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A high fructose diet impairs spatial memory in male rats

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ABSTRACT

Over the past three decades there has been a substantial increase in the amount of fructose consumed by North Americans. Recent evidence from rodents indicates that hippocampal insulin signaling facilitates memory and excessive fructose consumption produces hippocampal insulin resistance. Based on this evidence, the present study tested the hypothesis that a high fructose diet would impair hippocampal-dependent memory. Adult male Sprague–Dawley rats (postnatal day 61) were fed either a control (0% fructose) or high fructose diet (60% of calories). Food intake and body mass were measured regularly. After 19 weeks, the rats were given 3 days of training (8 trials/day) in a spatial version of the water maze task, and retention performance was probed 48 h later. The high fructose diet did not affect acquisition of the task, but did impair performance on the retention test. Specifically, rats fed a high fructose diet displayed significantly longer latencies to reach the area where the platform had been located, made significantly fewer approaches to that area, and spent significantly less time in the target quadrant than did control diet rats. There was no difference in swim speed between the two groups. The retention deficits correlated significantly with fructose-induced elevations of plasma triglyceride concentrations. Consequently, the impaired spatial water maze retention performance seen with the high fructose diet may have been attributable, at least in part, to fructose-induced increases in plasma triglycerides.

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1. Introduction

Over the past three decades there has been a substantial increase in the amount of fructose found in the North American diet. Several factors have contributed to the increase in the availability and per capita consumption of fructose (Hein, Storey, White, & Lineback, 2005; Sigman-Grant & Morita, 2003); most notably, technological advances in the late 1960s led to the development of a cost-effective method for producing large amounts of extremely sweet corn-based syrups containing high concentrations of fructose (high fructose corn syrup, HFCS; either 42% or 55% fructose; Hanover & White, 1993). Between 1970 and 1990, the consumption of HFCS increased by 20–40%, surpassing consumption increases in any other foods, (Bray, Nielsen, & Popkin, 2004; Havel, 2005), and by the year 2000, 42% of added sweeteners were corn syrups (Putnam & Allshouse, 1999). In addition, fructose is added to food in the form of fruit juice concentrates (over 60% of calories in apple juice), crystalline fructose (almost 100% fructose), and sucrose (50% fructose; Hanover & White, 1993). Fructose, in many forms, is added to countless foods including carbonated beverages, fruit products, baked goods, cereals, and dairy products (Hanover & White, 1993). Indeed, North Americans would be greatly challenged to purchase processed foods not containing some form of fructose.

A high fructose diet causes numerous pathological changes, including oxidative stress, glucose intolerance, insulin resistance, type 2 diabetes, liver disease, hypertension, and cardiovascular disease (Busserolles, Gueux, Rock, Mazur, & Rayssiguier, 2002; Elliott, Keim, Stern, Teff, & Havel, 2002; Hwang, Ho, Hoffman, & Reaven, 1987; Montonen, Jarvinen, Knekt, Heliovaara, & Reunanen, 2007; Nandhini, Thirunavukkarasu, Ravichandran, & Anuradha, 2005; Zavaroni, Sander, Scott, & Reaven, 1980). Furthermore, a study from one of the present investigators showed that the damaging effects of a high fructose diet extend directly to the brain (Mielke et al., 2005). Specifically, placing male Syrian hamsters on a 60% fructose diet for 6 weeks produced hippocampal insulin resistance. This finding is particularly significant given that the hippocampus is integral to many forms of learning and memory (Ergorul & Eichenbaum, 2004) and that converging lines of evidence indicate that neural insulin signaling facilitates hippocampal-dependent memory (Park, 2001). For instance, extensive evidence suggests that peripheral insulin resistance and type 2 diabetes are associated with deficits in hippocampal-dependent declarative memory (Convit, 2005; Messier, 2005; Stewart & Liolitsa, 1999; Strachan,

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Deary, Ewing, & Frier, 1997; Zhao et al., 1999). Moreover, learning and memory of a spatial water maze experience are correlated with activation of the hippocampal insulin signaling pathway (Dou, Chen, Dufour, Alkon, & Zhao, 2005; Zhao et al., 1999). Most importantly, direct infusions of insulin into the hippocampus enhance performance in a variety of memory tasks, and the memory-enhancing effects of hippocampal insulin administration are not observed in diabetic rats (Babri, Gholamipour, Rad, & Khameneh, 2006; McNay, Herzog, McCrimmon, & Sherwin, 2005; Moosavi, Naghdi, Maghsoudi, & Zahedi Asl, 2006).

