposed to SSBs during adolescence was due to nutrient deficiency. While the rats in the present study were not restricted calorically, the SSB-exposed groups consumed ~30 to 35% fewer chow kcals than the controls. This account is unlikely, however, for several reasons. First, adolescent SSB consumption did not produce differences in body weight from the controls, indicating the absence of any substantial nutrient deficiency that would restrict growth. Second, 40% caloric restriction during a comparable developmental period (PN25–67) did not impact spatial learning or memory in rats in a previous study (Alamy et al., 2005). It is

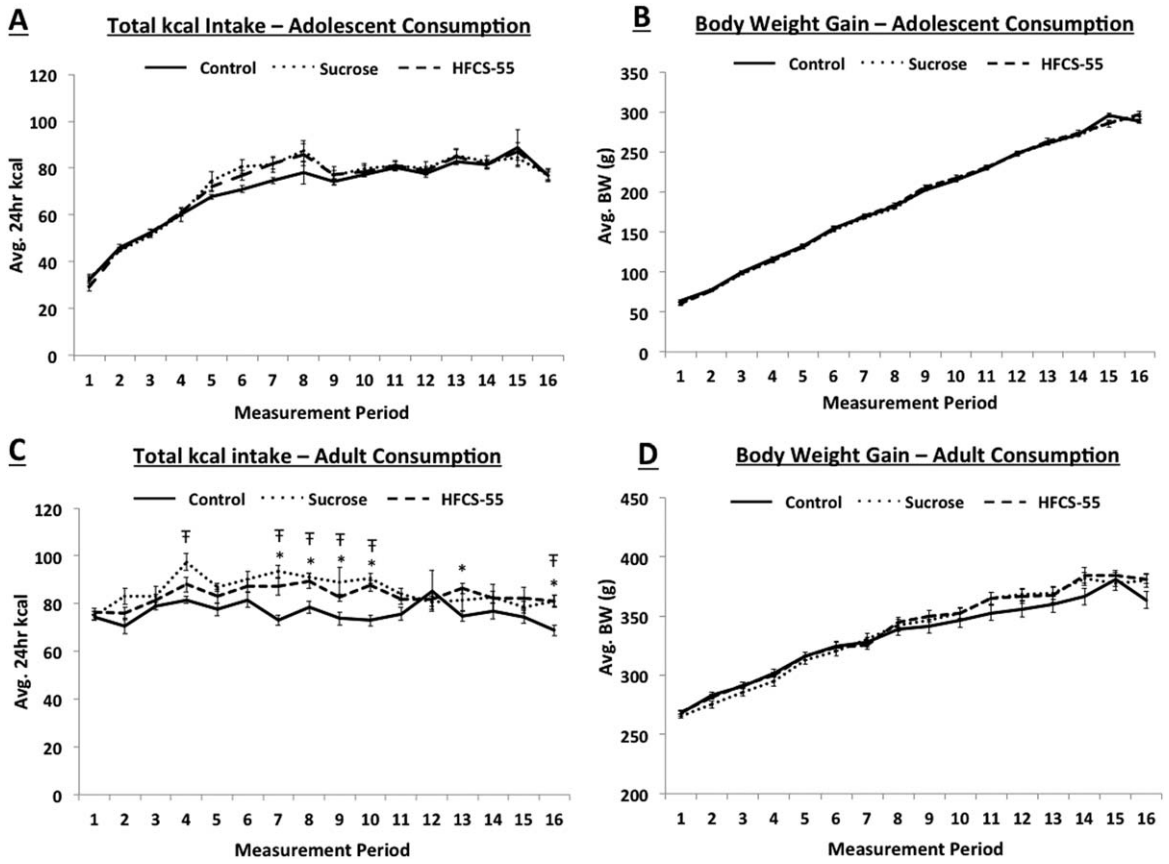

FIGURE 4. (A) Adolescent total 24 h kcal average intake (SSB + chow), (B) adolescent body weight gain, (C) adult total average 24 h kcal intake (SSB + chow), and (D) adult body weight gain during 30-day access period. Data are mean ± SEM; ∓$P < 0.05$ Sucrose vs. Control, *$P < 0.05$ HFCS-55 vs. Control.

also unlikely that potential nutrient restriction in the adolescent-exposed SSB groups contributed to the metabolic and neuroinflammation outcomes, as post weaning caloric restriction in rodent models is protective against obesity-related metabolic phenotypes later in life (Schroeder et al., 2010; Liu et al., 2013).

