Running head: BATTLE OF THE MACRONUTRIENTS

A Look into High Fat and High Fructose Diets and their Impact on Physiology and Spatial

Memory.

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Presented to the Department of Biology

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**ABSTRACT**

High fructose corn syrup (HFCS) and saturated fats are two of the main ingredients in the Western-style diet that have been implicated in the etiology of Type 2 diabetes mellitus (T2DM), which is associated with obesity and insulin resistance (1). However, most studies have looked into the effect of the Western style diet as a whole, which involves both high fat and high fructose together. To date, the two have yet to be compared side-by-side in a single research initiative. Therefore, the purpose of the current study is to explore the individual effects that result from a high fructose diet or a high fat diet.

Rats were fed a chow diet of a solid 60% fat, solid 55% fructose diet or a chow diet for 10 weeks. The rats were sacrificed and trunk blood, livers and fat pads were collected. Final serum insulin and triglyceride levels were measured using trunk blood assays.

Animals maintained on the high fat diet weighed significantly more by the end of the study (429.48g ±7.92), had higher percent body weight change (38.16%±0.583), higher body fat composition (3.16%±0.176) and had significantly higher fat pad weight (13.67g±0.902) than the high fructose fed group and the control group. However, the high fructose group had higher serum insulin levels (12.99ulU/mL±7.22) and higher serum total (2.39mg/mL±0.477) and true (0.754mg/mL±0.372) triglyceride levels than any group and exhibited significant cognitive impairments in the reverse Morris Water Maze task.

These data suggest that fat accumulation and weight gain are more influenced by the high fat component of the Western-style diet. However, insulin resistance and elevated

triglycerides in the blood are impacted more by high levels of fructose in the diet. Comparative

data between a high fat and a high fructose diet in a single study are novel and shed light on

the effects two of the individual components of a Western-style diet.

**INTRODUCTION**

In 1997 obesity was declared as "one of the greatest neglected public health problems of our time…" (19, 18). Although this statement was made 17 years ago, the rate of obesity in Western society has continued to rise. Indeed, approximately 35% of the adult population in the United States is considered obese with the worldwide percentage coming in at around 11% (1, 20). In the U.S. alone obesity related medical expenses are estimated to cost $147 billion per year with the personal medical expenses for an obese individual costing $1,429 more than those of a normal weight person (1). Of the many medical conditions associated with obesity, three of the most serious are metabolic syndrome, insulin insensitivity and type-2 diabetes mellitus (T2DM) (2). Although it is difficult to pin the cause for this rise in obesity and metabolic syndrome on a single factor, increased consumption of the Western-style diet is hypothesized to play an important role (25).

A Western style diet is characterized as a high intake of energy-dense foods that are created or altered by processing (17). High fructose corn syrup (HFCS) and saturated fats are two prime ingredients in this diet (21). In previous animal studies these calorie-dense ingredients exceed metabolic needs and consequently induce weight gain from increased body fat, higher circulating triglyceride levels and insulin insensitivity (4, 5). Therefore, human intake of the Western-style diet has been implicated in the etiology of insulin insensitivity, associated with T2DM and obesity (3).

Insulin insensitivity has recently been implicated in the development of cognitive impairments as well. Interestingly, it has been suggested that cognitive impairments observed in some overweight, insulin insensitive patients could develop along the same path as diabetic neuropathy, which is a loss of feeling in extremities caused by neuronal cell damage from hyperglycemia (22). Although there has yet to be definitive data to support this claim, there are several animal studies to indicate a connection between insulin insensitivity and decreased cognitive function. In 2011, McNay *et al.* found that peripheral insulin resistance induced by a high-calorie diet supplemented with a liquid solution of fructose appeared to be accompanied by central insulin resistance. This diet was proposed to have negative effects on the learning and memory function of the hippocampus by elevating triglyceride levels (15). Additionally, Molteni *et al.* found a high-fat diet supplemented with liquid sucrose induced insulin resistance that was implicated in neurodegeneration by decreasing brain derived neurotrophic factor (BDNF) levels (16). However, most behavioral studies have looked into the effect of a single diet which involves both high fat and high fructose combined. Therefore, it is pertinent to explore the singular effects of the Western-style diet components on insulin insensitivity and cognitive function.

