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A high fructose diet does not affect amphetamine self-administration or spatial water maze learning and memory in female rats

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ABSTRACT

High energy diets can have a detrimental effect on brain plasticity. For example, a high fructose diet impairs spatial memory in male rats. The aim of the present study was to determine whether a high fructose diet impairs another form of learning and memory: drug reinforcement learning. Female Sprague–Dawley rats were fed a high fructose diet (60%) from weaning at postnatal day (PND) 21, then allowed to acquire lever-pressing maintained by intravenous (i.v.) amphetamine at PND 68, 109, or 165. Acquisition was tested on a fixed ratio one (FR1) schedule of reinforcement (0.025 mg/kg/infusion, 1 h daily sessions, 10 sessions over 14 days), followed by testing for reinforcing efficacy on a progressive ratio (PR) schedule (0.025, 0.01, and 0.1 mg/kg/infusion), 14 days of abstinence, and within-session extinction and reinstatement tests. Subsequently, water maze acquisition and retention were tested in these subjects as well as a separate cohort tested in the water maze only. The diet had no effect on acquisition, reinforcing efficacy, extinction, or reinstatement of amphetamine seeking. Nor did the diet alter any measures of spatial memory. The high fructose diet did decrease body mass and increase relative liver and spleen mass, but did not affect plasma triglyceride concentrations consistently. Together with prior research on males, these results suggest that the metabolism of fructose and the effects of a high fructose diet on learning and memory may be sex-dependent.

1. Introduction

Diet can affect brain plasticity and cognitive functions such as learning and memory. Detrimental effects of high energy diets (e.g., high sugar and/or high fat) have been observed at both neural and behavioral levels of plasticity. For instance, consumption of high energy diets decreases hippocampal neurogenesis (Lindqvist et al., 2006), long-term potentiation (Stranahan et al., 2008), insulin-induced long-term depression (Mielke et al., 2005), and brain-derived neurotrophic factor (BDNF) concentrations (Park et al., 2010). Behaviorally, high energy diets impair spatial learning and/or memory in the radial arm maze (Greenwood and Winocur, 1990) and water maze (Jurdak et al., 2008; Ross et al., 2009), temporal memory in the variable-interval delayed alternation (VIDA) task (Greenwood and Winocur, 1990), and learning of an operant conditioning bar-pressing task (Mielke et al., 2006).

High energy diets, such as a high fructose diet, can alter metabolic homeostasis. Fructose is preferentially metabolized through the liver and increases hepatic triglyceride production (Zavaroni et al., 1982). When consumed in excessive amounts, a high fructose diet produces large increases in plasma triglyceride concentrations, liver mass (Bruckdorfer et al., 1972; Michaelis and Szepesi, 1973; D'Angelo et al., 2005; Ross et al., 2009), and liver lipid content (Bergheim et al., 2008; Kawasaki et al., 2009). The physiological effects of fructose, for the most part, are similar in males and females. A high fructose diet increases visceral adipose tissue (Alzamendi et al., 2009; Alzamendi et al., 2010; Zakula et al., 2011) and liver mass (Bruckdorfer et al., 1972; Bergstra et al., 1993) in both male and female rats. Fructose consumption does not usually increase body mass in either male or female rats (Lee et al., 2008; Kawasaki et al., 2009; Ross et al., 2009). On the other hand, fructose-induced elevations in plasma triglyceride concentrations are more robust in males than in females (Galipeau et al., 2002; Couchepin et al., 2008). In female rats, fructose consumption does not affect the estrous cycle (Light et al., 2009).

We reported previously that a high fructose diet impairs spatial water maze memory in male rats (Ross et al., 2009) and in the present study we sought to determine whether the memory-impairing effects of fructose would extend to other types of behavioral plasticity. We elected to test the effects of a high fructose diet on reinforcement learning that occurs during amphetamine self-administration because another high energy diet (high fat) impairs plasticity in an operant conditioning task as well as in the spatial water maze (Farr et al.,

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2008). Moreover, drug addiction can be considered a disorder of neuroplasticity (Kalivas and O'Brien, 2008). We also tested whether the memory-impairing effects of a high fructose diet would extend from male rats to female rats. Finally, we predicted that a high fructose diet would not increase plasma triglyceride concentrations in female rats as robustly as in male rats, and would not affect the estrous cycle, based on previous comparisons between sexes (Galipeau et al., 2002; Couchepin et al., 2008; Light et al., 2009).

2. Materials and methods

2.1. Experiment 1

2.1.1. Animals

Ten timed-pregnant dams (Sprague–Dawley rats, Charles River, Wilmington, MA) arrived 7–10 days before delivering litters. Day of birth was designated PND0 and at PND21 the female pups were weaned and placed in cages (two to three rats per cage), and were group-housed throughout the entire study. The animal care facility was controlled for temperature and humidity and rats were maintained on a 12 h light/dark schedule. All procedures were approved by Georgia State University's Institutional Animal Care and Use Committee and were in accordance with PHS guidelines as well as the EC Directive 86/609/EEC.

2.1.2. Diets

On the day of weaning, the pups were placed on either a control diet (n = 32; Research Diets, New Brunswick, NJ) or a 60% fructose diet (n = 31; Research Diets, New Brunswick, NJ). This concentration of fructose was chosen because it is used routinely (Kelley et al., 2004; Wu et al., 2004; Abdullah et al., 2009; Mohamed Salih et al., 2009; Liao et al., 2010) and produces spatial memory deficits in adolescent and adult male rats (Ross et al., 2008; Ross et al., 2009). Both diets contained equal amounts of carbohydrates (70%), proteins (20%), and lipids (10%) and were isocaloric. The control diet contained 60% corn starch; both diets included 10% maltodextrin as an additional carbohydrate for pelleting purposes. The diets were fed ad libitum and fresh food was replaced every 3 days. The rats were fed the diets for 47 days (short; control [n = 12], fructose [n = 14]), 88 days (middle; control [n = 9], fructose [n = 5]), or 144 days (long; control [n = 11], fructose [n = 12]) before the start of behavioral testing. Litter effects were controlled by ensuring that each diet duration group was comprised of rats from at least two litters. The short and middle durations were selected to test for possible developmental differences in the effects of a high fructose diet. The long duration was chosen because a high fructose diet produces a memory deficit in adult male rats after approximately 130 days (Ross et al., 2009). The rats were fed their respective diets throughout the entire study.