Adolescence is a critical period for the development for a multitude of behavioral and biological systems (Spear, 2000; Chambers et al., 2003; Sun et al., 2012; Boersma et al., 2014). Previous data show that adolescent Western diet intake in rats yields contextual memory impairment in a conditioned place preference paradigm (Privitera et al., 2011), as well as in hippocampal-dependent spatial memory tasks (Boitard et al., 2012; Valladolid-Acebes et al., 2013). These studies highlight adolescence as a sensitive period for Western diet-induced cognitive perturbations; however, they do not address the effects of sugar consumption independent of elevated fat intake. Importantly, these studies also observed elevated body weight gain following adolescent Western diet consumption, a consequence that was not produced by adolescent SSB consumption in this study. In humans, a recent study reported that habitual consumption of SFAs in prepubescent children had negative correlations with performance in hippocampal-dependent relational memory tasks, even after adjustment for body mass index (Baym et al., 2014). Present data expand these results by showing that added sugars can also negatively impact hippocampal function independent of excessive total kcal intake and body weight gain, and further, that adolescence is a critical period where metabolic and neuronal systems are particularly vulnerable to dietary sugar. Future studies are needed to establish whether the cognitive and biological impact of simple carbohydrate consumption is also heightened during other critical periods of development (e.g., prenatal, infancy).

The impact of elevated sucrose vs. elevated fat ingestion (independently) on learning and memory function has been previously examined in a series of studies where adult rats were given 5–8 week *ad libitum* access to either a high fat food (Crisco) or a 32% sucrose solution in addition to their normal chow diet (Jurdak et al., 2008; Jurdak and Kanarek, 2009). While both groups consumed more kcal and gained more weight than controls, only rats given the sucrose solution showed significant impairment in novel object recognition and the Morris water maze (a hippocampal-dependent spatial memory task). A series of studies from Ross and coworkers

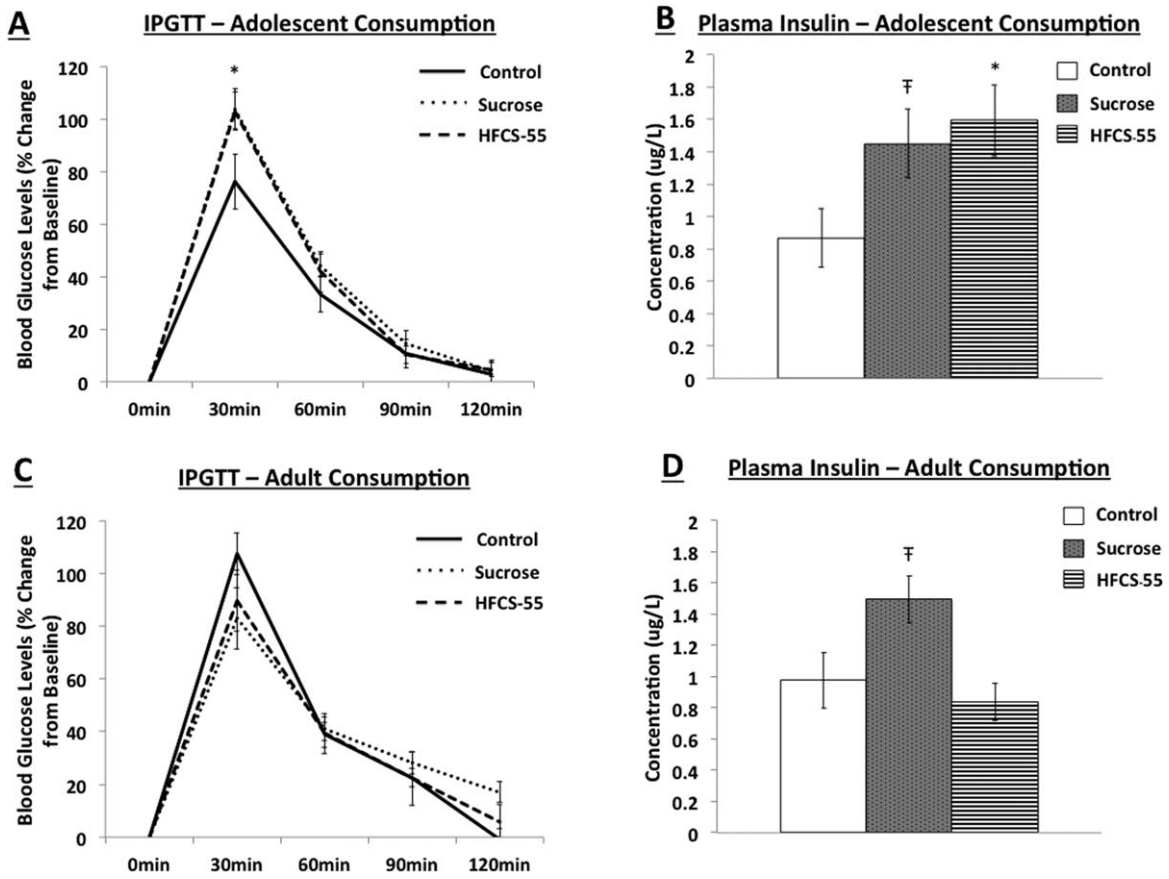

FIGURE 5. (A) Depicts the percentage change in baseline blood glucose levels following IP injections of dextrose solution and, (B) depicts plasma insulin levels in the adolescent groups; (C) and (D) depict comparable data for the adult groups. Data are mean ± SEM; ∓$P < 0.05$ Sucrose vs. Control, *$P < 0.05$ HFCS-55 vs. Control.

