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Reduced Cerebrovascular Reactivity and Increased Resting Cerebral Perfusion in Rats Exposed to a Cafeteria Diet

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Abstract—To better understand the effects of a diet high in fat, sugar, and sodium on cerebrovascular function, Sprague Dawley rats were chronically exposed to a Cafeteria diet. Resting cerebral perfusion and cerebrovascular reactivity was quantified using continuous arterial spin labeling (CASL) magnetic resonance imaging (MRI). In addition, structural changes to the cerebrovasculature and susceptibility to ischemic lesion were examined. Compared to control animals fed standard chow (SD), Cafeteria diet (CAF) rats exhibited increased resting brain perfusion in the hippocampus and reduced cerebrovascular reactivity in response to 10% inspired CO_2 challenges in both the hippocampus and the neocortex. CAF rats switched to chow for one month (SWT) exhibited improved resting perfusion in the hippocampus as well as improved cerebrovascular reactivity in the neocortex. However, the diet switch did not correct cerebrovascular reactivity in the hippocampus. These changes were not accompanied by alterations in the structural integrity of the cerebral microvasculature, examined using rat endothelial cell antigen-1 (RECA-1) and immunoglobulin G (IgG) immunostaining. Also, the extent of tissue damage induced by endothelin-1 injection into sensorimotor cortex was not affected by the Cafeteria diet. These results demonstrate that short-term consumption of an ultra-processed diet reduces cerebrovascular reactivity. This effect persists after dietary normalization despite recovery of peripheral symptomatology. **© 2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: Cafeteria diet, continuous arterial spin labeling, metabolic syndrome, cerebrovascular reactivity, processed food.

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Abbreviations: AP, anterior-posterior axis; ARRIVE guidelines, Animal Research, Reporting of In Vivo Experiments' guidelines established by the National Centre for the Replacement, Refinement & Reduction of Animals in Research; ASL, arterial spin labeling, perfusion scanning technique that using an intrinsic tracer; BBB, blood–brain barrier; CA1 and CA3, hippocampal cornu ammonis sub-regions 1 and 3; CAF, rats fed Cafeteria diet; CASL, type of ASL imaging where tracer labeling is 'continuous'; CBF, cerebral blood flow; Cerebrovascular reactivity, change in CBF in response to a vasodilatory or vasoconstrictive stimulus; Cx, cingulate cortex; DAB, 3, 3-diaminobenzidine; data blurring, modify an output dataset so as to achieve a specified full width at half maximum 'smoothness'; DG, dentate gyrus region of the hippocampus; endothelin-1, endogenous vasoconstrictor, used to model transient ischemic stroke; EPI, echo planar images, method of MRI data acquisition; FiCO2, fractional concentration of inspired CO2; FOV, field of view; full affine registration, method to superimpose two volumes, using affine transformation; gradient, coil used to vary the magnetic field across the imaging volume; H&E, hematoxylin and eosin; Hc, hippocampus; HDL, high-density lipoprotein; hemodynamic response function, mathematical model of the shape of the hemodynamic response; hypercapnia, condition of elevated CO2 in the blood, typically defined as over 45 mmHg; IgG, immunoglobulin G; isocenter, centre point of the magnetic field; kcal, kilocalories; ML, medial–lateral axis; MRI, magnetic resonance imaging; PBS, phosphate-buffered saline; perfusion, passage of blood through blood vessels in the brain; PFA, paraformaldehyde; RARE, rapid acquisition with relaxation enhancement type of MRI pulse sequence; RECA-1, rat endothelial cell antigen-1; REML, restricted maximum likelihood a form of maximum likelihood estimation; RF, radiofrequency; ROI, region of interest; SD, rats fed standard chow diet; SEM, standard error of the mean; streptozotocin-induced type 1 diabetes, diabetes induced by chemical destruction of pancreatic beta cells; SWT, CAF rats switched to the SD diet after one month; T2 MRI, MRI sequence using long TE and TR times to generate structural images of tissue; tag-control time series, collection of magnetically labeled, 'tagged', and unlabeled control images; $tcPCO_2$, transcutaneous partial pressure of CO2; TE, echo time between the RF pulse and signal sampling; TR, repetition time between two excitation pulses; tri-pilot images, a localizer scan to aide in positioning of the subject in the MRI scanner; ultra-processed foods, food items comprised almost exclusively of processed substances refined from whole foods; voxel, value represented in three dimensional space.

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INTRODUCTION

Metabolic syndrome affects 20–40% of the world population and is increasing in prevalence (Batsis et al., 2007). It is defined as the combination of any three of the following five characteristics: abdominal obesity, reduced high-density lipoprotein (HDL) cholesterol, elevated triglycerides, raised fasted blood glucose, and hypertension (Alberti et al., 2009). Despite the ability of dietary interventions to correct peripheral features of metabolic syndrome (Salas-Salvadó et al., 2011; The Look AHEAD Research Group, 2014), cardiovascular mortality risk is often not improved (Mozaffarian, 2016), begging the question of whether chronic consumption of a diet high in fat, sugar, and sodium can cause irreparable damage to the vasculature.