Given that fructose is preferentially metabolized by the liver into lipids (Havel, 2005; Topping & Mayes, 1971) and produces large increases in plasma triglyceride (TG) concentrations (Basciano, Federico, & Adeli, 2005; Havel, 2005; Kelley, Allan, & Azhar, 2004; Le et al., 2006; Park et al., 1992), a high fructose diet is analogous to a high fat diet in many metabolic ways. Importantly, rats fed a diet high in saturated fatty acids exhibit impaired performance on a number of hippocampal-dependent memory tasks (Greenwood & Winocur, 1990; Greenwood & Winocur, 1996; McNay et al., 2005). Moreover, high fat diets produce insulin resistance in the brain (Banas, Rouch, Kassis, Markaki, & Gerozissis, 2008), and injecting TGs directly into the brain ventricles impairs memory (Farr et al., 2008). Collectively, the reviewed evidence led us to hypothesize that a high fructose diet would impair hippocampal-dependent memory, and that the deficits would be attributable, at least in part, to fructose-induced increases in plasma TGs. Consequently, the present experiment tested the effects of feeding rats a high fructose diet on hippocampal-dependent spatial water maze learning and memory, and sought to determine whether any deficits would be correlated with fructose-induced increases in plasma TGs.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River, Wilmington, MA) aged 53 days upon arrival were used. Rats are an excellent animal model to study the effects of fructose intake because their metabolism of fructose closely resembles that of humans (Bar-On & Stein, 1968; Mayes, 1993; Van Den Berg, 1986). The present research focused on male rats, given that men are the greatest consumers of fructose (French, Lin, & Guthrie, 2003; Park & Yetley, 1993; Vos, Kimmons, Gillespie, Welsh, & Blanck, 2008).

The rats were weighed the day they arrived and again during each of the 3 days before the diet change, which occurred one week after their arrival. Rats were matched on absolute body mass and percent body mass change during the habituation week and assigned to either the control (0% fructose; $n = 14$) or fructose-fed (60% fructose; $n = 15$) group. In order to measure food intake, the animals were housed in suspended cages with wire mesh bottoms (Hazelton Systems, Aberdeen, MD). All procedures were approved by the Georgia State University Institutional Animal Care and Use Committee and are in accordance with PHS guidelines.

2.2. Diets

The fructose-fed group was provided *ad libitum* with a diet that consisted of 60% fructose (Research Diets, New Brunswick, NJ). The 60% fructose concentration was chosen because this amount produces hippocampal insulin resistance in hamsters (Mielke et al., 2005), leads to peripheral pathology in rats similar to the pathology associated with fructose consumption in humans (Elliott et al., 2002; Montonen et al., 2007), and is the amount used most extensively in rodent studies (de Moura, Ribeiro, de Oliveira, Stevanato, & de Mello, 2008; Kelley et al., 2004; Shapiro et al., 2008; Suga et al., 2000; Taghibiglou et al., 2002; Tobey, Mondon, Zavaroni, & Reaven, 1982). The control group was fed a diet of standard rat chow (60% vegetable starch; Research Diets, New Brunswick, NJ) *ad libitum*. Both diets contained equal percentages of carbohydrates (70%), proteins (20%), and lipids (10%), and both diets were also isocaloric on a weight basis (kcal/gm). The rats were fed the diets for 18 weeks, and behavioral testing was performed during the nineteenth week.

2.3. Body mass and food intake

Rat body mass and food intake were recorded for 1 week out of every 3 weeks until behavioral tests were performed. To measure food intake, pellets in each hopper and dried spillage from under each cage were weighed and then subtracted from the amount placed in the hopper the previous day. Average daily kcal consumption was calculated by multiplying the average grams of food consumed daily by kcal per gram of food.

2.4. Spatial water maze

The spatial water maze task was used to assess learning and memory for several reasons. First, the task is dependent on the integrity of the hippocampus for successful performance (Bolhuis, Stewart, & Forrest, 1994; Clark, Broadbent, & Squire, 2005; Korol, Abel, Church, Barnes, & McNaughton, 1993; Martin, de Hoz, & Morris, 2005; Morris, Garrud, Rawlins, & O'Keefe, 1982; Mumby, Astur, Weisend, & Sutherland, 1999; Sutherland et al., 2001). Secondly, spatial water maze training increases hippocampal insulin signaling (Zhao et al., 1999). Third, hippocampal infusions of insulin enhance spatial water maze performance (Choopani, Moosavi, & Naghdi, 2008; Moosavi, Naghdi, & Choopani, 2007; Moosavi et al., 2006; Zhao et al., 1999).

For water maze acquisition, the rats were trained to locate a submerged platform (26 cm in height and 10 cm in diameter) in a circular pool (0.46 m in depth and 1.35 m in diameter). Acquisition consisted of eight training trials per day for three consecutive days. Immediately before the first training trial of each day, rats were placed on the platform for 30 s and were then placed in the water facing the wall of the pool in one of three randomly determined quadrants. The fourth quadrant contained the platform and was referred to as the target quadrant. If the rats did not reach the platform within 60 s, then they were guided by hand to the platform. Rats were allowed to remain on the platform for 15 s at the end of each trial and were then placed in an empty cage for a 30 s inter-trial interval. Latency to reach the platform was used as the measure of acquisition. Retention of the training was tested 48 h after the last training day. Rats were placed in the pool facing the wall in a randomly determined quadrant and allowed to swim for 20 s. The platform was not present, and retention measures during the probe test included: (1) time spent in the target quadrant, (2) latency to cross the platform location (target) and (3) number of target approaches. Swim speed was also measured.

2.5. Postmortem measures

Two to three days after the retention test, the rats were fasted for 4 h then anesthetized with isoflurane gas (5% in 95% oxygen) and euthanized by decapitation. Trunk blood was collected immediately in heparinized tubes and centrifuged to collect plasma, which was then stored at −80° C until the assays were performed. Given that the liver is the primary site of fructose metabolism (Havel, 2005; Topping & Mayes, 1971), the liver was also extracted and weighed.

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