demonstrated that 3–4 months access to a high (60% kcal) fructose diet (fat content equal to control diet), beginning either immediately before adolescence at PN21 (Ross et al., 2012) or in young adulthood at PN∼60 (Ross et al., 2009), impaired learning and memory in a Morris water maze task. Another study (Kendig et al., 2013) reported that 10% sucrose solution access either during adolescence or young adulthood impaired spatial memory in a Morris water maze relative to a control group that was given daily access to an artificial sweetener. Collectively these studies suggest that sugar consumption can have considerable impact on hippocampal function, and in some conditions, can be more effective than elevated fat intake for producing deleterious effects on memory. Our data extend these findings and show that adolescence is a particularly vulnerable period for the detrimental effects of sugar consumption on cognitive function. Four weeks *ad libitum* access to 11% sucrose or 11% HFCS-55 solution, the most commonly used sweeteners in the United States, had no impact on spatial memory when consumed for 30 days during young adulthood, whereas this was not the case for adolescent-exposed rats.

Other results in this study show that adolescent (but not adult) consumption of added sugars disrupts peripheral glucose regulation and elevates hepatic inflammatory markers, both of which are associated with excessive sugar consumption (Tran et al., 2009; Wang et al., 2013; Shawky et al., 2014; Vasiljevic et al., 2014). Adolescent rats given 11% HFCS-55 solution demonstrated impaired glucose tolerance, whereas consumption of either sucrose or HFCS-55 yielded increased fasting plasma insulin levels and increased protein expression of the pro-inflammatory cytokine, IL-1β, in the liver. Interestingly, we also observed increased plasma insulin levels in the adult sucrose exposed group, however, this group did not demonstrate concurrent glucose intolerance, cognitive impairment, or elevated inflammatory markers. Overall, these results suggest that adolescent exposure to simple sugars increases the risk for peripheral metabolic dysfunction and hepatic inflammation independent of consuming a high fat diet, and also independent of excess overall kcal intake and/or body weight gain. The extent that these biological alterations are causally related to the observed learning and memory deficits requires further investigation. Indeed, both peripheral and central insulin