Elucidating the separate effects of the two macronutrients also becomes increasingly important when considering the different ways fructose and fat are metabolized in the body. In contrast to glucose, which is taken up by cells through the insulin dependent GLUT4 transporter, fructose enters cells via an insulin independent GLUT5 transporter located in the

liver. A product of fructose metabolism is triglycerides and since GLUT5 is not regulated by

insulin, fructose intake provides for an unregulated source of triglycerides in the blood stream

and liver. This contributes to increased lipogenesis especially in the liver, which is implicated in

the development of non-alcoholic fatty liver disease (6, 11, 27). Excess fat consumption,

however, impacts insulin signaling by increasing inflammatory adipokines, which inhibit key

glycolytic enzymes. The resulting reduction in ATP production promotes further energy intake

and gluconeogenesis (10, 23). Therefore, metabolic differences may produce varied

physiological and behavioral outcomes that are obscured in studies using a single combined

Western-style diet.

Furthermore, in previous studies, sweetener has been administered as a liquid

supplement (12). Although this is a reasonable research model due to the fact that humans

consume fructose primarily in sodas, juice and sports drinks, fructose also makes an

appearance in many popular solid foods such as bread, peanut butter and many baby foods (24,

25). Additionally, rats are not able to regulate liquid calories as well as they can regulate the

solid calories they consume. As a result, fructose administered in liquid form may be consumed

in higher quantities than the accompanying solid diet (14). Thus, in order to create a meaningful

comparison between the two macronutrients, they must be administered through the same

consumption medium: solid food.

Therefore, the purpose of the current study is to explore the physiological and

behavioral effects that result from a solid high fructose diet or a solid high fat diet.

Interestingly, animals fed a high fat diet developed visceral adiposity after nine weeks on the diet, independent of metabolic and behavioral effects. Whereas the high fructose fed animals did not gain significant body weight, but they showed increased serum insulin and triglyceride levels in addition to impairments in cognitive flexibility. Our results are suggestive of different mechanisms of action between the two macronutrients both on physiology and behavior

**METHODS**

**Animals**

Thirty-two male, experimentally naïve, Sprague-Dawley rats (Harlan Laboratories, Inc., MD) approximately 6 weeks of age were used. Animals were individually housed in clear plastic shoebox cages (369 x 156 x 132mm) in a temperature and humidity controlled room (21°C) maintained on a 12:12 light cycle (lights on: 0800-2000).

All experimental procedures were performed with the approval of the Washington and Lee University Animal Care and Use Committee.

**Dietary Conditions**

The rats were weighed 1 day after arrival and then 4 days later. During the acclimation period, animals were maintained on *ad lib* Harlan-Teklad Rat Chow (Harlan Laboratories, Inc., MD) and water.  The difference between the 2$^{nd}$ day weight and the 4$^{th}$ day weight was calculated and then the animals were assigned diet groups so that the high and low weight gainers were evenly distributed among the three groups: High Fat (HF) n=11, High Fructose

(HFru) n=11 and Control (C) n=10. The HF group was provided with *ad lib* water and high-fat

chow (60% kcal/g of fat, 20% kcal/g of carbohydrate from corn starch; Product #: D08060104,

Research Diets, Inc., New Brunswick, NJ). The HFru group was allowed *ad lib* water and high-

fructose chow (55% kcal/g of fructose, 10% kcal/g of fat; Product #: D05111802, Research Diets,

Inc., New Brunswick, NJ). The control group was maintained on the original *ad lib* chow diet

(5.8% kcal of fat, 44.3% kcal of carbohydrate; Harlan Laboratories, Inc., MD) and water. Fresh

diet, chow and water were provided as needed throughout the study. Food was weighed for

each rat for four days during the 7th week of diet exposure to measure food intake per group.

**6-week Fasting Blood Glucose and Insulin Sensitivity**

Fasting blood glucose levels were measured 6 weeks after animals had been given

access to the experimental diets. After an overnight fast, blood samples were collected by a tail

vein snip. Blood glucose was determined by using an AccuCheck Compact Plus blood glucose

meter. Blood was collected in heparnized capillary tubes, spun and plasma was collected on the

same day.  Then the samples were frozen at 4°C. tested for plasma insulin with an insulin ELISA

(Crystal Chem, Inc., Downers Grove, IL). The data were analyzed for insulin sensitivity using the

HOMA-IR[1] and QUICKI[2] index.