2.1.3. Drugs

d-Amphetamine sulfate salt was purchased from Sigma Chemicals (St. Louis, MO) and dissolved in sterile saline in a stock concentration. Infusion volume was varied on a daily basis for individual rats to provide one of four doses: 0.0, 0.01, 0.025, and 0.1 mg/kg/infusion. Methohexital sodium (1% Brevital Sodium) was purchased from King Pharmaceuticals, Inc. (Bristol, TN). The antibiotic Timentin (Ticarcillin Disodium and Clavulanate Potassium) was purchased from GlaxoSmithKline (Research Triangle Park, NC).

2.1.4. Body mass and food intake measurements

Body mass was measured daily during the amphetamine self-administration and recess phases of experimentation (see Table 1). Food consumption was measured daily during the 14 days of recess between the self-administration and extinction/reinstatement tests. The mean consumption per rat was calculated as the total amount of food consumed per day per cage divided by the number of rats per cage.

2.1.5. Estrous cycle analysis

Vaginal lavage was conducted on all rats one week prior to surgery, throughout self-administration, and on the day of extinction/reinstatement. Smears were analyzed for a subset of rats in the short diet duration group (control [n = 5], fructose [n = 9]), the middle diet duration group (control [n = 7], fructose [n = 4]) and the long diet duration group (control [n = 11], fructose [n = 11]). The lavage was conducted at approximately 0900 h daily for one week prior to catheterization and daily during drug self-administration. A dropper containing approximately 0.25 ml of saline was inserted into the vaginal cavity, the fluid was drawn back into the dropper, and placed on a microscope slide. Vaginal smears were then stained with hematoxylin and eosin and analyzed under a microscope at 10× magnification. Diestrous was confirmed by the presence of large numbers of leukocytes (Marcondes et al., 2002) and the repeated occurrence of diestrous every 4 to 5 days served as the marker of cycling activity. The estrous cycle for each rat was rated as follows: 0 = not cyclic, 1 = abnormally cyclic, 2 = probably cyclic, but unclear, and 3 = obviously cyclic.

2.1.6. Procedures

2.1.6.1. Catheterization surgery. After 40, 82, or 137 (+/−3) days on the diets, catheters were implanted as described previously. Briefly, rats were anesthetized with an isoflurane/oxygen vapor mixture (5% for initial anesthetization and 1.5–3% during surgery) while catheter tubing was passed subcutaneously from a mid-scapular incision to the right jugular vein, inserted into the vein previously punctured with a 25 gage needle, and tied gently with suture thread. The tubing inserted into the vein was approximately 4 cm in length. Intravenous catheters were constructed as described (Caine et al., 1993) with minor modifications (Shahbazi et al., 2008). Silastic tubing was fitted onto a guide cannula (Plastics One; Roanoke, VA) bent at a right angle and encased in dental cement anchored with a 2.5-cm circular mesh for subcutaneous, midscapular placement. The silastic tubing was 12 cm long. Surgical clips were used to close the incision and secure

Table 1
Timeline for Experiment 1.

Diet	Surgery	Recovery	Fixed ratio	Progressive ratio			Recess	Extinction/ reinstatement	Water maze
			0.025 mg/kg/infusion	0.025 mg/kg/infusion	0.01/0.1 or 0.01/0.1 mg/kg/infusion	saline			
	Lavage (1 week before surgery)		Lavage, body mass	Lavage, body mass	Lavage, body mass	Lavage, body mass	Body mass, food intake	Lavage	
PND 21	40, 82, 137 days on diet[a]	5–7 d	10 d	3 d	3 d/3 d (6 d)	3 d	2 weeks	1 d	13–16 weeks, 19 weeks or 27 weeks on diet

[a] +/−3 days.

the catheter. During recovery, rats received approximately 0.2 ml Timentin (Ticarcillin Disodium and Clavulanate Potassium; 100 mg/ml, i.v.) twice daily on the first two days post-surgery, then once daily throughout the experiment. Catheters were also flushed daily with approximately 0.4 ml heparinized saline (100 USP units/1 ml).

2.1.6.2. Acquisition of amphetamine self-administration on a fixed ratio (FR) schedule. Amphetamine self-administration was conducted in operant chambers housed in sound-attenuating cubicles (MedAssociates, Inc.; St Albans, VT). Each chamber was equipped with two retractable levers (a right "active" lever and a left "inactive" lever), environmental cues, and a variable speed syringe pump outside the cubicle. At the start of each session, a wall-mounted house-light and white noise amplifier came on and two levers extended into the chamber. A single priming injection of amphetamine was provided at the start of each session. Presses on the inactive lever were recorded but had no scheduled consequences. Presses on the active lever triggered the pump for 2 s to deliver a 0.1 ml drug infusion. Each reinforced response activated a cue light above the lever that stayed on during the infusion. After each infusion, the cue light, house light, and white noise turned off for a 20 s time-out (TO). Drug delivery and data collection were controlled by Med Associates, Inc. software (Med PC IV).

Spontaneous acquisition of amphetamine self-administration was tested 5–7 days after surgery (PND 68, 109, or 165). Sessions were 1 h in duration and occurred daily 5 days per week for 2 weeks (10 sessions total) during the dark phase of the light/dark cycle. Sessions began when two levers extended into the chamber. Lever-pressing was reinforced by amphetamine (0.025 mg/kg/infusion i.v.) on a FR1, 20 s time-out (TO) schedule. The dose was chosen based on prior studies (Shahbazi et al., 2008).

