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Short exposure to a diet rich in both fat and sugar or sugar alone impairs place, but not object recognition memory in rats

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ABSTRACT

High energy diets have been shown to impair cognition however, the rapidity of these effects, and the dietary component/s responsible are currently unclear. We conducted two experiments in rats to examine the effects of short-term exposure to a diet rich in sugar and fat or rich in sugar on object (perirhinal-dependent) and place (hippocampal-dependent) recognition memory, and the role of inflammatory mediators in these responses. In Experiment 1, rats fed a cafeteria style diet containing chow supplemented with lard, cakes, biscuits, and a 10% sucrose solution performed worse on the place, but not the object recognition task, than chow fed control rats when tested after 5, 11, and 20 days. In Experiment 2, rats fed the cafeteria style diet either with or without sucrose and rats fed chow supplemented with sucrose also performed worse on the place, but not the object recognition task when tested after 5, 11, and 20 days. Rats fed the cafeteria diets consumed five times more energy than control rats and exhibited increased plasma leptin, insulin and triglyceride concentrations; these were not affected in the sucrose only rats. Rats exposed to sucrose exhibited both increased hippocampal inflammation (TNF-α and IL-1β mRNA) and oxidative stress, as indicated by an upregulation of NRF1 mRNA compared to control rats. In contrast, these markers were not significantly elevated in rats that received the cafeteria diet without added sucrose. Hippocampal BDNF and neuritin mRNA were similar across all groups. These results show that relatively short exposures to diets rich in both fat and sugar or rich in sugar, impair hippocampal-dependent place recognition memory prior to the emergence of weight differences, and suggest a role for oxidative stress and neuroinflammation in this impairment.

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1. Introduction

Many people in developed countries eat a diet that is rich in saturated fat and refined sugar (Kearney, 2010). Excessive intake of this diet leads to increased body weight, progression into obesity, and the development of metabolic and cardiovascular disorders (Bruce-Keller et al., 2009; Haslam and James, 2005). Epidemiological data has also associated the consumption of high energy diets with an increased risk of age related deficits and neurological diseases including dementia and Alzheimer's disease (Eskelinen et al., 2008; Grant et al., 2002; Solfrizzi et al., 2010). Studies with rodents have confirmed that the long-term intake of such a diet produces cognitive deficits, especially in spatial tasks that require the hippocampus (Heyward et al., 2012; McNay et al., 2010; Ross et al., 2009). Some of these studies have also identified changes in the hippocampus that may mediate the link between obesity and cognitive deficits. Such changes include oxidative stress, neuroinflammation, as well as decreased levels of neurotrophins (Molteni et al., 2004; Pistell et al., 2010).

Moreover there is very recent evidence that cognitive deficits can not only be produced by long-term excessive intake of a high energy diet but also by relative short exposures to such a diet. Holloway et al. (2011) reported that healthy adults who ate a high fat diet for 5 days performed worse on tasks measuring attention and speed of retrieval than they had prior to the diet. Kanoski and Davidson (2010) also found that rats exposed to a high fat and glucose diet performed worse on a spatial task than chow fed control rats after only 3 days whereas 30 days exposure was necessary for non-spatial memory impairments.

The present experiments constituted a further study of the effects of relatively short-term exposure to a high energy diet on cognition in rats. We set out to confirm and extend previous reports that the consumption of diets high in both fat and sugar is accompanied by impaired memory retention. The modern diet is replete with a diverse range of foods that are rich in fat and sugar and for this reason in the first experiment we chose a cafeteria style diet (cakes, biscuits, lard) supplemented with a 10% sucrose solution. To compare non-spatial and spatial memory we

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employed the object and place recognition tasks, which are respectively dependent on the perirhinal cortex and the hippocampus (Aggleton and Brown, 2005). We assessed performance on both tasks from 5 to 21 days diet exposure to examine changes in the magnitude of specific deficits. There is some evidence that the hippocampus is particularly sensitive to changes in dietary intake and impairments have been reported on hippocampal-dependent tasks prior to substantial weight gain (Kanoski and Davidson, 2010; Murray et al., 2009). Here we specifically aimed to test short, rather than the more commonly studied long term dietary interventions (3–12 months).

To assess the relative contributions of fat and sugar to the behavioral effects observed, our second experiment included two additional diet groups, a regular diet supplemented with 10% sucrose and the cafeteria style diet without sucrose. At the end of the study we assessed plasma leptin, insulin and triglycerides as well as hippocampal expression of inflammatory markers; tumor necrosis factor (TNF-α) and interleukin 1 (IL-1β), oxidative stress markers; nuclear respiratory factor 1 (NRF1), and sirtuin 3 (SIRT3), as well as brain-derived neurotrophic factor (BDNF) and neuritin. These markers were selected as CNS inflammation has been reported after as little as 1–3 days on a high energy diet (Hansen et al., 1998; Thaler et al., 2012) and obesity itself is characterized by a state of low grade, chronic inflammation (Bastard et al., 2006). In addition, oxidative stress is believed to be one of the first events following the consumption of a high energy diet and it may be responsible for the decreased levels of BDNF reported in long term diet studies (Molteni et al., 2004). NRF1 is involved in the activation of antioxidant response element-dependent genes (Ohtsuji et al., 2008) while SIRT3 has roles in metabolism, oxidative stress and cell survival (Weir et al., 2013). BDNF has been implicated in a number of processes postulated to underlie hippocampal-dependent learning and memory including long term potentiation, neurogenesis and synaptic plasticity (Stranahan et al., 2008; Yamada et al., 2002).

