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Research report

Brain and behavioral perturbations in rats following Western diet access ☆

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ABSTRACT

Energy dense "Western" diets (WD) are known to cause obesity as well as learning and memory impairments, blood–brain barrier damage, and psychological disturbances. Impaired glucose (GLUT1) and monocarboxylate (MCT1) transport may play a role in diet-induced dementia development. In contrast, ketogenic diets (KD) have been shown to be neuroprotective. We assessed the effect of 10, 40 and 90 days WD, KD and Chow maintenance on spontaneous alternation (SA) and vicarious trial and error (VTE) behaviors in male rats, then analyzed blood glucose, insulin, and ketone levels; and hippocampal GLUT1 and MCT1 mRNA. Compared to Chow and KD, rats fed WD had increased 90 day insulin levels. SA was decreased in WD rats at 10, but not 40 or 90 days. VTE was perturbed in WD-fed rats, particularly at 10 and 90 days, indicating hippocampal deficits. WD rats had lower hippocampal GLUT1 and MCT1 expression compared to Chow and KD, and KD rats had increased 90 day MCT1 expression compared to Chow and WD. These data suggest that WD reduces glucose and monocarboxylate transport at the hippocampus, which may result in learning and memory deficits. Further, KD consumption may be useful for MCT1 transporter recovery, which may benefit cognition.

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Introduction

In the United States more than one in three adults and one in six children can be classified as obese (Flegal, Carroll, Ogden, & Curtin, 2010; Ogden, Carroll, Kit, & Flegal, 2014). Obesity during childhood typically persists into adulthood (Deshmukh-Taskar et al., 2005; Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008), and is associated with increased disease risk as well as neurological and psychological deficits (Agranat-Meged et al., 2005; Cserjési, Molnár, Luminet, & Lénárd, 2007; Kamijo et al., 2014; Yau, Castro, Tagani, Tsui, & Convit, 2012).

Though obesity and the metabolic syndrome can develop via multiple routes, there is evidence that "Western" diets (WD) high in fat and sugar play a substantial role in their etiologies, as well as the often comorbid learning and memory deficits. In adult humans, WD not only induces weight gain, but also increases risk for dementia (de la Monte, 2009; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005). Hippocampal function appears to be particularly vulnerable to dietary insult. For example, adult rats fed WD diet show impairments on radial maze learning (Kanoski, Zhang, Zheng, & Davidson, 2010), Morris water maze performance (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Pistell et al., 2010; Stranahan et al., 2008; Wu, Ying, & Gomez-Pinilla, 2004), spontaneous alternation (Kaczmarczyk et al., 2013), deprivation-discrimination learning (Sample, in this issue), reversal learning (Kanoski, Meisel, Mullins, & Davidson, 2007); and feature negative discrimination (Davidson et al., 2012, 2013; Kanoski et al., 2010) but are not impaired on tasks such as simple discrimination and non-spatial maze learning, which do not depend on the hippocampus (Davidson et al., 2013; Kanoski et al., 2007, 2010). WD also reduces hippocampal BDNF (Molteni et al., 2002; Wu et al., 2004) and increases hippocampal blood–brain barrier (BBB) permeability (Davidson et al., 2012, 2013; Kanoski et al., 2010).

These deficits do not appear to be specific to adult animals. In juvenile rats, two months WD exposure is associated with impairments in spatial reference memory on the Morris water maze, delayed spatial reference learning, and an enhancement of lipopolysaccharide (LPS)-induced inflammation in the hippocampus (Boitard et al., 2012, 2014). Compared to their lean counterparts, obese human children also show impairments in academic performance and deficits in the inhibitory "NoGo" task (Kamijo et al., 2012), while adolescents with the metabolic syndrome have lower overall IQ, impaired attentional abilities, reduced mental flexibility, smaller hippocampal volumes, and damaged white matter tracts (Yau et al.,

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2012), suggesting that the hippocampus is vulnerable to dietary insults throughout development.

We have noted previously (Davidson et al., 2013; Kanoski et al., 2007) that diet composition plays a significant role in the development of these cognitive deficits. We have also noted that rats fed a very high fat ketogenic diet (KD) did not show hippocampal impairments when circulating ketone bodies were high, despite markedly increased body adiposity levels (Davidson et al., 2013).

KD is known to be an effective treatment for many types of epilepsy (Barañano & Hartman, 2008; Kwon, Jeong, Kim, Choi, & Son, 2008; Lutas & Yellen, 2013), and has been shown to exert numerous other neurological benefits. For instance, peripheral inflammation was significantly reduced in obese men after 12 weeks maintenance on KD (Forsythe et al., 2008), even prior to the onset of weight loss (Sharman et al., 2002; Sharman & Volek, 2004; Volek et al., 2004). Adults with Alzheimer's disease, probable Alzheimer's disease, mild cognitive impairment, and age-associated memory impairments have demonstrated improvements after consuming AC-1202, a medical food known to increase circulating ketone levels (Costantini, Vogel, Barr, & Henderson, 2007; Henderson et al., 2009).

Ketones act as an alternate energy source for neurons, particularly when there are problems with glucose transport. In De Vivo syndrome, which is characterized by a mutation to the SLC2A-1 gene, GLUT1 transporter levels are reduced or abolished, thereby preventing glucose from crossing the BBB. Individuals with De Vivo syndrome have a cluster of neurological and behavioral symptoms, including seizures, developmental delays, and cognitive deficits that include spatial deficits, suggesting that the hippocampus may be particularly affected by this condition (Akman et al., 2010; De Vivo & Wang, 2008). The majority of these symptoms can be improved or averted via maintenance on KD (Friedman et al., 2006; Ramm-Pettersen, Stabell, Nakken, & Selmer, 2014). This suggests that many of the deficits in De Vivo syndrome are not due to reduced glucose transport *per se*, but a general energy deficit within the brain which can be overcome by switching to a ketone metabolism.