**Morris Water Maze**

The Morris Water Maze (MWM) was used to access spatial learning and memory. A

circular, black high-density polyethylene pool (Lerio 2005, diameter: 62.5in, depth: 17.5in) was

filled with water to a depth of 37 cm and rendered opaque by orange-brown latex paint. The

water was maintained at a temperature of 23°C ± 2°C. The pool was divided into four, equal

quadrants: north (N), south (S), east (E), west (W). A video camera (Logitech, Newark, CA) was

centered above the pool to record every training and probe trial. A circular escape platform was

placed in the north-west quadrant. The escape platform was submerged 2 cm beneath the

surface of the water so that it was hidden from the animals' view. The platform remained in the

same position for all training trials. Visual cues were kept constant in the room for the duration

of testing and placed so that each quadrant had a unique visual cue.

Eight weeks after the diets began, rats were tested in the preliminary MWM. There were 4

training trials each day for 4 days. For each training trial the animal was gently placed in the

water at the edge of the pool with its head facing the wall. Animals were given 60 seconds to

reach the platform. Once the platform was reached the rat was allowed to remain on the

platform for 15 seconds. If the rat did not find the platform in 60 seconds it was guided to the

platform and then allowed to remain on the platform for 15 seconds. After each trial, animals

were removed from the pool and placed into a holding cage for 60 seconds. Once the animal

had completed testing for the day, it was towel dried and returned to its home cage. Start

quadrant positions were changed for each of the four training trials and the sequence of start

quadrant positions was changed daily. Latency to reach the platform was recorded on paper for

each training trial for all four days of training.

After 4 days of training trials, a probe trial was run 24 hours after the final training trial

assess long-term memory for the task. The platforms were removed from both pools, but the

visual cues in each room remained the same. Each animal was released in a start quadrant position directly diagonal from platform position (middle of SE quadrant) and allowed to swim for 60 seconds. Once 60 seconds elapsed, the rat was removed from the pool, towel dried and returned to their home cage. Number of times entering the correct quadrant and number of platform position crosseswere counted for each rat in the probe trials.

Upon completion of the preliminary MWM, a reverse MWM task was performed to assess cognitive flexibility in our animals. The platform was situated directly diagonal to the original platform position (south-east quadrant). Four days of reversal training trials and a probe trial on the 5$^{th}$ day followed the same protocol as previously outlined.

After completion of the reversal probe a marked platform test was performed to assess visual acuity. The water in the pool was lowered so that the top of the platform was visible to the rats and a red flag was affixed to the platform to increase visibility. Each rat performed the visual acuity test four times, each time the platform was placed in a different quadrant. The visual acuity test was recorded on video, and time to reach the platform was recorded on paper.

Both probe trial video recordings were coded for total distance, distance in target quadrant, time in target quadrant, target quadrant entries and annulus crossings using the Manual Tracking plugin for ImageJ (US National Institutes of Health, Bethesda, MD, USA).

**Tissue Collection**

After 9 weeks of dietary exposure, the animals were fasted 4-6 hours and animals were deeply anesthetized with isoflurane and rapidly decapitated. Trunk blood was immediately collected, allowed to clot overnight then spun down to separate the serum, which was stored at 4°C. Final blood glucose was measured with trunk blood using an AccuCheck Compact Plus blood glucose meter. Brains were rapidly removed on ice and punches were taken from the hypothalamus, cerebellum and both sides of the hippocampus. Tissue samples were flash frozen with liquid nitrogen and stored at -80°C. Whole livers and abdominal and gonadal fat pads were removed and weighed then two samples were cut out and frozen immediately after removal with liquid nitrogen then placed on dry ice before storage at -80°C.

**Postmortum Measures**

Final serum insulin sensitivity was determined by an insulin ELISA assay and data were analyzed for insulin resistance and sensitivity using the HOMA-IR[1] and QUICKI[2]. (Crystal Chem, Inc., Downers Grove, IL). Serum triglycerides were determined using a triglyceride quantification assay (Sigma-Aldrich, St. Louis, MO) and serum TNF-a and IL-6 were measured using an ELISA assay (Invitrogen, Camarillo, CA). Liver lipid extractions were performed by the Folch method (9).