2.1.6.3. Amphetamine self-administration on a progressive ratio (PR) schedule. After the acquisition phase, all rats were allowed to self-administer the same dose of amphetamine (0.025 mg/kg/infusion) for 3 days on a progressive ratio (PR) schedule of reinforcement (see Table 1). Subsequently, all rats were tested on both a lower and a higher dose (0.01 and 0.1 mg/kg/infusion) for 3 days each, in varied order, followed in all cases by saline substitution for a final 3 days of testing. Sessions were the same as for FR (cues and TO), except for the change to PR schedule and extension of session duration to a maximum of 6 h. On PR, the number of presses required to obtain a single infusion increased gradually within a session through the series 1, 2, 4, 6, 9, 12, 16, 20, 36, 48, 63, 83, etc., as calculated by the following formula: Required Number Presses $= 5\ e^{(0.2*\text{Step Number})} - 5$ (Roberts et al., 1989).

Patency of i.v. catheters was tested 1 day before the first session and weekly during the remainder of self-administration phases by administering 0.1–0.4 ml of the ultra-short-acting barbiturate anesthetic Brevital Sodium through the catheter. If muscle tone was not lost within 3 s, the catheter was assumed to be faulty and the subject was not included in analyses for the week prior to the failed test. If catheters were faulty before the end of the progressive ratio testing, subjects were excluded from all progressive ratio analyses.

2.1.6.4. Extinction and reinstatement. After the 14 days of abstinence from amphetamine self-administration, a within-session extinction and reinstatement test was conducted (Grimm et al., 2001; Grimm et al., 2003). Six 1-h extinction sessions were followed by a single 1-h cue-induced reinstatement session. During extinction, rats were connected to the metal coil tether but not the infusion tubing, the white noise remained off, and house light remained on. Neither cue, lights, nor TO signals were presented after presses on either lever. Five-min breaks occurred between each successive session, during which the two levers retracted and the house light turned off.

The cue-induced reinstatement test began with the onset of the house light, white noise, and a 5 s cue-light, followed by a 20 s TO during which the house light, white noise, and cue light were turned off. During the remainder of the cue-induced reinstatement session, presses on the active lever produced cue sequences identical to those presented during amphetamine self-administration, and the pump went on, although the syringe was not loaded. The only difference between self-administration and cue-induced reinstatement sessions was that drug solution was not infused during reinstatement.

2.1.6.5. Spatial memory testing. Spatial memory was tested in a circular water maze approximately 1.35 m wide and 0.46 m deep, filled with water (20 ± 3 °C). A clear, Plexiglas platform (11.5 cm diameter) was submerged 1 cm below the surface of the water and was not visible to the rats. Curtains hung on two sides of the pool and one visual pattern was pasted on each curtain. For purposes of analysis, the water maze was divided into four virtual quadrants, with the fourth quadrant containing the platform. Acquisition training began by placing the rat on the platform for 30 s and then placing it in the water in a random quadrant facing the pool wall. During training and testing, the rat was placed in quadrants 1 through 3 in random order and allowed 60 s maximum to reach the platform. If the rat did not find the platform in 60 s, the researcher gently guided it to the platform. Between trials, rats were placed in an empty Plexiglas cage with a heat lamp for 30 s. All rats were given eight trials the first day. The next day, the rats were trained to a criterion of swimming to the platform in less than 8 s for three consecutive trials (for a maximum of 3 days of training, eight trials per day). Two days after the last training trial, memory was tested in a single probe test. For this test, the platform was removed from the pool and the rat was placed in the pool in a random quadrant (1–3) and its swimming behavior was measured for 10 s. Retention measures included: 1) time spent in the target quadrant, 2) distance swam to the platform location (target; i.e., pathlength), and 3) average distance from the target over time (i.e., proximity).

2.1.7. Post-mortem measures

Forty-eight hours after the retention test, the rats were fasted for 4 h then anesthetized with isoflurane gas (5% in 95% oxygen) and decapitated. Trunk blood was collected in heparinized tubes and centrifuged to collect plasma, which was then stored at −80 °C. The livers were extracted and weighed. Plasma triglycerides were measured by spectrophotometry using a Serum Triglyceride Determination Kit (Sigma, St. Louis, MO). Samples were run in duplicate and according to the manufacturer's instructions.

2.1.8. Statistical analyses

Body mass (g), average food intake per cage (kcal), and the number of amphetamine infusions during self-administration on the FR schedule of reinforcement were analyzed using three-way mixed-measures ANOVAs, with diet type and diet duration as between-subjects factors and days as a repeated measure. Total drug intake (mg/kg) summed over sessions during FR testing was compared using the diet type × diet duration interaction term from the three-way ANOVA just described. For self-administration on the PR schedule, infusions per session on the last day of exposure to each different dose were compared using three-way mixed-measures ANOVA, with diet type and diet duration as between-subjects factors and dose as a repeated-measure. For extinction and reinstatement tests, presses on the active or inactive levers were analyzed using three-way mixed-measures ANOVA, with diet type and diet duration as between-subjects factors and session as a repeated measure (six extinction sessions and one reinstatement session). Follow-up tests were conducted using one-way repeated-measures ANOVAs with diet duration as the between-subjects factor and session as a repeated measure. For spatial memory tests, time spent in the target quadrant and proximity were analyzed using a two-way between-subjects

ANOVA (diet type and diet duration). Pathlength and liver/body ratios were not normally distributed and could not be corrected through transformations; therefore, three planned Mann–Whitney U tests were performed to analyze the effect of diet in each diet duration group. Plasma triglycerides were analyzed using two-way between-subjects ANOVA, with a natural log transformation first conducted on the data in order to normalize the distribution. A Chi-Square analysis was performed on the estrous cycle ratings to determine if the diet affected estrous cycle. P values less than 0.05 were considered statistically significant. Topscan Software (Cleversys, Inc., Reston, VA), Microsoft Excel Version 5.0, and/or Statistical Package for the Social Sciences (SPSS) Version 16.0 were used to conduct the analyses.

