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Research Paper

Amelioration of Metabolic Syndrome-Associated Cognitive Impairments in Mice via a Reduction in Dietary Fat Content or Infusion of Non-Diabetic Plasma

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ABSTRACT

Obesity, metabolic syndrome (MetS) and type 2 diabetes (T2D) are associated with decreased cognitive function. While weight loss and T2D remission result in improvements in metabolism and vascular function, it is less clear if these benefits extend to cognitive performance. Here, we highlight the malleable nature of MetS-associated cognitive dysfunction using a mouse model of high fat diet (HFD)-induced MetS. While learning and memory was generally unaffected in mice with type 1 diabetes (T1D), multiple cognitive impairments were associated with MetS, including deficits in novel object recognition, cued fear memory, and spatial learning and memory. However, a brief reduction in dietary fat content in chronic HFD-fed mice led to a complete rescue of cognitive function. Cerebral blood volume (CBV), a measure of vascular perfusion, was decreased during MetS, was associated with long term memory, and recovered following the intervention. Finally, repeated infusion of plasma collected from age-matched, low fat diet-fed mice improved memory in HFD mice, and was associated with a distinct metabolic profile. Thus, the cognitive dysfunction accompanying MetS appears to be amenable to treatment, related to cerebrovascular function, and mitigated by systemic factors.

1. Introduction

Diabetes has reached epidemic proportions, and projected rates predict that nearly 600 million people throughout the world will have diabetes within the next 20 years (Guariguata et al., 2014). Type 2 Diabetes (T2D), characterized by obesity and insulin resistance (IR), accounts for over 90% of all diabetes incidence (Engelgau et al., 2004). Aside from traditional complications, T2D poses an additional health risk in the form of cognitive decline and dementia. While learning and memory is generally unaffected during type 1 diabetes (T1D) (Brands et al., 2005), individuals with T2D often demonstrate multiple cognitive impairments (Kodl and Seaquist, 2008) and their risk of developing dementia is significantly increased compared to non-diabetic individuals (Cheng et al., 2012). Furthermore, obesity, IR and metabolic syndrome (MetS) are also associated with decreased cognitive function and an increased risk of dementia even in the absence of overt diabetes (Baker et al.,

Abbreviations: ADMA, Asymmetric dimethylarginine; BW, Body weight; BDNF, Brain-derived neurotrophic factor; Br Fat, Brown adipose tissue; CBV, Cerebral blood volume; C-X-C motif, Chemokine; Cxcl1, Ligand 1; CH, Cholesterol; DG, Diacylglycerol; FFA, Free fatty acids; GLP-1, Glucagon-like peptide 1; GlcCer, Glucosylceramide; HFD, High fat diet; GL, Glycerolipid; GPL, Glycerophospholipid; IR, Insulin resistance; ITT, Insulin tolerance test; IFNγ, Interferon-γ; Il-1b, Interleukin-1β; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-12p70, Interleukin-12p70; LFD, Low fat diet; LPA, Lysophosphatidic acid; MetS, Metabolic syndrome; OGTT, Oral glucose tolerance test; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PG, Phosphatidylglycerol; PGP, Phosphatidylglycerolphosphate; PI, Phosphatidylinositol; PS, Phosphatidylserine; SC Fat, Subcutaneous adipose tissue; KB, Total ketone bodies; TG, Triglycerides; TNFα, Tumor necrosis factor-α; T1D, Type 1 Diabetes; T2D, Type 2 Diabetes; V Fat, Visceral adipose tissue.

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2011; Gunstad et al., 2010; Kim and Feldman, 2015; Matsuzaki et al., 2010; Schrijvers et al., 2010).

Sedentary lifestyle and caloric excess are the primary contributors to obesity, which in turn is the major modifiable risk factor for MetS and T2D (Ershow, 2009). Thus, diet-induced obesity comprises a critical risk factor for the development of cognitive impairment. Weight loss is associated with improvements in general metabolism, vascular function and cardiovascular mortality (Bigornia et al., 2010; Sjöström et al., 2012). While less clear, evidence suggests that the benefits of weight loss may also extend to cognitive performance (Espeland et al., 2014) and the risk of developing dementia (Siervo et al., 2011). In addition to an inverse association between IR and memory, a possible association between improved insulin sensitivity and improved cognition would suggest that IR plays an important role during cognitive decline (Brinkworth et al., 2009; Witte et al., 2009). Thus, lifestyle changes such as weight loss may represent an effective therapeutic approach to preventing or ameliorating cognitive decline due to their established benefits on insulin sensitivity and endothelial function (Blumenthal et al., 2010; Mavri et al., 2011; Rudofsky et al., 2011). However, controlled long-term studies in humans are challenging, and the mechanisms of action remain undetermined.

While the precise biological mechanisms by which obesity and weight loss affect cognitive function are unclear, several plausible pathways exist, including oxidative stress, inflammation, metabolic impairments and vascular dysfunction (Bruce-Keller et al., 2009). Of these potential mechanisms, cerebrovascular function represents an intriguing potential link between diabetes and cognition, as individuals with T2D show deficits in the maintenance and regulation of cerebral blood flow (CBF) compared to non-diabetic controls (Kim et al., 2008; Novak et al., 2006).