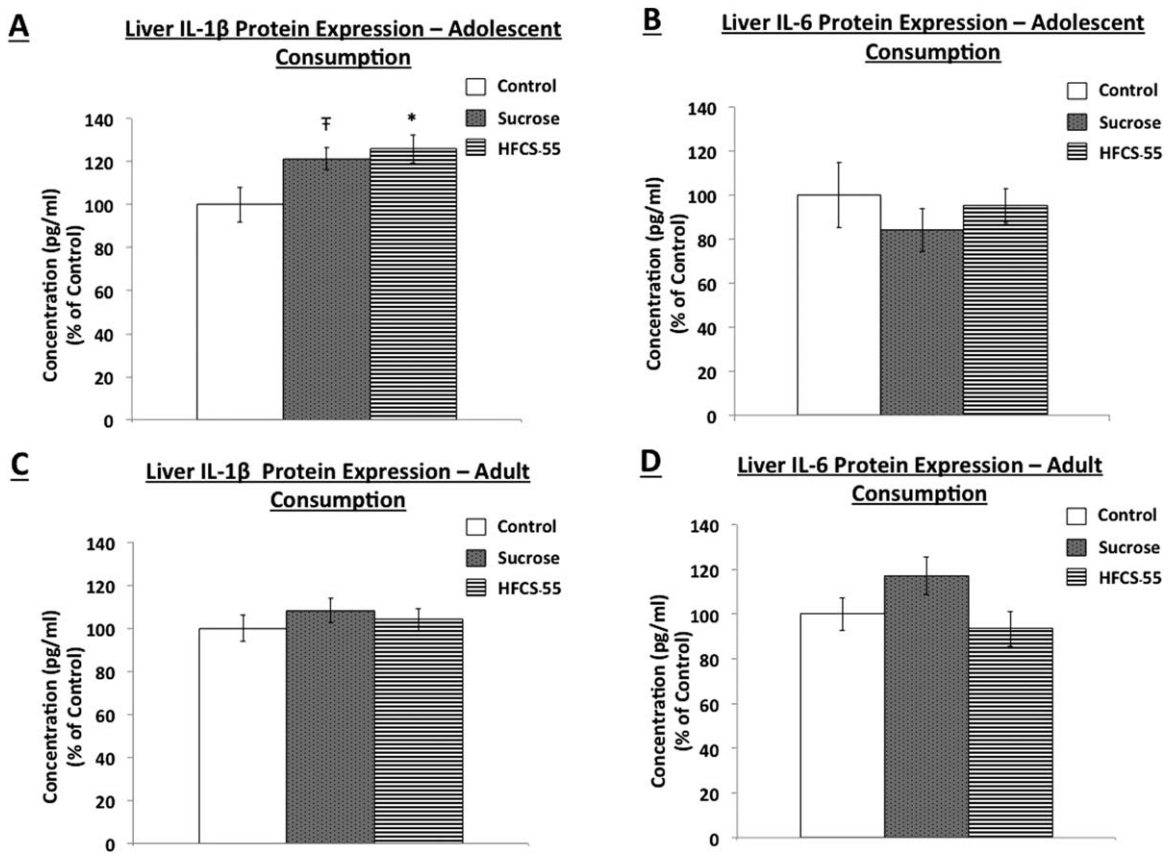

FIGURE 6. Protein concentrations (pg/mL) of IL-1β and IL-6 in liver tissue for the (A, B) adolescent group and (C, D) adult group. Data are mean ± SEM; ∓$P < 0.05$ Sucrose vs. Control, *$P < 0.05$ HFCS-55 vs. Control.

resistance are strongly associated with cognitive impairment and Alzheimer's pathology [see (Watson and Craft, 2004; Craft, 2005, 2007) for review].

In addition to elevated expression of IL-1β in liver tissue, the adolescent-exposed HFCS-55 group also demonstrated increases in protein expression of the pro-inflammatory cytokines, IL-6 and IL-1β, in the dorsal hippocampus, the subregion of the hippocampus that is particularly important for spatial learning and memory (Bannerman et al., 2004; Fanselow and Dong, 2010). Neuroinflammatory markers in the hippocampus typically precede hippocampal dysfunction and Alzheimer's pathology (Shaftel et al., 2008; McNaull et al., 2010), and this has been purported as a potential mechanism for Western diet-induced memory dysfunction (White et al., 2009; Pistell et al., 2010). Previous findings show that Western diet intake during critical periods of development can elevate neuroinflammation later in life. Rat dams fed a high fat diet for 4 weeks before mating and throughout pregnancy produced offspring with increased pro-inflammatory cytokine protein expression in the hippocampus and cortex at birth and into weaning and adulthood (White et al., 2009; Bilbo and Tsang, 2010). The current study demonstrates that adolescence is also a critical period of development for dietary influences on neuroinflammation, representing a potential neurobiological mechanism for the hippocampal-dependent memory impairment in rats consuming HFCS-55 during adolescence.

While adolescent exposure to either the HFCS-55 or sucrose solution increased circulating insulin levels and hepatic pro-inflammatory cytokine expression, spatial learning, and memory deficits relative to control rats were more marked in the HFCS-55 group, as were markers of neuroinflammation in the hippocampus. Taken together, these results suggest that neuroinflammation in the hippocampus may be more indicative of memory impairment than measures of glucose intolerance and hepatic inflammation. Given that overall levels of fructose intake were not significantly different between the adolescent-exposed sucrose and HFCS-55 groups, whereas glucose intake was lower in the HFCS-55 group, the ratio of fructose to glucose consumption may influence memory function. However, we note that interpretations regarding the differential effects of HFCS-55 vs. sucrose in our study should be made with caution given that significant differences in Barnes maze performance and hippocampal cytokine expression were observed between the HFCS-55 and the control group, but not between the HFCS-55 and the sucrose group. Systematic follow-up work is required to determine the relative impact of consuming