2.2. Experiment 2

In order to rule out the possibility that the amphetamine self-administration experience affected memory performance in the water maze task, Experiment 2 tested the effects of the high fructose diet on water maze learning and memory in a separate group of drug-naïve rats. Procedures were similar to Experiment 1: Five timed-pregnant dams were used. Female pups were fed the control diet ($n=16$) or the high fructose diet ($n=15$) from the start of weaning until water maze testing, which occurred at times matched to the middle diet duration used in Experiment 1 (Table 1), which is approximately 19 weeks on the diet. In contrast to Experiment 1, the rats in Experiment 2 did not receive drug reinforcement tests prior to water maze training. Body mass and food intake were recorded daily throughout the entire period of exposure to the experimental diets (i.e., from PND21 to the day of water maze testing). Estrous cycles were tracked in the same manner as conducted for Experiment 1, but were tracked several weeks before spatial memory testing began and continued throughout the duration of testing. Due to the observation of several unusually large spleens in Experiment 1, spleens were extracted from rats in Experiment 2 and weighed. Spatial memory measures of time spent in the target quadrant, pathlength, proximity, as well as liver and spleen mass were all analyzed using Independent Samples T-tests. Body mass and food intake were analyzed using mixed-measures ANOVA, with diet type as the between-subjects factor, and days as the repeated measure.

3. Results

3.1. Experiment 1

3.1.1. Body mass and food intake

Experimental diet affected body mass, such that rats fed a 60% fructose diet exhibited significantly lower body mass than controls, regardless of diet duration or day (Fig. 1A). Rats in the shorter diet durations weighed less than rats in the longer diet durations, and all rats gained mass during the course of the experiment. That is, the main effects of diet [$F(1, 48)=8.62$, $p<0.01$], diet duration [$F(2, 48)=18.94$, $p<0.001$], and days [$F(36,1728)=134.80$, $p<0.001$] were significant. A significant day by duration interaction [$F(72,1728)=5.89$, $p<0.001$] indicated that rats in the shorter diet durations gained mass at a faster rate than rats in the longer diet durations. Food intake during recess from amphetamine-related testing did not differ as a function of diet (Fig. 1B). In addition, food intake did not differ as a function of diet duration, nor did it interact significantly. Only a main effect of days was significant [$F(13,273)=5.75$, $p<0.001$], as food intake varied across days, but without reliable upward or downward trends over the 14 days of measurements.

3.1.2. Estrous cycle

The 60% fructose diet did not affect the estrous cycle [$\chi^2(3)=.801$, $p>.05$] (data not shown).

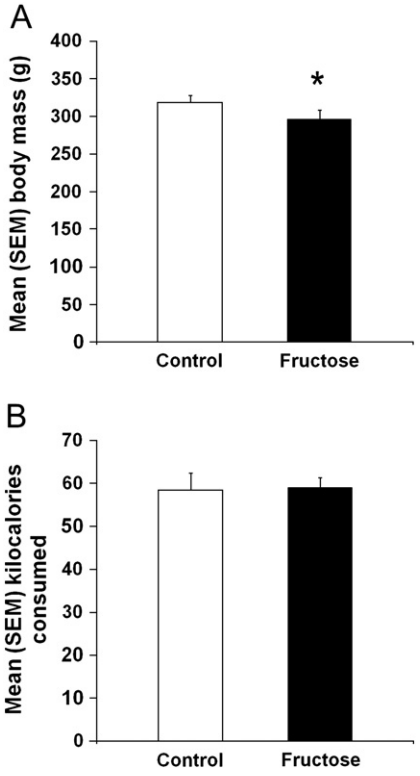

Fig. 1. The high fructose diet decreased the mean (±SEM) (A) body mass, but did not affect the mean (±SEM) (B) kilocalories consumed per day (collapsed across diet duration).

3.1.3. Amphetamine self-administration

3.1.3.1. FR testing. One rat failed the Brevital test for the catheter patency, and thus was not included in the self-administration experiments. The number of amphetamine infusions per session over the 10-day acquisition period on the FR1 schedule of reinforcement did not significantly differ as a function of diet or diet duration (Fig. 2A–C). Neither main effects of diet or diet duration, nor interactions involving those factors were significant. Only the main effect of days was significant [$F(9,504)=57.25$, $p<0.001$], due to increasing numbers of infusions over the acquisition period. No significant differences in total intake were observed (data not shown).

3.1.3.2. PR testing. The data from three rats that did not exhibit stable lever-pressing on the FR schedule, two rats that did not maintain lever-pressing from the FR to PR schedule, and three rats with catheter problems were not included in the PR analyses. The number of amphetamine infusions per session earned on a PR schedule of reinforcement did not significantly differ as a function of diet or diet duration, although the number of infusions earned was dose-dependent as expected (Table 2). Neither the main effect of diet, nor interactions involving diet were significant. The significant main effect of dose [$F(3,144)=166.50$, $p<0.001$] revealed the expected monotonic function of increasing infusions earned with increasing doses on a PR schedule of drug self-administration. Finally, a main effect of diet duration [$F(2,48)=4.59$, $p<0.05$] indicated that the number of infusions earned by rats in the short diet duration was greater than those in the middle and long durations, but only when factors of diet and dose were ignored.