1)

$$\text{HOMA-IR} = \frac{\text{(fasting insulin) x (fasting glucose)}}{2430}$$

2)

$$\text{QUICKI} = \frac{1}{\log(\text{fasting insulin}) + \log(\text{fasting glucose})}$$

**Data Analysis**

Univariate ANOVAs with a Tukey Post-Hoc analysis were performed using Statistical

Package for the Social Sciences Version for Windows (SPSS Inc, Chicago, IL). Student's t-tests

were performed using Microsoft Excel (Microsoft Corporation, WA). Significance was accepted

at $p<0.05$ and all data were reported as mean ± SEM unless otherwise indicated.

**RESULTS**

**Physiologic Data**

*Body Weight, Adiposity and Calorie Intake*

After ten weeks on the diet, high fat animals had significantly higher body weight than the high

fructose and control fed groups (F=8.62, p<0.001). The high fat fed animals also had a

significantly higher percent body weight change (F=5.84, p<0.008). Additionally, fat pads were

collected at sacrifice and the high fat fed animals had larger fat pads (F=7.06, p<0.000) than the

other two groups, but when normalized to fat pad weight per 100g of body weight the high fat

and high fructose animals were both significantly higher than the control animals (F=5.26,

p<0.05; seeTable 1).

The control group and high fat group consumed significantly more food (F=3.83, p<0.033) than

the high fructose group. Despite this similarity in food consumption, the high fat group

consumed significantly more kilo-calories than either group (F=11.96, p<0.000; see Table 1).

*Liver Data*

Whole livers were weighed at sacrifice before two samples were removed and frozen. There

was no significant difference in whole liver weight among the three groups (Table 1).

Additionally, there was no significant difference in liver lipids after extraction by the Folch

method (Table 1).

*Fasting Blood Glucose, Serum Insulin, Triglycerides and Cytokines*

Trunk blood was used to assess the HOMA-IR index and QUICKI index, however there was no

significant difference among the groups. There was no significant difference among the groups

for fasting blood glucose (Table 2). HOMA-IR (HF: 0.3261±0.062, HFru: 0.6632±0.202, C:

0.4524±0.111) or QUICKI (HF: 0.3801±0.025, HFru: 0.35±0.026, C: 0.35±0.020).

Fasting serum insulin and triglycerides were also determined using trunk blood samples. The

high fructose group had significantly higher serum insulin (F=3.90, p<0.032) and significantly

higher serum triglyceride levels (F=13.68, p<0.000; see Table 2). However, there was no

significant difference among the groups for either inflammatory cytokine TNF-α or IL-6 (Table 2).

**Behavioral Data**

*Preliminary Morris Water Maze Probe*

There was no significant difference in total distance (HF: 777.6±25.40 cm, HFru: 706.3±32.24 cm; see Figure 1a), distance in target quadrant (HF: 199.8±22.63 cm, HFru: 162.7±21.00 cm; see Figure 1b), time in target quadrant (HF: 12.95±1.41 s, HFru: 16.74±3.78 s; see Figure 1c), target quadrant entries (HF: 5.36±0.432, HFru: 4.5±0.279; see Figure 1d) or annulus crossings in the preliminary MWM probe trial (HF: 1.77±0.537, HFru: 0.9±0.233; see Figure 1e).

*Reverse Morris Water Maze Probe*

Animals fed the high fructose diet covered significantly less total distance (t=0.03, p<0.05; see Figure 2a) and entered the target quadrant (t=0.02, p<0.05; see Figure 2d) significantly less in the reverse MWM probe. No significance was observed between the high fat and high fructose groups for distance in target quadrant (HF: 173.7±22.62 cm, HFru: 134±18.90 cm; see Figure 2b), time in target quadrant (HF: 19.0±4.18 s, HFru: 11.52±2.26 s; see Figure 2c) or annulus crossings (HF: 1.64±0.364, HFru: 1.14±0.270; see Figure 2e).