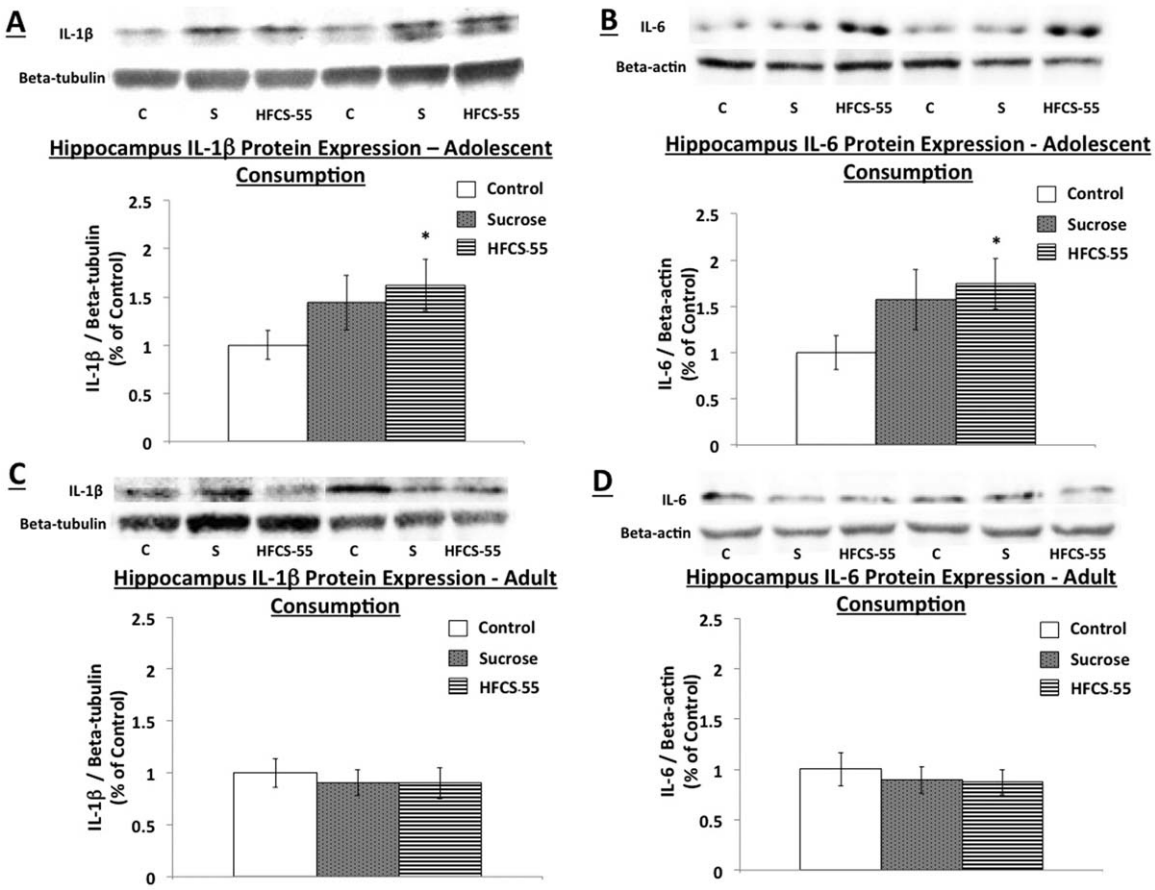

FIGURE 7. Protein expression of IL-1β and IL-6 in the dorsal hippocampus. (A, B) depicts elevated IL-1β and IL-6 expression in the adolescent group and (C, D) shows the adult group (no differences). Representative Western blot series are depicted. Data are mean-± SEM;*$P < 0.05$ HFCS-55 vs. Control.

fructose, glucose, and varying fructose–glucose ratios on cognitive and neurobiological outcomes.

The adolescent rats in this study consumed approximately 35–40% of their total kcal from SSBs. This is higher than the estimated average intake among U.S children (ages 12–19 years), who consume approximately 17% of their total kcal intake from added sugars (Ervin et al., 2012). Therefore, present data are more relevant to individuals consuming SSBs in excess than to those consuming SSBs in moderation. Overall, our results show that excessive consumption of added sugars during adolescence (in concentrations commonly consumed in human populations in SSBs) alters peripheral glucose metabolism, impairs hippocampal-dependent memory function, and increases hepatic and hippocampal markers of inflammation in rats. These negative behavioral and biological outcomes were not observed when sucrose and HFCS were consumed for the same period of time in adult rats. Overall these data have important implications regarding the impact of consuming added sugars in excess during critical periods of development, and highlight the fact that both cognitive and metabolic disruptions can arise from adolescent consumption of HFCS-55 and sucrose.

Acknowledgments

The authors thank the following individuals for notable contributions to this work: Joel Hahn, MaryAnn Bohland Matveyenko, Casey Donovan, Hrant Gevorgian, Trosdamad Missaelian, Joanna Liang, Jessica Thai, Ashley Lam, Mehul Trivedi, and the EXSC 409 Fall 2013 students.

REFERENCES

Ackroff K, Sclafani A. 2011. Rats' preferences for high fructose corn syrup vs. sucrose and sugar mixtures. Physiol Behav 102:548–552.