Under normal circumstances, GLUT1 expression increases in response to low, and decreases in response to high, circulating glucose levels, thereby maintaining glucose homeostasis within the brain interstitial fluid (Kumagai, Kang, Boado, & Pardridge, 1995; Pardridge, Triguero, & Farrell, 1990). When glucose levels are low, the primary source of energy for neuronal tissues becomes monocarboxylates, which include lactate, pyruvate, leucine, and ketone bodies such as beta-hydroxybutyrate (BHB), all of which are escorted across the BBB via the MCT1 transporter, which unlike GLUT1 is typically regulated via positive feedback mechanisms in proportion to monocarboxylates (Cortes-Campos et al., 2011; Nehlig, 2004; Vannucci & Simpson, 2003). Therefore, under conditions of starvation (where glucose levels are low, but ketone bodies are relatively high), expression of both GLUT1 and MCT1 is increased. Low levels of both transporters have been associated with cognitive deficits (De Vivo & Wang, 2008; Ding, Yao, Rettberg, Chen, & Brinton, 2013). Low GLUT1 levels have been measured in patients with AD (Bailey, Rivara, Rocher, & Hof, 2004; Mooradian, Chung, & Shah, 1997; Wu et al., 2005), particularly in regions such as the hippocampus and neocortex (Kalaria & Harik, 1989); MCT1 levels are significantly lower in mouse models of AD (Ding, Yao, Rettberg et al., 2013).

While it is unknown whether this is the result of degeneration at the neurovascular unit or an adaptive response to chronic hyperglycemia, it is clear that AD and related syndromes are associated with progressive reductions in glucose metabolism at the hippocampus and cortex (de la Monte, 2009; Mosconi, 2005; Mosconi et al., 2009), which suggests that the dementia-afflicted neurons may be deprived of energy for extended periods of time. Because GLUT1 and MCT1 transporters can be regulated quickly and play a role in cognitive function, we hypothesized that they may play a role in WD-induced cognitive deficits.

These experiments were conducted with three objectives in mind. First, we assessed the role of short- (10 day), moderate- (40 day) and long-term (90 day) exposure to WD and KD on body weight, markers of the metabolic syndrome, and circulating BHB levels. Our second goal was to determine the relationship between diet and exposure duration on behavior. We accomplished this by analyzing spontaneous alternation (SA) behavior, a task which is noninvasive and, importantly, requires no food restriction. Because we wished to investigate changes in hippocampal functioning as a result of diet, we assessed vicarious trial and error (VTE) behaviors during the SA task.

VTE is measured by recording the total number of head turns an animal performs at choice points during a maze task. There is evidence (Schmidt, Papale, Redish, & Markus, 2013) that these behaviors are analogous to the "mental time travel" humans engage in during task acquisition (Suddendorf & Corballis, 2007), whereby an individual accesses declarative memories of past events in order to predict future outcomes. During planning and goal-directed learning, the hippocampus is strongly activated (Addis, Moscovitch, & McAndrews, 2007; Addis & Schacter, 2008; Buckner & Carroll, 2007), and animals with hippocampal lesions do not engage in VTE behaviors (Hu & Amsel, 1995; Voss et al., 2011). Therefore, this measure served as an index of hippocampal involvement.

Finally, because we hypothesized that high circulating glucose levels could decrease expression of GLUT1 transporter at the hippocampus, and because we were interested in the effects of WD and KD on the MCT1 transporter, we performed qPCR on hippocampal homogenates for GLUT1 and MCT1 mRNA expression.

Materials and methods

Animals and diets

Male Sprague-Dawley rats (n = 93; Harlan Laboratories, Indianapolis, IN) weighing between 275 and 300 g were housed individually in hanging-wire cages in a temperature- and humidity-controlled room, and maintained on a 12 h light/dark cycle. Rats were provided with *ad libitum* tap water. All procedures were approved by the Purdue University Animal Care and Use Committee.

Animals were handled for two weeks prior to experimentation, and regular body weight measurements began six days prior to experimental diet administration. During the acclimation period, rats were maintained on standard chow (2018, Harlan Teklad, Indianapolis, IN), after which they were weight-matched into diet treatment groups. Diets included Chow, a high-fat, high-dextrose "Western" diet (WD; Harlan TD.10768), and a low-carbohydrate, high-fat ketogenic diet (KD; Research Diets, New Brunswick, NJ; D06040601); for macronutrient composition, see Table 1. Rats from each diet group were then matched into groups based on exposure duration, and were fed their diets *ad libitum* for 10 (n = 10 per diet), 40 (n = 10 per diet) or 90 (n = 11 per diet) days, except for the two hours immediately prior to glucose testing and sacrifice. For Chow and WD rats, food was delivered in stainless steel hoppers. KD rats received their food in small, enameled cups, which were

Table 1
Macronutrient composition of diets.

	Chow Harlan 2018	**WD** Harlan TD.10768	**KD** Research Diets D06040601
% kCal fat	18	38	80
% kCal dextrose	–	20	–
% kCal other carb.	58	18	5
% kCal protein	24	24	15
Caloric density	**3.4 kCal/g**	**4.5 kCal/g**	**6.1 kCal/g**

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