2. Methods

2.1. Subjects

Male Sprague–Dawley rats (Experiment 1: 363–467 g; Experiment 2: 302–366 g; Animal Resource Centre, Perth, WA, Australia) were housed four per polypropylene cage (47 cm × 29 cm × 15 cm) in a temperature controlled (18–20 °C) colony room on a 12 h light/dark cycle (lights on at 07:00 h). Rats were acclimatized for 1 week, during which they were maintained *ad libitum* on standard rat chow (Gordon's Premium Rat and Mouse Breeder diet, NSW, Australia) and tap water. Prior to diet commencement rats were weight matched across groups and two home cages were assigned to each diet condition ($n = 8$ per group). All experimental procedures were approved by the Animal Care and Ethics Committee at the University of New South Wales.

2.2. Diets

The regular diet (RD) rats received chow (59% carbohydrate, 26% protein, 15% fat) and access to two water bottles in each cage throughout the experiment. The rats on the cafeteria diet (CAF S+) received chow, and access to one sucrose bottle (10% solution) and one water bottle in each cage. This was supplemented with a container (7.5 cm × 7.5 cm) of lard, and a selection of biscuits and cakes that changed every day (50% carbohydrate, 5% protein, 45% fat). For the second experiment, four diets were compared: RD and CAF S+ as above; a sugar group (S+) that received chow and access to one sucrose bottle (10% solution) and one water bottle (consuming 74% energy as carbohydrate, 17% protein, 9% fat over the course of the experiment) and a modified cafeteria group (CAF S−) that received the same diet as the CAF S+ rats but with access to two water bottles (49% carbohydrate, 4% protein, 47% fat). All food, water and sucrose were available *ad libitum* and replaced daily. Food and liquid consumption over 24 h was recorded at regular intervals. Items were weighed before presentation to the rats, and the remainder was weighed after 24 h. The amount eaten per cage was converted to energy (kJ) using data provided by the manufacturers and average intake was calculated assuming equal intake for each rat. Rats were weighed at the diet onset and at regular intervals across the experiment.

2.3. Object and place recognition tests

The apparatus consisted of an open-field arena (60 cm × 60 cm × 50 cm) constructed from black PVC plastic which was divided equally into 16 quadrants. A video-camera was positioned directly above the arena to record behavior. The objects used were commercial products (e.g., 1.25 L soft drink bottles, coffee mugs, lunch box containers), made of a variety of materials (aluminium, glass, plastic and porcelain) and varying in both height (7.5–29 cm) and width (4.5–13 cm). Rats were acclimatized to the empty arena for 10 min per day on 2 consecutive days, and testing commenced the next day. Specifically, half of the rats from each diet group were assessed on the object task and the other half on the place recognition task on the first day of testing and vice versa for the second day of testing. For both tasks, each rat was placed into the center of the arena with two identical objects (located in two of the middle four quadrants) and allowed to explore for 5 min (familiarization phase). The rat was then removed for 5 min (retention phase) and the arena and objects were cleaned with 80% ethanol. For the object test phase, two objects were placed into the same positions as the familiarisation trial. One of these objects was identical to the sample object previously presented and the other was a novel object. In the place test phase, two identical objects to those used in familiarisation were presented; one remained in its original location while the other was moved to one of the four corner quadrants of the arena. The test phase lasted for 3 min. Following the completion of baseline measures, the diets were commenced and rats received 3 additional object and place memory tasks after 5–6, 11–12 and 20–21 days.

Each object was only used for one trial per rat. Rats were tested at the same time of day and the object order and location were counterbalanced between rats and across trials. Exploration was defined as the rat's head within 2 cm of the object with the neck extended and vibrissae moving around the object. Data were scored using Macropod ODlog® software by the experimenter and a second observer naïve to group allocation. The correlation between the two observers was high ($r > .90$). Data are reported as the Exploration Ratio, which was the time spent exploring the novel object divided by the time spent exploring both objects ($t_{novel}/(t_{novel} + t_{old})$).

2.4. Sample collection

In Experiment 2, rats were anesthetized (xylazine/ketamine 15/100 mg/kg i.p.) between 09:00 and 13:00 h, 6–8 days after the completion of their final object and place recognition task. All rats had access to their respective diets until cull. Body weight, naso-anal length and girth (base of ribcage) were measured. A cardiac blood sample was centrifuged (Microspin 12) and the plasma separated and stored at −20 °C for subsequent determination of plasma leptin, insulin and triglycerides. Rats were then killed by decapitation. White adipose tissue (WAT) (retroperitoneal (RP), visceral, and gonadal deposits), and organs (adrenal, kidney, liver)

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