Alamy M, Errami M, Taghzouti K, Saddiki-Traki F, Bengelloun WA. 2005. Effects of postweaning undernutrition on exploratory

behavior, memory and sensory reactivity in rats: Implication of the dopaminergic system. Physiol Behav 86:195–202.
Avena NM, Rada P, Hoebel BG. 2008. Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 32:20–39.
Avena NM, Bocarsly ME, Hoebel BG. 2012. Animal models of sugar and fat bingeing: Relationship to food addiction and increased body weight. Methods Mol Biol 829:351–365.
Bannerman DM, Rawlins JN, McHugh SB, Deacon RM, Yee BK, Bast T, Zhang WN, Pothuizen HH, Feldon J. 2004. Regional dissociations within the hippocampus—Memory and anxiety. Neurosci Biobehav Rev 28:273–283.
Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, Moore RD, Scudder MR, Kramer AF, Hillman CH, Cohen NJ. 2014. Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. Am J Clin Nutr 99: 1026–1032.
Benito-Leon J, Mitchell AJ, Hernandez-Gallego J, Bermejo-Pareja F. 2013. Obesity and impaired cognitive functioning in the elderly: A population-based cross-sectional study (NEDICES). Eur J Neurol 20:899–906, e76–e77.
Bilbo SD, Tsang V. 2010. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB J 24: 2104–2115.
Bocarsly ME, Powell ES, Avena NM, Hoebel BG. 2010. High-fructose corn syrup causes characteristics of obesity in rats: Increased body weight, body fat and triglyceride levels. Pharmacol Biochem Behav 97:101–106.
Boersma GJ, Bale TL, Casanello P, Lara HE, Lucion AB, Suchecki D, Tamashiro KL. 2014. Long-term impact of early life events on physiology and behaviour. J Neuroendocrinol 26:587–602.
Boitard C, Etchamendy N, Sauvant J, Aubert A, Tronel S, Marighetto A, Laye S, Ferreira G. 2012. Juvenile, but not adult exposure to high-fat diet impairs relational memory and hippocampal neurogenesis in mice. Hippocampus 22:2095–2100.
Bray GA. 2013. Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Adv Nutr 4:220–225.
Bray GA, Nielsen SJ, Popkin BM. 2004. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity.[see comment][erratum appears in Am J Clin Nutr. 2004. Am J Clin Nutr 79:537–543.
Brenhouse HC, Andersen SL. 2011. Developmental trajectories during adolescence in males and females: A cross-species understanding of underlying brain changes. Neurosci Biobehav Rev 35:1687–1703.
Chambers RA, Taylor JR, Potenza MN. 2003. Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. Am J Psychiatry 160:1041–1052.
Chang Q, Gold PE. 2003. Intra-hippocampal lidocaine injections impair acquisition of a place task and facilitate acquisition of a response task in rats. Behav Brain Res 144:19–24.
Craft S. 2005. Insulin resistance syndrome and Alzheimer's disease: Age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol Aging 26(Suppl 1):65–69.
Craft S. 2007. Insulin resistance and Alzheimer's disease pathogenesis: Potential mechanisms and implications for treatment. Curr Alzheimer Res 4:147–152.
Darling JN, Ross AP, Bartness TJ, Parent MB. 2013. Predicting the effects of a high-energy diet on fatty liver and hippocampal-dependent memory in male rats. Obesity (Silver Spring) 21:910–917.
Duffey KJ, Popkin BM. 2007. Shifts in patterns and consumption of beverages between 1965 and 2002. Obesity (Silver Spring) 15: 2739–2747.
Ervin RB, Kit BK, Carroll MD, Ogden CL. 2012. Consumption of added sugar among U.S. children and adolescents, 2005–2008. NCHS Data Brief:1–8.
Fanselow MS, Dong HW. 2010. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65:7–19.