3.1.3.3. Extinction and reinstatement testing. After 14 days of abstinence from amphetamine self-administration, no significant differences in the number of active lever-presses were observed across diet or diet

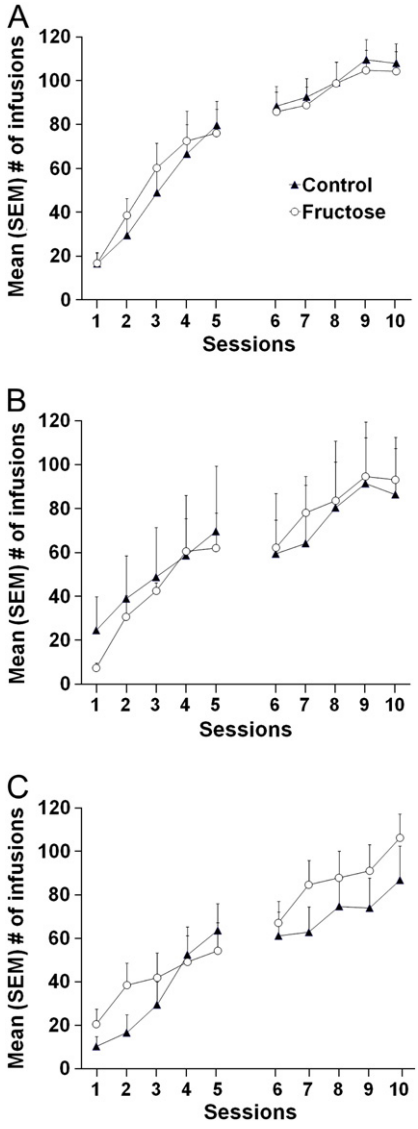

Fig. 2. The high fructose diet did not affect the mean (±SEM) number of amphetamine infusions earned during a fixed ratio schedule of reinforcement in the (A) short (47 days) diet duration, (B) middle (~88 days) diet duration, (C) long (144 days) diet.

duration groups in the extinction/reinstatement tests. The expected gradual decline in active lever-pressing occurred over the six extinction sessions followed by a robust increase in the single reinstatement session (Table 2). Neither main effects of diet or diet duration, nor most interactions involving those terms were significant. The main effect of sessions was significant [$F(6,282) = 78.28$, $p < 0.001$], as was the interaction between session and duration [$F(12,282) = 3.080$, $p < 0.001$]. Follow-up testing on the interaction did not reveal significant specific effects. With regard to the number of inactive lever-presses, no significant differences were observed across diet or diet duration groups, and levels of pressing remained low throughout the extinction and reinstatement sessions (data not shown).

3.1.4. Spatial memory testing

One rat died after the first day of water maze training from unknown causes. For this experiment, some of the earlier water maze behavior was videotaped and later digitized for analysis using the Topscan Software. There were some difficulties in tracking the rats' movements on some of these files. As a result, sample sizes differ slightly across the various measures. The results of this experiment indicated that there was no significant effect of the 60% fructose diet on any of the water maze memory measures in rats that had previously participated in the amphetamine self-administration test (Table 3). In addition, the effects of the diet did not interact significantly with duration on the diet. There was, however, a significant main effect of diet duration [$F(2, 44) = 3.999$, $p < .05$]. Post hoc tests with Tukey adjustment revealed that rats fed the diets for the short duration had significantly lower proximity score than rats fed the diets for the middle or long durations (both $p < .05$).

3.1.5. Postmortem measures

The plasma from one rat was lost due to technical error. For fasting triglycerides concentrations, the main effects of diet [$F(1, 55) = 9.934$, $p < .05$], and the interaction of the diet and diet duration [$F(2, 55) = 4.361$, $p < .05$] were significant (Table 4). Tukey post-hoc tests, however, showed no significant differences between any of the groups. The 60% fructose diet increased liver mass to body mass ratio in the shortest diet duration [$U = 7$, $p < .05$, $r = .77$] but not in the middle and longest diet durations (Fig. 3A–C).

3.2. Experiment 2

3.2.1. Body mass and food intake

As in Experiment 1, rats fed a 60% fructose diet in Experiment 2 had significantly lower body mass than controls (Fig. 4A). Both diet groups gained mass at the same rate. Thus, there was a main effect of diet [$F(1, 29) = 5.69$, $p < .05$], but the interaction between day and diet was not significant. Food intake did not significantly differ as a function of diet (Fig. 4B).

3.2.2. Estrous cycle

The 60% fructose diet did not affect the estrous cycle [$\chi^2(1) = .278$, $p > .05$] (data not shown).

3.2.3. Spatial memory testing

The 60% fructose diet did not significantly affect any of the measures of memory (Table 3).

Table 2
Amphetamine self-adminstration. Mean (±SEM) number of infusions earned on the last of three days with each dose on the progressive ratio (PR) schedule. Sum of active lever presses made during the six 1-h extinction sessions, and mean (±SEM) number of active lever presses made during the single 1-h reinstatement session.

Experiment 1: amphetamine self-administration						
Diet duration	47 days		~88 days		144 days	
Progressive ratio	Control (n = 11)	Fructose (n = 13)	Control (n = 9)	Fructose (n = 3)	Control (n = 10)	Fructose (n = 8)
saline (0 mg/kg/infusion)	6.9 ± 0.6	6.4 ± 0.6	7.9 ± 0.9	7.4 ± 1.5	7.5 ± 0.5	7.38 ± 0.8
0.01 (mg/kg/infusion)	7.9 ± 0.8	8.5 ± 0.7	9 ± 0.8	8.3 ± 1.6	11.2 ± 1.4	10.9 ± 1.5
0.025 (mg/kg/infusion)	10.6 ± 1	12.6 ± 0.8	12.6 ± 1.6	14 ± 4.5	16.5 ± 1.6	13.9 ± 1.5
0.1 (mg/kg/infusion)	20.5 ± 1	20.7 ± 1.4	21.9 ± 2.1	22 ± 3.4	21.9 ± 1.2	23.5 ± 1.4
Extinction	197.8	134.8	121.2	126.3	125.8	153.8
Reinstatement	92.8 ± 8.1	93.7 ± 18.6	133.7 ± 26.5	177.3 ± 52.9	117.9 ± 25.3	102.9 ± 14.3

Table 3
Memory retention measures for the spatial water maze. Sample sizes differ due to difficulties in analyzing behavior previously recorded on videotapes. The high fructose diet did not affect mean (±SEM) time spent swimming in the target quadrant, mean (±SEM) pathlength, or mean (±SEM) proximity to the target in the spatial water maze.