**TABLE 1.** Body weights, fat pad weights, food intake, kcal consumption, liver weight and liver lipids

|  | High Fat | High Fructose | Control |
|---|---|---|---|
| Final Body Weight (g) | 429.48 ± 7.92[a] | 381.42 ± 11.0[b] | 385.26 ± 8.10[b] |
| Fat Pad Weight/100g BW | 2.71 ± 0.172[a] | 2.77 ± 0.252[a] | 1.97 ± 0.108[b] |
| Food Intake (g) | 23.52 ± 1.92[a] | 20.67 ± 1.33[b] | 26.82 ± 1.28[a] |
| kcal Consumed (kcal) | 123.22 ± 10.1[a] | 79.59 ± 5.13[b] | 83.14 ± 3.97[b] |
| Liver Weight (g) | 13.06 ± 0.471 | 14.38 ± 0.566 | 12.81 ± 0.373 |
| Liver Lipids (%) | 33.08 ± 5.37 | 19.78 ± 1.65 | 22.26 ± 3.81 |

Data are presented as mean ± SEM. Differeing superscript letters indicate differences between dietary conditions $P<0.05$.

**TABLE 2.** Cytokine, fasting serum insulin, fasting blood glucose and true serum triglycerides

|  | High Fat | High Fructose | Control |
|---|---|---|---|
| IL-6 (pg/mL) | 190.4 ± 44.2 | 199.9 ± 55.9 | 258.6 ± 90.7 |
| TNF-α (pg/mL) | 19.42 ± 2.02 | 21.42 ± 2.20 | 20.66 ± 4.01 |
| Insulin (ulU/mL) | 6.33 ± 1.18[b] | 12.99 ± 2.28[a] | 8.22 ± 1.68[b] |
| Glucose (mmol/L) | 122.5 ± 3.16 | 103.2 ± 14.91 | 127.4 ± 9.62 |
| Triglycerides (mg/mL) | 0.275 ± 0.032[b] | 0.754 ± 0.118[a] | 0.294 ± 0.036[b] |