Francis HM, Stevenson RJ. 2011. Higher reported saturated fat and refined sugar intake is associated with reduced hippocampal-dependent memory and sensitivity to interoceptive signals. Behav Neurosci 125:943–955.
Francis H, Stevenson R. 2013. The longer-term impacts of Western diet on human cognition and the brain. Appetite 63:119–128.
Freeman LR, Haley-Zitlin V, Rosenberger DS, Granholm AC. 2014. Damaging effects of a high-fat diet to the brain and cognition: A review of proposed mechanisms. Nutr Neurosci 17:241–251.
Goran MI, Dumke K, Bouret SG, Kayser B, Walker RW, Blumberg B. 2013. The obesogenic effect of high fructose exposure during early development. Nat Rev Endocrinol 9:494–500.
Granholm A, Bimonte-Nelson H, Moore A, Nelson M, Freeman L, Sambamurti K. 2008. Effects of a saturated fat and high cholesterol diet on memory and hippocampal morphology in the middle-aged rat. J Alzheimers Dis 14:133–145.
Grissom N, Bowman N, Reyes TM. 2014. Epigenetic programming of reward function in offspring: A role for maternal diet. Mamm Genome 25:41–48.
Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E. 2006. Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disord 11:e15–e19.
Hu FB, van Dam RM, Liu S. 2001. Diet and risk of Type II diabetes: The role of types of fat and carbohydrate. Diabetologia 44:805–817.
Jen KL, Rochon C, Zhong SB, Whitcomb L. 1991. Fructose and sucrose feeding during pregnancy and lactation in rats changes maternal and pup fuel metabolism. J Nutr 121:1999–2005.
Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, Shafiu M, Segal M, Glassock RJ, Shimada M and others. 2009. Hypothesis: Could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev 30:96–116.
Jurdak N, Kanarek RB. 2009. Sucrose-induced obesity impairs novel object recognition learning in young rats. Physiol Behav 96:1–5.
Jurdak N, Lichtenstein AH, Kanarek RB. 2008. Diet-induced obesity and spatial cognition in young male rats. Nutr Neurosci 11:48–54.
Kanoski SE. 2012. Cognitive and neuronal systems underlying obesity. Physiol Behav 106:337–344.
Kanoski SE, Davidson TL. 2010. Different patterns of memory impairments accompany short- and longer-term maintenance on a high-energy diet. J Exp Psychol Anim Behav Process 36:313–319.
Kanoski SE, Davidson TL. 2011. Western diet consumption and cognitive impairment: Links to hippocampal dysfunction and obesity. Physiol Behav 103:59–68.
Kanoski SE, Meisel RL, Mullins AJ, Davidson TL. 2007. The effects of energy-rich diets on discrimination reversal learning and on BDNF in the hippocampus and prefrontal cortex of the rat. Behav Brain Res 182:57–66.
Kanoski SE, Zhang Y, Zheng W, Davidson TL. 2010. The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. J Alzheimers Dis 21:207–219.
Kanoski SE, Hayes MR, Greenwald HS, Fortin SM, Gianessi CA, Gilbert JR, Grill HJ. 2011. Hippocampal leptin signaling reduces food intake and modulates food-related memory processing. Neuropsychopharmacology 36:1859–1870.
Kant AK. 2003. Reported consumption of low-nutrient-density foods by American children and adolescents: nutritional and health correlates, NHANES III, 1988 to 1994. Arch Pediatr Adolesc Med 157:789–796.
Kendig MD, Boakes RA, Rooney KB, Corbit LH. 2013. Chronic restricted access to 10% sucrose solution in adolescent and young adult rats impairs spatial memory and alters sensitivity to outcome devaluation. Physiol Behav 120:164–172.
la Fleur SE, Luijendijk MC, van der Zwaal EM, Brans MA, Adan RA. 2014. The snacking rat as model of human obesity: Effects of