	Experiment 1						Experiment 2 (drug-naïve)	
Diet duration	13–16 weeks		19 weeks		27 weeks		~19 weeks	
Diet	Control	Fructose	Control	Fructose	Control	Fructose	Control (n=16)	Fructose (n=15)
Time spent in target quadrant	3.8±.6 (n=8)	3.8±.5 (n=10)	2±.5 (n=8)	3.5±1.4 (n=4)	3.1±.6 (n=11)	2.7±.5 (n=12)	2.9±.5	3.9±.4
Pathlength	48.4±16 (n=9)	102±31 (n=9)	163.4±33 (n=7)	175.9±27.9 (n=4)	122.6±35.5 (n=10)	154.8±45.4 (n=9)	179.8±21.2	213.9±30.3
Proximity	41.2±3.7 (n=10)	46.2±1.8 (n=12)	61.1±5.6 (n=8)	48.2±6 (n=4)	52.2±4.9 (n=9)	56.9±7.2 (n=7)	56.1±5.3	47.3±2.3

3.2.4. Postmortem measures

The plasma triglyceride data from one control rat was excluded from the analysis because the triglyceride concentration for this rat was repeatedly too dilute to fit within the standard curve. The 60% fructose diet did not affect fasting plasma triglyceride concentrations (Table 4). Fructose-fed rats had significantly increased liver mass to body mass ratio [$t(29) = -9.576$, $p<.001$] (Fig. 5A) and spleen mass to body mass ratio [$t(27) = -3.298$, $p<.01$] (Fig. 5B).

4. Discussion

In the present study, feeding a 60% fructose diet to female rats decreased body mass, increased both liver and spleen mass, but did not affect plasma triglyceride concentrations consistently. The high fructose diet also failed to impair several types of behavioral plasticity in the female subjects. Specifically, consuming this diet for up to 20 weeks did not affect rates of acquisition of amphetamine self-administration, the number of infusions earned on either a FR or PR schedule of reinforcement, nor the number of active lever presses during extinction/reinstatement sessions. The high fructose diet also failed to affect hippocampal-dependent spatial memory as assessed by the time spent in the target quadrant of the water maze, the pathlength taken to the target, or how close the rat swam to the target overall during the retention test (i.e., proximity). The lack of fructose-induced memory impairment in the water maze was not due to previous amphetamine exposure, because rats in Experiment 2 were amphetamine-naïve and still showed no deficits in water maze performance.

These findings do not support our hypothesis that the memory-impairing effects of a high fructose diet extend from male (Ross et al., 2009) to female rats. These findings are consistent with preliminary data from our lab suggesting that a high fat/high sucrose diet does not impair water maze memory in female rats as it does in male rats (Darling et al., unpublished). Further, another study has reported that a high fat diet impairs learning of passive avoidance and contextual fear conditioning tasks in male but not female mice (Hwang et al., 2010).

As we expected, the elevation in plasma triglyceride concentrations produced by a high fructose diet was not as robust in the present study involving female rats as previously reported for male rats (Galipeau et al., 2002; Ross et al., 2008; Ross et al., 2009). Although main effects of diet on plasma triglyceride concentrations were

Table 4
The high fructose diet did not affect plasma triglyceride concentrations.

Plasma triglyceride concentrations (mg/ml)		
	Control	Fructose
Experiment 1		
13–16 weeks	0.368±.09 (n=12)	0.992±.12 (n=14)
19 weeks	0.42±.11 (n=9)	0.63±.22 (n=4)
27 weeks	0.497±.11 (n=10)	0.822±.19 (n=12)
Experiment 2		
~19 weeks	0.79±.18 (n=15)	0.71±.17 (n=15)

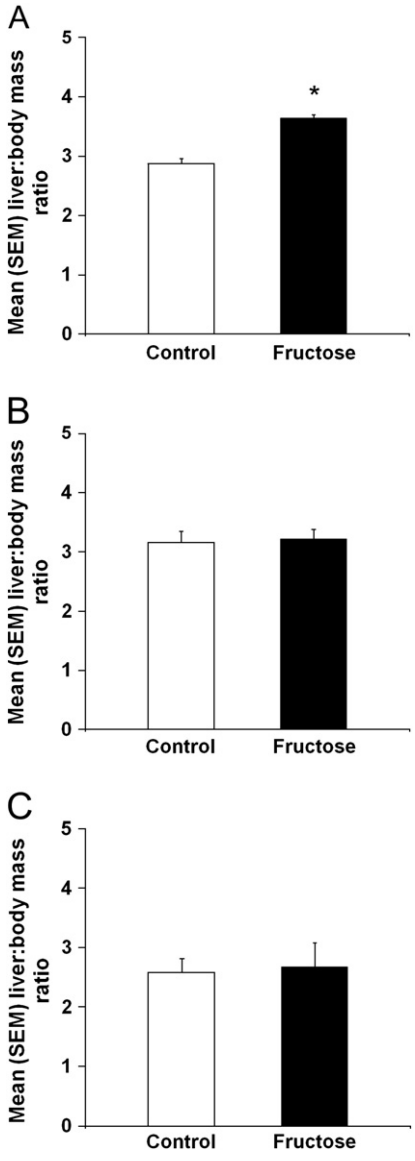

Fig. 3. The high fructose diet significantly increased the mean (± SEM) liver mass (relative to body mass) for rats in the (A) short diet duration group, but not for rats in the (B) middle, or (C) long diet duration groups.