Data are presented as mean ± SEM. Differeing superscript letters indicate differences between dietary conditions $P<0.05$.
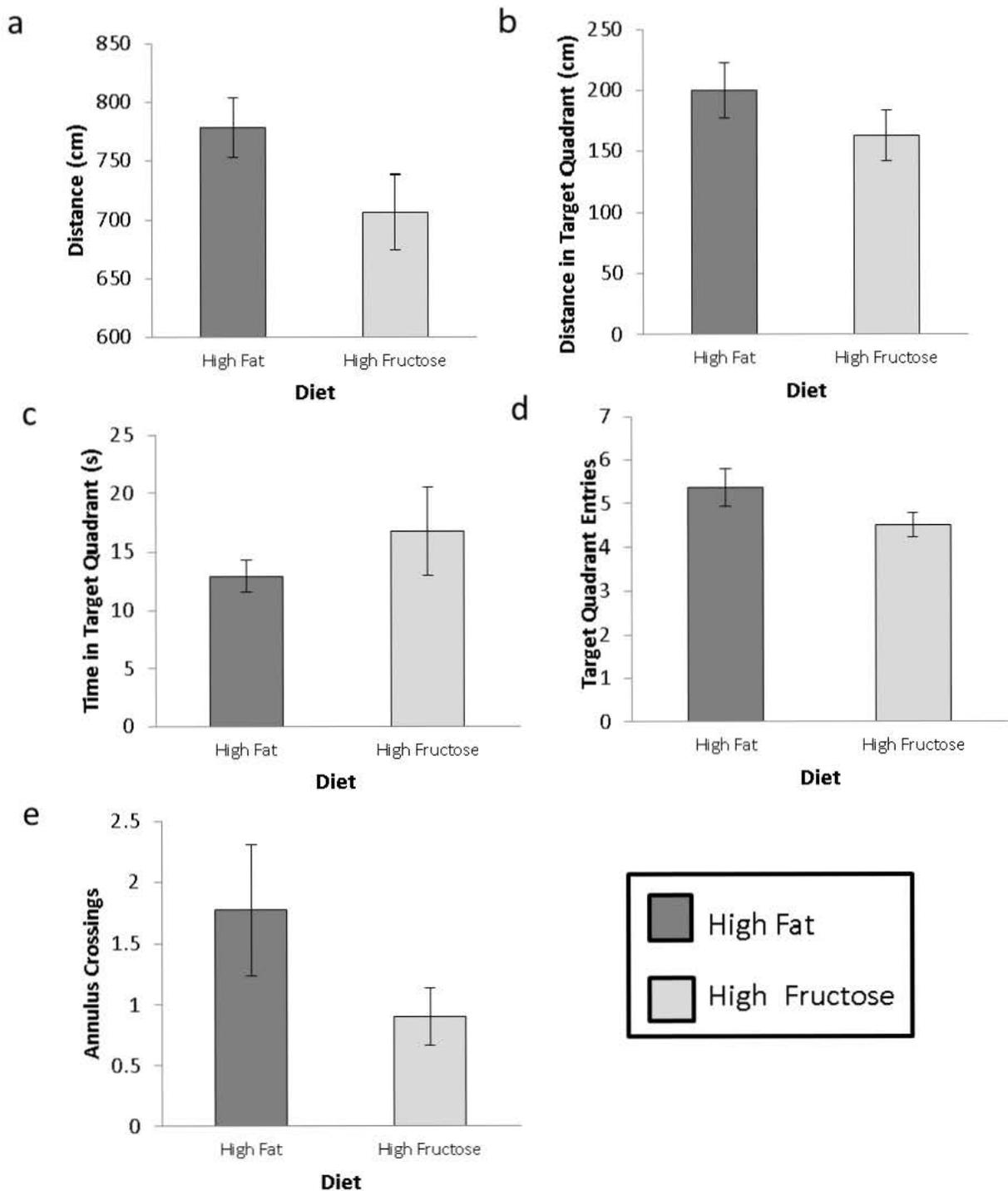
Figure 1. Preliminary MWM probe: (a) Total distance during probe trial. (b) Distance traveled in target quadrant. (c) Time spent in target quadrant. (d) Number of entries into the target quadrant. (d) Number of annulus crossings. Data are presented as mean ± SD; $p<0.05$.
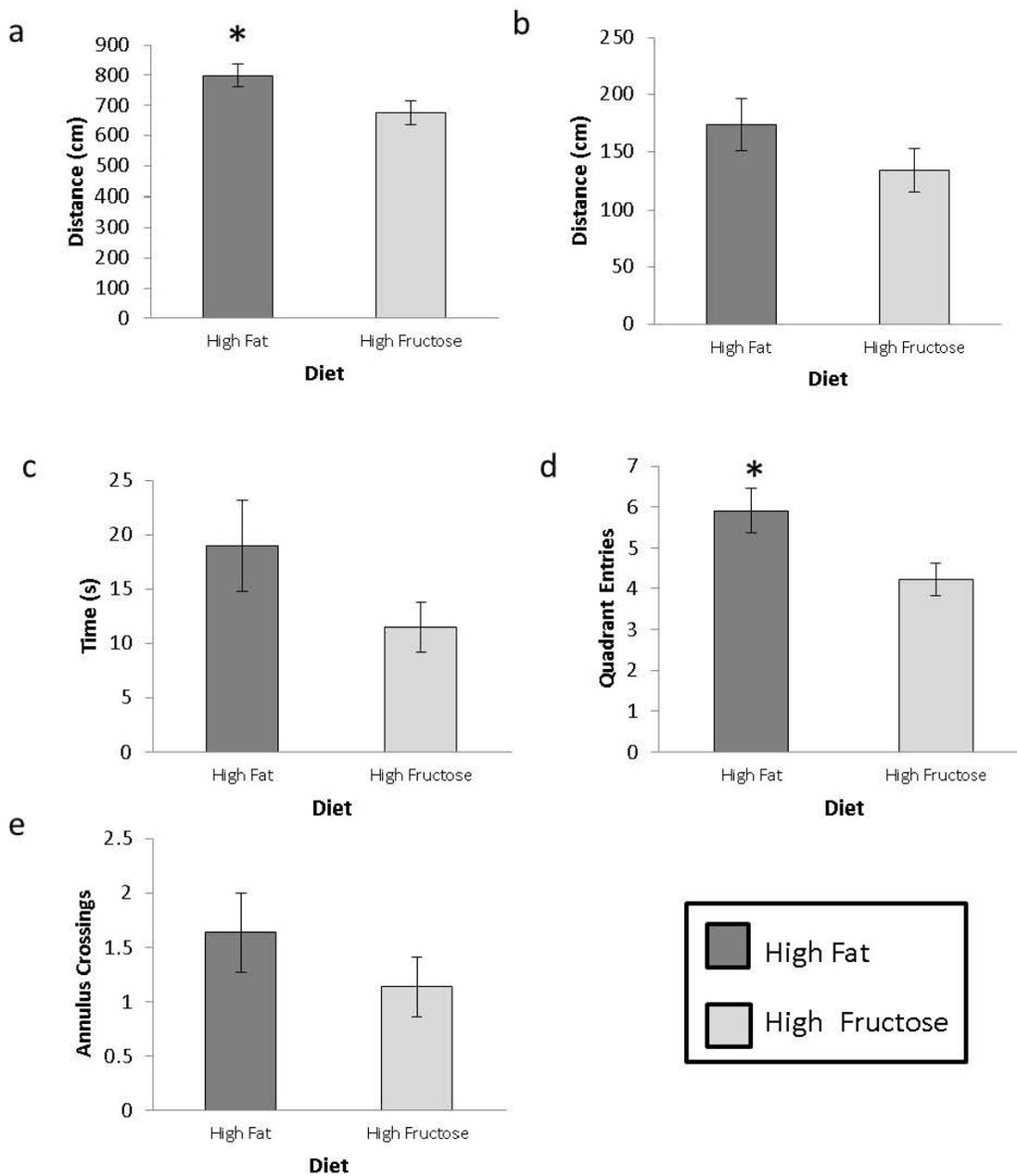
**Figure 2.** Reverse MWM probe: (a) Total distance during probe trial. (b) Distance traveled in target quadrant. (c) Time spent in target quadrant. (d) Number of entries into the target quadrant. (d) Number of annulus crossings. Data are presented as mean ± SD; $p < 0.05$.