a free-choice high-fat high-sugar diet on meal patterns. Int J Obes (Lond) 38:643–649.
Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, Sowers J. 2013. Obesity-related hypertension: Pathogenesis, cardiovascular risk, and treatment—A position paper of the The Obesity Society and The American Society of Hypertension. J Clin Hypertens (Greenwich) 15:14–33.
Liu HW, Srinivasan M, Mahmood S, Smiraglia DJ, Patel MS. 2013. Adult-onset obesity induced by early life overnutrition could be reversed by moderate caloric restriction. Am J Physiol Endocrinol Metab 305:E785–E794.
Marriott BP, Olsho L, Hadden L, Connor P. 2010. Intake of added sugars and selected nutrients in the United States, National Health and Nutrition Examination Survey (NHANES) 2003–2006. Crit Rev Food Sci Nutr 50:228–258.
Martin AA, Davidson TL. 2014. Human cognitive function and the obesogenic environment. Physiol Behav.
McNaull BB, Todd S, McGuinness B, Passmore AP. 2010. Inflammation and anti-inflammatory strategies for Alzheimer's disease—A mini-review. Gerontology 56:3–14.
Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F. 2002. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience 112:803–814.
Murray AJ, Knight NS, Cochlin LE, McAleese S, Deacon RM, Rawlins JN, Clarke K. 2009. Deterioration of physical performance and cognitive function in rats with short-term high-fat feeding. FASEB J 23:4353–4360.
Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK, Bruce-Keller AJ. 2010. Cognitive impairment following high fat diet consumption is associated with brain inflammation. J Neuroimmunol 219:25–32.
Privitera GJ, Zavala AR, Sanabria F, Sotak KL. 2011. High fat diet intake during pre and periadolescence impairs learning of a conditioned place preference in adulthood. Behav Brain Funct 7:21.
Rawana S, Clark K, Zhong S, Buison A, Chackunkal S, Jen KL. 1993. Low dose fructose ingestion during gestation and lactation affects carbohydrate metabolism in rat dams and their offspring. J Nutr 123:2158–2165.
Reedy J, Krebs-Smith SM. 2010. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. J Am Diet Assoc 110:1477–1484.
Rosenfeld CS, Ferguson SA. 2014. Barnes maze testing strategies with small and large rodent models. J Vis Exp:e51194.
Ross AP, Bartness TJ, Mielke JG, Parent MB. 2009. A high fructose diet impairs spatial memory in male rats. Neurobiol Learn Mem 92:410–416.
Ross AP, Bruggeman EC, Kasumu AW, Mielke JG, Parent MB. 2012. Non-alcoholic fatty liver disease impairs hippocampal-dependent memory in male rats. Physiol Behav 106:133–141.
Rudenga KJ, Small DM. 2013. Ventromedial prefrontal cortex response to concentrated sucrose reflects liking rather than sweet quality coding. Chem Senses 38:585–594.
Sanchez-Lozada LG, Mu W, Roncal C, Sautin YY, Abdelmalek M, Reungjui S, Le M, Nakagawa T, Lan HY, Yu X, Johnson RJ. 2010. Comparison of free fructose and glucose to sucrose in the ability to cause fatty liver. Eur J Nutr 49:1–9.
Schroeder M, Moran TH, Weller A. 2010. Attenuation of obesity by early-life food restriction in genetically hyperphagic male OLETF rats: Peripheral mechanisms. Horm Behav 57:455–462.
Shaftel SS, Griffin WS, O'Banion MK. 2008. The role of interleukin-1 in neuroinflammation and Alzheimer disease: An evolving perspective. J Neuroinflammation 5:7.
Shawky NM, Shehatou GS, Abdel Rahim M, Suddek GM, Gameil NM. 2014. Levocetirizine ameliorates high fructose diet-induced insulin resistance, vascular dysfunction and hepatic steatosis in rats. Eur J Pharmacol 740C:353–363.
Sheludiakova A, Rooney K, Boakes RA. 2012. Metabolic and behavioural effects of sucrose and fructose/glucose drinks in the rat. Eur J Nutr 51:445–454.
Spear LP. 2000. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 24:417–463.
Stice E, Burger KS, Yokum S. 2013. Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions. Am J Clin Nutr 98:1377–1384.
Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, Egan JM, Mattson MP. 2008. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus 18:1085–1088.
Sun B, Purcell RH, Terrillion CE, Yan J, Moran TH, Tamashiro KL. 2012. Maternal high-fat diet during gestation or suckling differentially affects offspring leptin sensitivity and obesity. Diabetes 61: 2833–2841.
Te Morenga L, Mallard S, Mann J. 2013. Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ 346:e7492.
Tirelli E, Laviola G, Adriani W. 2003. Ontogenesis of behavioral sensitization and conditioned place preference induced by psychostimulants in laboratory rodents. Neurosci Biobehav Rev 27:163–178.
Tran LT, Yuen VG, McNeill JH. 2009. The fructose-fed rat: A review on the mechanisms of fructose-induced insulin resistance and hypertension. Mol Cell Biochem 332:145–159.
Valladolid-Acebes I, Fole A, Martin M, Morales L, Cano MV, Ruiz-Gayo M, Del Olmo N. 2013. Spatial memory impairment and changes in hippocampal morphology are triggered by high-fat diets in adolescent mice. Is there a role of leptin? Neurobiol Learn Mem 106:18–25.
Vasiljevic A, Bursac B, Djordjevic A, Milutinovic DV, Nikolic M, Matic G, Velickovic N. 2014. Hepatic inflammation induced by high-fructose diet is associated with altered 11betaHSD1 expression in the liver of Wistar rats. Eur J Nutr 53:1393–1402.
Veldhuizen MG, Douglas D, Aschenbrenner K, Gitelman DR, Small DM. 2011. The anterior insular cortex represents breaches of taste identity expectation. J Neurosci 31:14735–14744.
Vickers MH, Clayton ZE, Yap C, Sloboda DM. 2011. Maternal fructose intake during pregnancy and lactation alters placental growth and leads to sex-specific changes in fetal and neonatal endocrine function. Endocrinology 152:1378–1387.
Vucetic Z, Kimmel J, Totoki K, Hollenbeck E, Reyes TM. 2010. Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. Endocrinology 151:4756–4764.
Wang X, Zhang DM, Gu TT, Ding XQ, Fan CY, Zhu Q, Shi YW, Hong Y, Kong LD. 2013. Morin reduces hepatic inflammation-associated lipid accumulation in high fructose-fed rats via inhibiting sphingosine kinase 1/sphingosine 1-phosphate signaling pathway. Biochem Pharmacol 86:1791–1804.
Watson GS, Craft S. 2004. Modulation of memory by insulin and glucose: Neuropsychological observations in Alzheimer's disease. Eur J Pharmacol 490:97–113.
White CL, Pistell PJ, Purpera MN, Gupta S, Fernandez-Kim SO, Hise TL, Keller JN, Ingram DK, Morrison CD, Bruce-Keller AJ. 2009. Effects of high fat diet on Morris maze performance, oxidative stress, and inflammation in rats: Contributions of maternal diet. Neurobiol Dis 35:3–13.