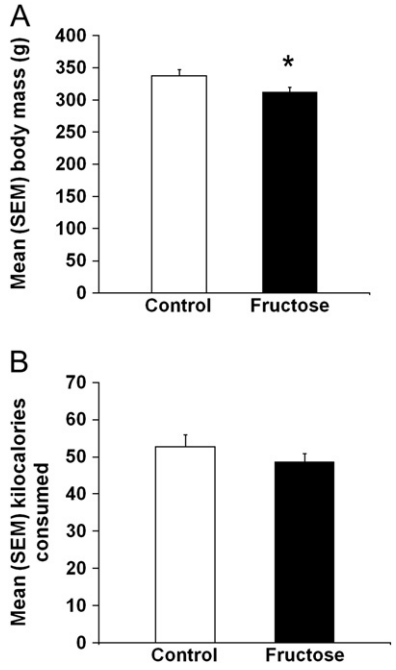

Fig. 4. The high fructose diet significantly decreased the mean (± SEM) (A) body mass but did not affect the mean (±SEM) (B) kilocalories consumed per day in drug-naïve rats.

statistically significant (as was the interaction between diet and diet duration), these increases were not robust enough to be confirmed in post-hoc tests on individual groups, perhaps due to varying sample sizes. The present finding is consistent with previous research showing that fructose-induced increases in plasma triglyceride concentrations are smaller in female rats and female humans than in male rats and male humans (Galipeau et al., 2002; Couchepin et al., 2008). It is possible that estrogen blunts the effect of fructose on triglyceride concentrations in females. Indeed, estrogen increases the rate of fatty acid oxidation in the liver (Paquette et al., 2009), and in female mice fed a high fat diet, estrogen reduces hepatic triglyceride content (Bryzgalova et al., 2008). Given that a high fructose diet increases hepatic de novo lipogenesis and releases these triglycerides into the blood (Zavaroni et al., 1982), estrogen could attenuate these fructose-induced increases in plasma triglycerides. Although we did not do so in the present study, it would be important to test the effects of a high fructose diet on ovariectomized rats in order to consider interactions of diet and estrogen on metabolism.

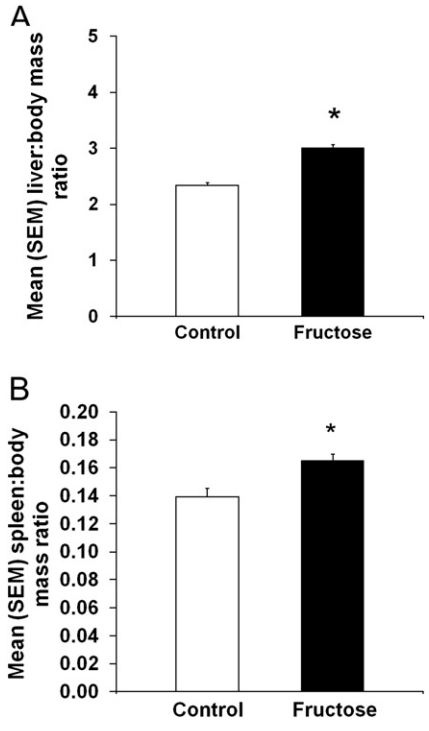

Fig. 5. The high fructose diet increased mean (±SEM) (A) liver mass and (B) spleen mass, (relative to body mass) in drug-naïve rats.

In the present study, several of the physiological effects of the high fructose diet are congruent with previous research. For instance, the present findings showed that the high fructose diet did not affect estrous cycling significantly, which agrees with previous findings (Light et al., 2009). Also consistent with previous findings is the present finding that a high fructose diet increased liver mass relative to body mass (Bruckdorfer et al., 1972; Michaelis and Szepesi, 1973; Bergstra et al., 1993; Ross et al., 2009). Finally, the present data mirror previous findings that female rats fed a high fat diet for 3 months (Altunkaynak et al., 2007), as well as magnesium-deficient male rats fed a high sucrose diet for 2 weeks (Busserolles et al., 2003), have increased spleen mass. In contrast to female rats, we have previously found that a 16-week high fructose diet does not significantly increase spleen mass in male rats (Ross et al., unpublished).

Several possible explanations should be considered when interpreting the finding that a high fructose diet increased spleen mass. First, splenomegaly often indicates an increased immune response or an inflammatory condition (Eichner, 1979). A high fructose diet does increase certain inflammatory markers, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the blood (Qin et al., 2010), and fructose in drinking water produces aortic and vascular inflammation in rats (Tan et al., 2008). Although elevated levels of inflammatory molecules (i.e., TNF-α) are not a consistent effect of a high fructose diet (Abdullah et al., 2009), inflammation of the liver is a reliable effect of a high fructose diet (Kelley et al., 2004; Abdullah et al., 2009; Kawasaki et al., 2009). Given that the liver mass of the present female rats was significantly increased, hepatic inflammation may have been present. Thus, liver inflammation could have produced a heightened immune response and subsequent increase in spleen mass. An alternative possibility is that the high fructose diet did not enlarge the spleen and liver, but rather that the organs appear larger because of the decrease in body mass. That is, it is possible that the diet affected muscle, fat and bone without affecting organs. It is more likely that the organs are enlarged, however, because we found previously that a high fructose diet increased liver mass in male rats without affecting their body mass (Ross et al., 2009). Moreover, the livers from rats in Experiment 1 and Experiment 2 of the present study are still significantly larger than control livers, even when not corrected for body mass ($p<.01$). Similarly, when spleen mass is not corrected for body mass in Experiment 2, there still is a tendency for the spleens to be enlarged ($p=0.09$).

The present finding that a high fructose diet decreased body mass was unexpected, because many studies do not find fructose-induced changes in body mass in male (Abdullah et al., 2009; Qin et al., 2009; Ross et al., 2009) or female (Galipeau et al., 2002; Lee et al., 2008) rats. The fructose-induced decrease in body mass in the present study could not be attributed to reduced food intake, because the amount of kilocalories consumed did not differ between the groups. The decrease in body mass also is not related to amphetamine intake, because a fructose-induced decrease in body mass also was observed in the amphetamine-naïve rats in Experiment 2. Thus, it remains unclear why fructose consumption led to a decrease in body mass in the present study. Previous research has shown that fructose-fed male rats treated with estrogen have reduced body mass (Vasudevan et al., 2005), suggesting that estrogen may alter the metabolic effects of

fructose. Future studies may test the role of estrogen in the metabolic consequences of a high fructose diet by using ovariectomized rats.