**DISCUSSION**

High fat and high fructose diets produced two distinct sets of physiological and behavioral responses in young male rats. Rats on the high-fat diet developed signs of visceral adiposity by the end of the study, including higher end body weight and heavier total fat pad weight. High fat fed rats also consumed more kilocalories over a four day period, which may explain the greater fat deposition and weight gain in these animals. However, it was the high fructose fed rats that developed metabolic and cognitive impairments such as: elevated serum insulin, high triglyceride levels and impaired performance in Morris Water Maze reversal. These results indicate that separate components of the Western-style diet may induce considerably different effects on physiology and behavior.

The rats fed a 55% fructose diet had significantly higher serum insulin levels by the end of the study. However, they exhibited fasting glucose levels that were comparable to the other two groups. Therefore, the high-fructose fed animals secrete more insulin in response to a normal level of circulating glucose, which suggests a development of insulin insensitivity in our high fructose fed group. Interestingly, our high fat fed rats did not appear to develop insulin insensitivity in response to the 60% fat diet and had serum insulin levels comparable to the control group. Previous studies found that insulin resistance actually developed independently of adiposity in rats fed a diet made up of 40% calories from fat (5). However, Clegg *et al.* were measuring central insulin resistance, which was not examined in the present study. The animals were also older than ours and previous studies have shown that diet-induced obesity, insulin

resistance and other consequences occur more often in older animals than their younger counter parts (12).

Neither dietary group displayed significantly higher levels of serum TNF-α and IL-6 in a post-mortum trunk blood ELISA panel when compared to the control. The development of obesity has been found to cause oxidative stress and the release of inflammatory cytokines from fat, or adipokines such as nuclear factor-KB, tumor necrosis factor a (TNF-a) and interleukin-6 (IL-6) (8). The release of these adipokines is one proposed mechanism for the development of insulin resistance in obese animals. If this mechanism is correct, the lack of high adipokines could be a possible explanation for why the high fat fed group did not appear to develop insulin resistance. However, our high fructose animals appeared to have insulin dysregulation, but did not exhibit significant lipogenesis or adipokine levels. Therefore, there is a distinct possibility that a threshold exists for adipokines to take effect on insulin signaling in animals fed a high fat diet. Our animals may not have reached that critical point in nine weeks, in which case, a longer term dietary study is necessary.

