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A physiological characterization of the Cafeteria diet model of metabolic syndrome in the rat

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HIGHLIGHTS

- A palatable Cafeteria diet reliably models human-like metabolic syndrome in the rat.
- The Cafeteria diet increases Iba1 + microglial cell density in the hippocampus.
- Spatial memory, determined using the Barnes maze, is not impaired by Cafeteria diet.
- Metabolic syndrome and inflammation are reversed by standard diet-feeding.

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ABSTRACT

Many promising findings from pre-clinical research have failed to translate to the clinic due to their inability to incorporate human disease co-morbidity. A variety of rodent diets and feeding durations are currently used in models of human metabolic syndrome, obesity and diabetes. One model, the Cafeteria (CAF) diet, makes use of grocery store-purchased food items that more closely approximate the human ultra-processed diet than commercial high-fat or high-sugar rodent diets. The present study describes the development of metabolic syndrome in rats fed a CAF diet as well as the recovery of metabolic syndrome following a healthy "lifestyle" change. In addition, we explored the effects of CAF diet on spatial learning and memory and on neuroinflammation. Three-week old male Sprague-Dawley rats were fed a CAF diet for three months that consisted of 16 highly palatable human food items along with standard chow and a 12% sucrose solution to mimic soda consumption. Thereafter, a sub-group of CAF diet rats was switched to a chow diet (SWT) for one month. Both CAF and SWT groups were compared to control rats maintained on a standard chow diet (SD). Prior to the diet switch, CAF and SWT animals developed features akin to metabolic syndrome. Both groups of rats displayed significant abdominal obesity with increased visceral adiposity, hyperinsulinemia, glucose intolerance and dyslipidemia with elevated serum triglyceride levels and reduced HDL cholesterol. Switching to a chow diet for one month completely reversed these features in SWT animals. Although acquisition of the Barnes maze was not affected by the CAF diet, these animals exhibited greater hippocampal neuroinflammation compared to both SD and SWT rats as assessed by Iba1 staining. These results demonstrate that the CAF diet is very effective in creating metabolic syndrome with hippocampal inflammation in rats over a relatively short time span. This model may be of great heuristic importance in determining potential reversibility of metabolic and cerebrovascular pathologies across the lifespan and as a co-morbid factor in other disease models such as stroke.

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1. Introduction

Cerebrovascular disease (CVD) is a significant risk factor for cognitive impairment which includes vascular dementia [1]. A constellation of metabolic abnormalities, collectively known as metabolic syndrome,

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has been estimated to increase the risk for CVD by 50% [2]. A consensus agreement by the International Diabetes Federation and the American Heart Association/National Heart, Lung and Blood Institute identifies the criteria of metabolic syndrome as: abdominal obesity, reduced HDL cholesterol, elevated triglyceride, glucose intolerance and hypertension [3]. Diagnosis requires that any three out of these five criteria be present. Epidemiologically, the primary cause of metabolic syndrome is an unhealthy lifestyle, in particular a highly processed diet rich in fat, sugar and sodium combined with physical inactivity [4]. Many animal studies have attempted to model metabolic syndrome using high-caloric diets, though most isolate a single nutritional component (e.g. fat from lard, fructose, etc.) to study its effects. In doing so, these regimens do not fully recapitulate metabolic syndrome due to the loss of the large nutritional and sensorial diversity typical of human diets [5]. Moreover, despite the role of high sodium in increasing CVD risk, it is rarely included in animal dietary models [6]. This reductionist approach in modeling human diet has hindered the translation of preclinical research to the clinic.

The role of nutritional variability on food palatability is well understood by the food industry. Complex food combinations have been extensively explored by food chemists in the development of "ultra-processed" foods and beverages, demonstrated to be at the core of the current global obesity epidemic [7]. Combining high levels of fat with sugar results in greater food, and therefore caloric intake as sweet flavors render energy dense foods more palatable by masking their high fat content [8]. Given that ultra-processed foods provide close to 60% of the caloric intake of Americans and contribute 90% of energy from added sugars [9], understanding the role of this complex diet on CVD risk factors is of great importance. The closest equivalent to the human ultra-processed food diet is the Cafeteria diet (CAF) which provides animals with nutritionally varied, energy dense and highly palatable grocery store-purchased food, thereby mirroring the key obesogenic features of the human diet [10,11].

Clinical management of metabolic syndrome recommends the adoption of a healthy lifestyle [12] which greatly reduces its peripheral features [13]. Nonetheless, it is still unclear whether CVD risk, particularly stroke incidence and mortality, can be reduced after long-term metabolic dysregulation. Clinical lifestyle modification recommendations are based on the results of retrospective or case control studies that compare healthy individuals with metabolic syndrome patients [14]. A large prospective study examining the effects of adopting a healthy diet paired with moderate exercise in overweight patients with type 2 diabetes, the Look AHEAD study, failed to demonstrate reduced CVD risk after nearly ten years of adherence to the healthy lifestyle [15]. Use of appropriate animal models could be extremely useful in addressing the reversibility of CVD risk following treatment of metabolic syndrome and thereby facilitate the development of new clinical interventions.