Several explanations should be considered for the present finding that a high fructose diet did not impair amphetamine self-administration or spatial water maze performance. One possibility is that estrogen may protect against the deleterious effects of the diet on plasticity. This interpretation is consistent with previous data showing that estrogen treatment reverses working memory deficits produced by streptozotocin-induced diabetes in male rats (Lannert et al., 1998), and that replacing estrogen in ovariectomized female mice improves performance in the spatial water maze (Rissanen et al., 1999). Estrogen has specific protective actions in the hippocampus. For example, lateral ventricle infusions of β-estradiol prevent neuronal loss in the CA1 region after transient forebrain ischemia in male gerbils (Sudo et al., 1997). In addition, estrogen replacement in ovariectomized female rats prevents reductions in hippocampal BDNF mRNA (Singh et al., 1995). Thus, estrogen appears to be neuroprotective in non-human animals, and may even enhance memory in humans, as well (Henderson, 2009).

A second possible reason why the high fructose diet did not impair learning and memory in the present experiments could be that it did not sufficiently elevate plasma triglyceride concentrations. In mice, injecting triglycerides directly into the brain impairs memory on a foot shock avoidance task (Farr et al., 2008), and lowering triglyceride levels with gemfibrozil in obese mice improves learning and memory in the water maze (Farr et al., 2008). A similar effect of gemfibrozil is observed in elderly humans with cerebrovascular disease (Rogers et al., 1989). In our previous study with male rats, the 60% fructose diet increased plasma triglyceride concentrations by approximately 100% and these increases correlated positively with memory deficits (Ross et al., 2009). In contrast, the same fructose concentration in the present study produced highly variable effects on plasma triglyceride concentrations in the female rats. In Experiment 1, the high fructose diet increased plasma triglyceride concentrations by 11–57% for the two longer diet durations and did not increase triglycerides at all in Experiment 2. The fructose diet did, however, increase plasma triglycerides by ~175% in the rats fed the diet for the shortest duration in Experiment 1, which should have impaired memory if fructose diets impair memory via elevated plasma triglyceride concentrations.

It is possible that group-housing or time of day prevented any impairing effects of the fructose diet on plasticity in the present study. In the current study, the female rats were group-housed. In a previous study from our lab, in which the diet impaired memory, the male rats were single-housed (Ross et al., 2009). Social isolation can have a profound effect on brain function (Hall et al., 1998). For example, although exercise normally increases neurogenesis, exercise reduces neurogenesis in single-housed rats (Stranahan et al., 2006). Therefore, it is possible that the social interaction the female rats received in our study as a result of being group-housed had a protective effect on memory. Another methodological difference between the present study and our previous studies involving male rats is that all of the behavioral tests in the present study were conducted in the dark phase of the light cycle. In our previous study in which a high fructose diet impaired memory, the behavioral tests were conducted in the light phase. Although rats are known to be nocturnal, and thus are more alert and awake during the dark phase, the majority of memory studies in rats have been conducted in the light phase (Boukouvalas et al., 2008; Alzoubi et al., 2009; White et al., 2009).

An interesting finding is that in addition to not *impairing* plasticity, the high fructose diet did not *enhance* plasticity in the amphetamine self-administration. This is a novel finding, because one study has found that a high sucrose diet cross-sensitizes female rats to the reinforcing effects of amphetamine (Avena and Hoebel, 2003). Our study differed from this study in a number of ways. First, our study used fructose-fed, as opposed to sucrose-fed, rats. Sucrose is comprised of one fructose and one glucose molecule, and thus may exert different physiological and behavioral effects compared with fructose alone. Second, we provided the high fructose diet ad libitum, rather than intermittently or in a choice paradigm. Given that ad libitum access to a high sucrose diet did not affect cocaine self-administration in another study (Vendruscolo et al., 2010), it is the manner of consumption, rather than the type of sugar, that is more likely to determine the effects of a high sugar diet on drug reinforcement. Indeed, intermittent access to sucrose is associated with excessive intake of the sugar ("binging"), and increases binding of dopamine (D1) receptors in the nucleus accumbens (Rada et al., 2005), a brain area believed to play an integral role in the reinforcing effects of drugs. Given that there were no increases in food intake between the diet groups in the present study, we can infer that the rats in our study most likely did not binge on fructose, and most likely did not have changes in D1 receptors in the nucleus accumbens. Future experiments should test intermittent access to fructose in order to compare directly with the previous findings with sucrose.

It is curious to note that in the present study, the youngest rats (i.e., those in the short diet duration group), regardless of which diet they were fed, earned more infusions on the PR schedule of reinforcement and had lower proximity scores in the water maze task than older rats. These findings suggest that younger rats are more sensitive to the reinforcing effects of amphetamine (or that amphetamine has a higher efficacy as a reinforcer) and that younger rats may remember the location of the spatial water maze target better than older rats.

In conclusion, the present study suggests that female rats may be insensitive to the deleterious effects of a high fructose diet. Fructose feeding did not impair behavioral plasticity in either the amphetamine self-administration task or the spatial water maze. Although there are methodological differences with previous studies employing males, the present findings suggest that there may be a protective mechanism among females or that the cognitive impairments from the diet do not extend to all types of learning tasks. Whether a high fructose diet impairs such non-hippocampal-dependent forms of plasticity in male rats remains unknown. Future studies should explore the potential protective effects of estrogen against fructose-related impairment of brain plasticity, as well as the effects of a high fructose diet on amphetamine self-administration in male subjects.

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