Whereas peripheral vascular dysfunction has been thoroughly described in individuals with metabolic syndrome (Limberg et al., 2013; Shimabukuro et al., 2016; Walther et al., 2015), limited reports exist regarding its effects on the cerebrovasculature. Nonetheless, some results suggest that metabolic syndrome also impairs cerebrovascular hemodynamics. In a retrospective study, Giannopoulos et al. analyzed transcranial Doppler data from metabolic syndrome patients with atherosclerotic disease and found a significant correlation between reduced cerebrovascular reactivity to hypercapnia and metabolic syndrome (Giannopoulos et al., 2010). These results were further confirmed in a more recent prospective study (Tyndall et al., 2016). In rats fed a high-fat diet, a similar reduction in functional hyperemia upon whisker stimulation was observed using laser Doppler imaging (Li et al., 2013).

Although transcranial Doppler offers certain advantages over other imaging techniques, it is limited to measuring blood velocity in major cerebral arteries that supply pial vessels (Sorond et al., 2010). In contrast, magnetic resonance imaging (MRI) allows for the evaluation of cerebral blood flow (CBF) throughout the brain. Arterial spin labeling (ASL) is particularly useful as it quantifies CBF by noninvasive generation of an endogenous tracer through magnetic labeling of blood water in the carotids (Borogovac and Asllani, 2012).

A deterioration in cerebrovascular hemodynamics is often accompanied by changes in vessel structure and vascular network architecture, such as the thickening of arteriolar walls that occurs in hypertension (Rizzoni et al., 2009) and the increase in aberrant angiogenesis of the diabetic brain (Prakash et al., 2013a). These structural changes, which result from shear stress and hypoxia, are accompanied by damage to vascular cell layers that cause endothelial cell death (Ergul et al., 2014), microvessel rarefication (Sokolova et al., 1985), and increased blood–brain barrier permeability (Li et al., 2010). Such aberrant changes in vessel structure, coupled with a reduction in cerebrovascular reactivity, increase tissue damage and worsen functional outcomes following stroke in animal models (Li et al., 2013; Prakash et al., 2013b).

Our understanding of the cerebrovasculature has been greatly enhanced by the use of animal models. However, rodent studies often utilize genetically engineered strains to mimic human disease (Russell and Proctor, 2006). Genetic mutations alone rarely cause overt disease in humans whereas in metabolic syndrome and related disorders, diets comprised of ultra-processed foods high in fat, sugar, and sodium, combined with a sedentary lifestyle play a much greater role (Groop, 2000). Consumption of ultra-processed foods, which are food items comprised almost exclusively of processed substances refined from whole foods, has greatly increased in industrialized nations since the 1980s (Monteiro et al., 2013). Unfortunately, common commercial rodent diets focus on isolated nutrients and rarely recapitulate the full gamut of human metabolic syndrome features (Lai et al., 2014). The Cafeteria diet, on the other hand, provides animals with a varied selection of human grocery store, ultra-processed foods and more accurately reflects human disease co-morbidities (Higa et al., 2014; Sampey et al., 2011). We have previously shown that a Cafeteria diet is capable of generating metabolic syndrome in rats, with increased visceral adiposity, dyslipidemia, and insulin resistance (Gomez-Smith et al., 2016). In addition to these peripheral effects, inflammation was also increased in the hippocampus of Cafeteria diet-fed rats. Notably, the metabolic perturbations and hippocampal neuroinflammation were fully resolved by switching animals to a healthy standard chow diet for one month.

To date, cerebrovascular hemodynamics and microvascular structure have not been studied in the Cafeteria diet model of metabolic syndrome despite the clear link between ultra-processed diets and cardiovascular disease risk (Malik et al., 2010). In the current study, we investigated cerebrovascular reactivity to hypercapnia in an established rat model of metabolic syndrome using continuous arterial spin labeling (CASL), a highly sensitive and noninvasive imaging method to evaluate CBF. To further complement these measurements, we examined the structure of the cerebral microvasculature, including vessel area, integrity of the blood–brain barrier (BBB), and susceptibility to an ischemic insult. Cafeteria diet-fed rats were compared to both standard chow-fed rats and rats switched from the Cafeteria to a standard chow diet.

EXPERIMENTAL PROCEDURES

A flow-chart describing the different experiments and the timing of procedures is provided in Fig. 1.

Animals and diets

Animal procedures followed the guidelines established by the Canadian Council on Animal Care and were approved by the Animal Care Committees of the University of Ottawa and the Sunnybrook Research Institute. Experiments have been reported following the ARRIVE guidelines. Three-week-old male Sprague Dawley rats (Charles River Laboratories, Montreal, Canada) were used for all experiments. A total of 48 rats were used in all experiments, 18 for the Magnetic Resonance Imaging experiment and 30 for histological studies. Rats were pair-housed and maintained on a 12-h reverse

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