Multiple studies have demonstrated varying neurobiological deficits and cognitive impairments in rodent models of obesity, IR and diabetes (Gault et al., 2010; Li et al., 2002; Stranahan et al., 2008a, 2008b; Winocur et al., 2005). In the present study, we employed a commonly used mouse model of chronic high fat diet (HFD) consumption in order to assess whether the cognitive impairments associated with MetS can be mitigated. The prevalence of cognitive impairment is higher in women (Hebert et al., 2013), and while age is the strongest risk factor for cognitive decline and dementia, it has become increasingly clear that cognitive decline in late life is due in large part to vascular risk factors such as diabetes during middle age (Debette et al., 2011). Therefore, we induced MetS through chronic administration of a HFD in "middle aged" female mice and analyzed the metabolic, cognitive and cerebrovascular effects of MetS during old age. We then tested the restorative potential of weight loss and improvements in peripheral metabolism on cerebrovascular function and cognition by reducing the dietary fat content in HFD-fed mice over a one month period.

Given the established peripheral vascular impairments associated with T2D and the importance of cerebrovascular function for cognition, it is plausible that circulating factors could affect brain function during T2D. In fact, past studies involving shared circulations suggest that systemic factors can modulate obesity and T2D (Coleman, 2010). Additionally, there has been increased interest in the role of systemic factors in modulating health during old age, as a series of studies have shown that young blood has numerous rejuvenating properties (Loffredo et al., 2013; Ruckh et al., 2012; Salpeter et al., 2013). These studies strongly suggest that factors present in a young systemic circulation are able to reverse certain aspects of aging, including brain function (Katsimpardi et al., 2014; Villeda et al., 2014). For example, exposure to young blood enhanced neuronal spine density and synaptic plasticity (Villeda et al., 2014) and induced vascular remodeling and neurogenesis (Katsimpardi et al., 2014) in old mice. Additionally, pancreatic beta cells exposed to a young systemic circulation demonstrate increased replication (Salpeter et al., 2013). To date, these experiments have all focused on aging and age differences between donors and recipients, and the therapeutic capacity of systemic factors has yet to be explored in the context of specific disease states and age-matched donors and recipients. Therefore, to assess whether similar cognitive benefits extend beyond aging to the context of MetS, we tested the hypothesis that repeated infusion of "healthy" plasma collected from age-matched, low fat diet (LFD)-fed mice could improve cognitive function in mice with MetS.

2. Materials and Methods

2.1. Experimental Animals and Diet

Wild type female mice on a C57BL/6 background (Jackson Labs) were employed in this study. Female mice were used as the prevalence of cognitive impairment is higher in women (Hebert et al., 2013). Additionally, vascular risk factors during middle age drive development of dementia in later life (Debette et al., 2011). Therefore, mice were fed a specialized diet beginning at 9 months of age, and metabolic and cognitive analyses were carried out at 14 and/or 15 months of age. T1D was induced by five days of sequential intraperitoneal low-dose streptozotocin (STZ) injections, at 12 months of age, as described (Johnson et al., 2011). Obesity and MetS were induced by administration of a high fat diet (HFD) (60% kcal from fat, Research Diets D12492, New Brunswick, NJ, USA). Control mice (and T1D mice) were fed an ingredient-matched low fat diet (LFD) (10% kcal from fat, Research Diets D12450B). The constituent components of the employed diets are shown as follows (Ingredient (grams in HFD; grams in LFD)): Casein (200; 200), L-cystine (3; 3), corn starch (0; 315), maltodextrin 10 (125; 35), sucrose (68; 350), cellulose BW200 (50; 50), soybean oil (25; 25), lard (245; 20), mineral mix S10026 (10; 10), di-calcium phosphate (13; 13), calcium carbonate (5.5; 5.5), potassium citrate (16.5; 16.5), vitamin mix V10001 (10; 10), choline bitartrate (2; 2) and FD&C dye #1 (blue 0.05; yellow 0.05). Metabolic and behavioral measures (with the exception of the water maze involving multiple platform locations) were completed in one cohort of mice, while a second cohort was employed for the water maze involving multiple platform locations and cerebral blood volume measures, and a final cohort employed for the plasma infusion studies. All mice were housed on a 12 hour light/dark cycle (5:00 AM–5:00 PM). Plasma samples for fasting metabolic measures were taken at ~1:00 PM following a four hour fast. Periods of 4 to 6 h of fasting are considered to be adequate for a definition of fasting in mice as it avoids massive reduction in body fat content and glycogen stores (Mutel et al., 2011; Pacini et al., 2013). Behavioral tests were typically assessed beginning at ~9:00 AM. For adipose tissue measurements, the left epididymal fat pad (visceral) and left inguinal fat pad (subcutaneous) were weighed. All procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with IACUC approval at Oregon Health & Sciences University.

2.2. Biochemical Measurements

For the glucose tolerance test, mice were administered an oral gavage of glucose solution (2 mg/g body weight). For the insulin tolerance test, mice were intravenously injected with 0.75 U/kg of human insulin (Gibco). Blood glucose was measured using a glucometer (One Touch Ultra) at indicated time points. Plasma triglycerides (Cayman Chemicals), free fatty acids (ZenBio), glucose, total cholesterol and ketone bodies (Wako), and plasma insulin (Millipore) were measured following a four-hour fast. GLP-1 was measured using a commercial ELISA (RayBioTech). Plasma protein levels of interferon-γ, interleukin-1β, interleukin-6, KC/GRO (Cxcl1), interleukin-10, interleukin-12p70 and tumor necrosis factor-α were assessed in a sandwich immunoassay format (7-Plex assay kit) according to the manufacturer's instructions (MesoScale Discovery). For glucose uptake, mice were injected following a four hour fast with 0.75 μCi of 2-[1,2-^{3}H (N)]-deoxy-D-glucose (Perkin Elmer), diluted in 100 μl of 0.25 g/ml glucose solution, via the tail vein. Twenty minutes after injection, mice were intraperitoneally administered a lethal dose of