Therefore it is essential to take a closer look into other explanations for the dichotomy between the metabolic and visceral data in our high fructose animals. One possible explanation for these interesting results could stem from the unique metabolism of fructose. Fructose enters liver cells through the unregulated GLUT5 transporter that does not require insulin signaling, so fructose can still be absorbed into cells whether an individual is insulin insensitive or not. Thus, the deleterious effects of fructose can persist even in those with impaired insulin

signaling. One of the main consequences of unregulated fructose uptake is the large levels of triglycerides produced. Triglycerides are made more efficiently and in greater amounts in the presence of large quantities of fructose and subsequently contribute to high levels of triglycerides in the blood and liver (11). We did not see significant lipid accumulation in the livers of our high fructose animals. However, we know that they did have increased triglyceride production in response to the high fructose treatment due to the fact that they showed elevated serum triglycerides, which are hypothesized to be the cause of increased normalized body fat also observed in the high fructose animals.

Increased triglycerides have also been implicated in the development of cognitive impairments when they cross the blood brain barrier. Indeed, Farr and colleagues conducted a study where direct injection of triglycerides into the brain was shown to have detrimental consequences on learning and memory (6). Thus, high fructose diets are proposed to have indirect effects on the learning and memory function of the hippocampus by elevating serum triglycerides levels not only in the periphery, but also centrally (27). Our high fructose fed animals had significantly higher serum triglyceride levels, but they did not exhibit cognitive impairment in the preliminary Morris Water Maze. However, in the reverse Morris Water Maze they were found to enter the target quadrant significantly less and travel less total distance than the high fat animals. The reversal aspect of the Morris Water Maze measures working memory, cognitive flexibility and the ability for animals to not only remember where the platform is, but to ignore where it previously was. Therefore, having significantly decreased

entry into the target quadrant suggests working memory impairment in the high fructose fed animals.

A possible mechanism for this cognitive deficiency could be reduced BDNF, which is involved in new neuron development and neural plasticity in the brain. Low levels of BDNF were found to accompany impaired glucose metabolism and impaired insulin sensitivity in humans and play a part in both body weight dysregulation and memory impairment observed in the animals (13). Two previous studies have explored fructose-induced insulin insensitivity and cognitive impairment by supplementing a high-energy diet with liquid high fructose corn syrup. These animals exhibited insulin insensitivity, reduced hippocampal BDNF and higher cognitive impairment on spatial learning tasks than nonsupplemented rats (27). Due to the presence of insulin insensitivity and cognitive decline in our fructose fed animals, exploration in BDNF is a logical next step in the project. Therefore, brain punches from the hippocampus and hypothalamus were obtained from our animals in order to do a subsequent study on the potential impact of high fructose on BDNF and brain function.

In light of our findings, it is increasingly important to develop a juvenile animal model to expand our understanding of the development of obesity, metabolic syndrome and memory impairment early in life. Thus, in the present study we chose to begin our experiment with six week old rats, which corresponds roughly to a post-pubescent adolescent human. This allows for the exploration of the singular effects of a high-fat or high-fructose diet on developing mammals. Also, this study is the first, to date, that explores the effect solid high fat and solid

high fructose individually on young animals. Other studies that examine the Western-style diet use either liquid high fructose with solid fat or a combination fat and fructose in one solid diet. In order to create a model that adequately compares the singular effects of high fructose and high fat on the developing animal, it was necessary for us to provide both diets in solid form. Therefore, we eliminated the potential confounding variable of macronutrient administration method by offering both diets as solid pellets. Additionally, the combination of high fat and high fructose in one diet has been previously shown to induce obesity and insulin dysregulation, but these studies cannot definitively find if one component of the diet causes different maladies. As can be observed from the present results, combining fat and fructose in one diet may occlude some of the hidden differences in the physiological and behavioral action of each macronutrient.

These data suggest that separate components of the Western-style diet influence different facets of the development of metabolic syndrome and cognitive dysfunction. High-fat contributes to increased adiposity and weight gain while, high-fructose impacts the development of hypertriglyceridemia, insulin dysregulation and working memory impairment. Although individual parts of the Western-style diet have been shown to cause negative consequences on their own in this study, the high fat component and the high fructose component may also exacerbate each other. This could be what makes the combination of the two macronutrients in the Western-style diet so detrimental to human health. However,

subsequent work directly comparing the individual components and a combination are

necessary to elucidate this proposition.

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