In addition to increasing CVD risk, metabolic syndrome is also a prominent risk factor for "covert" ischemic insults and dementia affecting a range of cognitive domains including memory, language, visuospatial ability and executive function [16,17]. Cognitive impairments have been studied in rats fed standard high-fat and -sugar diets using a wide variety of behavioural paradigms including, but not limited to, the radial arm maze [18], the Morris water maze [19,20] and conditional discrimination learning tasks [21]. These commonly used cognitive tests rely heavily on stressful aversive stimuli (e.g. water maze) or food deprivation, which are problematic for dietary studies. Given the negative effects of stress on behavioural outcome measures [22], cognitive tasks that minimize these confounding factors are preferred. For example, unlike the Morris water maze, the Barnes maze relies on mildly aversive noise and light stimuli to motivate animals and thus may be useful in assessing the effects of CAF diet-feeding on spatial memory.

One mechanism by which metabolic syndrome and diet have been hypothesized to play a role in cognitive decline is through chronic low-grade inflammation [23]. Indeed, nutritional signals act to maintain energetic homeostasis through vagal and humoral systems that significantly overlap with immune pathways [24]. These nutritional and immune signals circulate systemically, reaching the brain to modify hypothalamic-controlled feeding behavior while simultaneously influencing learning and memory function in the hippocampus through modulators of synaptic plasticity such as BDNF. Chronic exposure to conditions of excessive caloric intake results in abnormal feeding patterns, aberrant immune responses and cognitive deficits [25]. Within the central nervous system, resident microglia are the primary cellular target of these inflammatory signals, responding to stress signals such as chronic energy imbalance by undergoing rapid expansion and activation [26]. Recently, Beilharz et al. [27] demonstrated that a CAF diet, when combined with a 10% sucrose solution, can very quickly upregulate mRNA expression of neuroinflammatory markers such as TNFα and IL1β in the hippocampus. It remains to be demonstrated whether the CAF diet can also promote microglial cell population expansion.

In light of the need for better characterization of animal models to avoid clinical translation pitfalls and wasted research resources [28–30], the goal of our study was to assess the ability of the CAF diet to produce metabolic syndrome in Sprague-Dawley rats as well as the degree to which these features could be reversed through switching to a healthy diet. In addition, we examined the effects of the CAF diet on hippocampal spatial learning and memory using the Barnes maze as well as on neuroinflammation by quantifying microglial cell density.

2. Material and methods

2.1. Animals and diets

Experimental procedures followed the guidelines established by the Canadian Council on Animal Care and were approved by the Animal Care Committee of the University of Ottawa. A total of 55 male Sprague Dawley rats (Charles River Laboratories, Montreal, Canada) were used ($n = 18$ standard diet, SD; $n = 18$ Cafeteria diet, CAF; and $n = 19$ switch diet, SWT). Three-week old animals were pair-housed and maintained on a 12 h reverse light/dark cycle (8 am off/8 pm on). Following one week of habituation to the animal facility (with regular handling), rats were assigned to diet groups balanced by initial body weight. CAF diet-fed rats were provided with ad libitum access to regular chow (Teklad Global 18% Protein Rodent Diet; Harlan, Madison, WI) and a daily selection of three grocery store-purchased items from a list of 16 (Table 1) adapted from Sampey et al. [31]. CAF food items alternated through a list of pre-established combinations to ensure diversity and variety of foods presented. In addition, CAF diet animals had access to one water bottle and one bottle containing a 12% *w*/*v* sucrose solution (MP Biomedicals, Solon, OH). The control SD diet consisted of regular chow and water. SWT animals were fed the CAF diet for three months after which they were switched to the SD diet for one month. Both CAF and SD rats were maintained on their respective diets for the full duration (i.e. four months) of the experiment. Food from all three diet groups was weighed on a daily basis to calculate food intake. Nutritional composition of the three diets over the course of the experiment was calculated based on values provided by the product manufacturers. One subset of 37 animals was used for metabolic syndrome profiling and Barnes maze testing while a second group of 18 animals was used for visceral and subcutaneous fat analysis using MRI.

2.2. Blood sampling and metabolic syndrome profiling

Metabolic syndrome profiling was repeated in a subset of 37 animals ($n = 12$ SD, $n = 12$ CAF, $n = 13$ SWT) at two time points: immediately before switching SWT rats from the CAF diet to the SD diet (three months of feeding) and again one month later (four months of feeding).

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