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Brief Report

Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women☆,☆☆

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ABSTRACT

Background. Previous literature suggests that a higher ratio of palmitic acid (PA)/oleic acid (OA) in the diet induces inflammation, which may result in deficient brain insulin signaling, and, secondarily, impaired physical activity, sleep efficiency, and cognitive functioning.

Objective. We hypothesized that lowering the typical dietary PA/OA would affect the activation of relevant brain networks during a working memory task and would also lower secretion of pro-inflammatory cytokines.

Design. In 12 female subjects participating in a randomized, cross-over trial comparing 3-week high PA diet (HPA) and low PA and a high OA diet (HOA), we evaluated functional magnetic resonance imaging (fMRI) using an N-back test of working memory, cytokine secretion by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC), and plasma cytokine concentrations.

Results. Brain activation during the HPA diet compared to the HOA diet was increased in regions of the basal ganglia including the caudate and putamen ($p < 0.005$). In addition, compared to the HOA diet, during the HPA diet, the plasma concentrations of IL-6 ($p = 0.04$) and IL-1β ($p = 0.05$) were higher, and there was a higher secretion of IL-18 ($p = 0.015$) and a trend for higher IL-1β secretion ($p = 0.066$) from LPS-stimulated PBMCs.

Abbreviations: FA, fatty acid; fMRI, functional magnetic resonance imaging; HOA, low PA, high OA diet; HPA, high PA diet; IL, interleukin; LPS, lipopolysaccharide; MUFA, monounsaturated fatty acids; NLRP3, nucleotide oligomerization domain (NOD)-like receptor protein; OA, oleic acid; PA, palmitic acid; SFA, saturated fatty acids; TLR4, toll-like receptor-4; TNFα, tumor necrosis factor-α.

☆ This study has been registered at http://www.clinicaltrials.gov/ as University of Vermont Protocol Record R01DK082803.

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Conclusions. The HPA diet resulted in increased brain activation in the basal ganglia compared to the HOA diet as well as increased secretion of pro-inflammatory cytokines. These data provide evidence that short-term (2 week) diet interventions impact brain network activation during a working memory task and that these effects are reversible since the order of the study diets was randomized. These data are consistent with the hypothesis that lowering the dietary PA content via substitution with OA also could affect cognition.

1. Introduction

Cognition comprises a number of brain processes including memory, attention, problem-solving, and decision-making. Neuroscientists and physicians as well as lay people are interested in environmental factors that might enhance or impair cognition at any age, including diet, physical exercise, and sleep efficiency. Variations in dietary content of the saturated fatty acid (SFA), palmitic acid (PA; C16:0) and the monounsaturated FA (MUFA), oleic acid (OA; C18:1 n-9 or ω-9) have been linked to alterations in cognitive function in humans [1,2].

Specifically, Samieri et al. [1] reported the results of a sub-study conducted as part of a double-blind, placebo-controlled factorial trial of low dose aspirin and vitamin E supplements for the primary prevention of cardiovascular disease and cancer in women (Women's Health Study). Subjects aged ≥65 years underwent initial cognitive testing and then again at two follow-up points at approximately two-year intervals [1]. Based on the trajectory of change in cognitive function, global cognition and verbal memory were enhanced as a function of the MUFA/SFA ratio, particularly when comparing the extreme quintiles, respectively 0.9 and 1.3 [1].

In our previously published studies, we reported the results of a diet history obtained from our young adult volunteers in two separate cohorts during screening. Our subjects' "habitual" intake resulted in a MUFA/SFA ratio of 0.83 (Cohort 1) and 1.08 (Cohort 2) [3], similar to the lowest three quintiles of the Samieri study [1]. In two separate trials, we used the same, cross-over study paradigm in which we markedly lowered the PA intake by substituting OA, resulting in two highly contrasting MUFA/SFA ratios, one, the "HPA diet", (0.88) similar to the lowest quintile in the study by Samieri et al. [1] and to our subjects' "habitual diet" and a low PA/high OA diet ("HOA") with a ratio (10.1) [3,4] much higher than those in the fifth quintile of participants in the Women's Health Study. In these two distinct cohorts of young adults, we have studied the effects of lowering the PA intake on a number of outcome variables including insulin sensitivity, inflammation, physical activity, mood, muscle gene expression, and blood lipid profiles [3–6]. Notably, lowering the dietary PA/OA ratio increased physical activity and lowered mood disturbance [3].

Prior studies also have shown links between MUFA/SFA changes and behavioral and cognitive outcomes. Sartorius et al. [7] showed that a high SFA diet in mice as well as acute intraventricular injection of PA decreased activation of insulin signaling in the brain, decreased locomotor activity in response to acute intraventricular injection of insulin, and disrupted normal wakefulness and sleep behavior compared to a high MUFA diet. Blocking the activity of interleukin (IL)-6 in mice fed the high SFA diet enhanced physical activity [8]. Hanson et al. [2] found that feeding older adults a single meal high in both SFA and high glycemic load carbohydrates improved and impaired cognition acutely, respectively, in those with or without cognitive impairment. Other studies suggest that a high SFA diet adversely affects the hippocampus and memory in rats, possibly via induction of inflammatory pathways [9]. It is relevant to specifically emphasize our findings that lowering the habitual dietary PA/OA ratio (same as raising the MUFA/SFA ratio) was associated with lower circulating concentrations of IL-6 and tumor necrosis factor-α (TNFα) and lower secretion of IL-1β, IL-18, and TNFα by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs) [4,5].

In view of evidence that shifts in the dietary MUFA/SFA ratio affect cognition in the general population [1] and our own data relating to the reversible effects of this ratio on physical activity behavior and mood [3], we hypothesized that diets high or low in PA would differentially activate brain networks associated with working memory using functional magnetic resonance imaging (fMRI) as well as affect systemic inflammation.

2. Materials and Methods

2.1. *Subjects, Screening, and Design*

This study was approved by the University of Vermont (UVM) Institutional Review Board (IRB). The clinical aspects were managed at the UVM Clinical Research Center (CRC) and the imaging was completed at the UVM MRI Center for Biomedical Imaging. The subjects were derived from a subset of young adults participating in a randomized, double-masked, cross-over study of lean and obese adults in order to determine how dietary PA intake affected PA oxidation, insulin sensitivity, and inflammatory signaling ("parent protocol"), but our priorities for recruitment of women for the larger study necessitated our studying only women with respect to this sub-study using fMRI [5,10]. Supplementary Fig. 1 depicts the consort diagram for this sub-study. Twelve, healthy, lean or obese, but non-diabetic women aged 18–40 years were recruited (age range: 20–36 years, mean ± SEM = 26.5 ± 1.3 years; body mass index >18 < 25, n = 7, or >30, n = 5). Exclusion criteria were similar to our previous studies [5,10,11].

As previously reported [6], we used two dietary history techniques to assess our subjects' habitual intake. In the