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High-fat diets, insulin resistance and declining cognitive function

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Abstract

Results from our work in rats and others findings from human epidemiologic studies demonstrate deficits in cognitive performance following chronic ingestion of high fat, high saturated fat, diets. Yet, the precise physiologic mechanism underlying these deficits is not well understood. We report that older adults with insulin resistance show remarkably similar deficits in cognitive function and respond to glucose ingestion in a comparable manner to rodents fed a high-fat diet, suggesting that insulin resistance is a probable mediator of these diet-induced deficits. As insulin resistance worsens to overt type 2 diabetes, profound deficits in cognitive functions, especially those dependent on the medial temporal lobes, are apparent in both obese Zucker rats and humans with type 2 diabetes. Unlike the older adult with insulin resistance, glucose ingestion further impairs medial temporal lobe function in adults with type 2 diabetes. Collectively, the human and rodent data point to a role of diet-induced endocrine abnormalities, including the development of insulin resistance, as mediating the cognitive deficits associated with high fat consumption.
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1. Introduction

Numerous lifestyle characteristics, including diet, contribute to the risk of cognitive decline and dementia with aging. While study results have clear public health implications, elucidating mechanisms linking diet to cognitive dysfunction is more complicated. That is, diet quality may have direct effects on neuronal function but at the same time can be a major contributor to other chronic diseases, including type 2 diabetes mellitus (DM2), cardiovascular disease, hypertension and depression, all of which are considered independent risk factors for cognitive decline and dementia. Thus, it is unclear whether diet directly impacts on brain function or mediates its effects indirectly through risk modification of other chronic diseases.

Our studies identified that elevated dietary fat intake, especially saturated fatty acid intake, contributes to cognitive deficits in rats, with functions governed by the hippocampus and surrounding structures showing extreme vulnerability (for reviews, see [22,48]). This review compares results from the animal work with our studies in older adults with insulin resistance and DM2, leading to the hypothesis that at least one mechanism linking high fat, high saturated fat, intake to cognitive impairment is through the development of insulin resistance.

2. Human epidemiologic studies

Human epidemiologic studies report both adverse and protective effects of dietary fat intake, depending upon the

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quantity and quality of fat consumed. In both cross-sectional and prospective human epidemiologic studies of older adults, high fat intake, especially omega-6 and saturated fatty acids, associated with poorer performance on a variety of cognitive tasks [19,21,36,38]. Additionally, prospective studies have identified high fat intake, especially saturated and trans-unsaturated fats, as a risk factor for Alzheimer disease (AD) [20,28,34]. Since the level of dietary fat (40% of energy) used in our rat studies was designed to represent upper ranges of human consumption profiles, the parallel evidence from human and rodent studies helps validate our rodent model of the human experience.

By contrast, some [1,20,26,35], but not all [9,27], human prospective epidemiologic studies indicate that a high intake of omega-3 fatty acids and/or weekly intake of fish are both associated with lower AD risk. These findings are supported by studies indicating that AD patients have reduced plasma levels of omega-3 fatty acids [4,46]. While our own studies have not addressed the role of fish oils, others report protective effects of fish oil consumption in mouse models of AD (reviewed in [3]).

Thus, the collective evidence suggests a protective effect of diets which are low in overall fat content, but where the fat consumed has a high content of omega-3fatty acids, especially fish oils. Since this dietary fat profile has been implicated in the protection against numerous chronic diseases, we hypothesized that the primary impact of high-fat diets on cognitive function was mediated through promotion of other chronic diseases. On the basis of this hypothesis, we predicted that cognitive deficits similar to those apparent in our high-fat fed rodents would be observed in humans with either insulin resistance or DM2.

3. Role of insulin resistance

Numerous other papers in this supplement address the association between insulin resistance, DM2 and decline in cognitive function (see e.g. [2,8,32]) as well as potential biologic mechanisms that may be involved (see e.g. [5,6,39]) and consequently will not be reviewed here. We reported that even in healthy seniors, prior to the development of DM2, those individuals with poor glucose control (measured as incremental glucose area under the curve following ingestion of 50 g of glucose (gAUC)) perform worse on a variety of tasks including verbal memory [23,24] and that higher levels of haemoglobin A1c, an indicator of poor glucose control, were associated with poorer verbal memory in older adults with DM2 [15]. That is, measures of glucose control associate more strongly with cognitive tasks, such as verbal memory, that are dependent on the hippocampus and surrounding structures. Furthermore, cognitive deficits are observed throughout the continuum of declining glucose-regulatory status through to overt diabetes.

These findings parallel our results in rats fed high-fat diets [48] and in Zucker obese and insulin resistant rats [49]. Importantly, our Zucker obese rats were fed laboratory chow and not high-fat diets suggesting that the impact of high-fat diets may not be mediated directly through fat consumption per se. Rather, a common factor, such as insulin resistance, best explains our rodent and human findings.

More recently, we showed that even minor changes in glucose tolerance, which occur throughout the day, may impact cognitive function [17]. In collaboration with our colleague, Lynn Hasher, a group of 22 healthy adults, aged 73.5 ± 6.7 (mean $\pm$ S.D.), were tested on a variety of cognitive tasks, including paragraph recall and Stroop, to assess verbal memory and inhibitory control, respectively. Subjects were tested in both the morning and afternoon. On separate days, they consumed a 50 g glucose drink, again in the morning and afternoon, and blood glucose levels were assessed over a 2-h period. Consistent with other reports of declining glucose tolerance throughout the day (reviewed in [33]), the gAUC was greater in the afternoon relative to morning ($F_{1,20} = 12.56$, $p = 0.002$; Fig. 1). Cognitive performance was also poorer in the afternoon than in the morning, on both the paragraph recall (time of day: $F_{1,60.2} = 3.89$, $p = 0.053$; time of day $\times$ delay: $F_{1,60.2} = 0.07$, $p = 0.793$) and the inhibitory component of the Stroop task (Interference: $F_{1,59} = 4.87$, $p = 0.031$). Thus, while others report circadian rhythms in cognitive performance, with better performance in the morning in older adults [18] and rats [50], results from this study suggest that these circadian changes in cognitive function may occur in tandem with metabolic rhythms, including glucose tolerance, which also occur throughout the day.

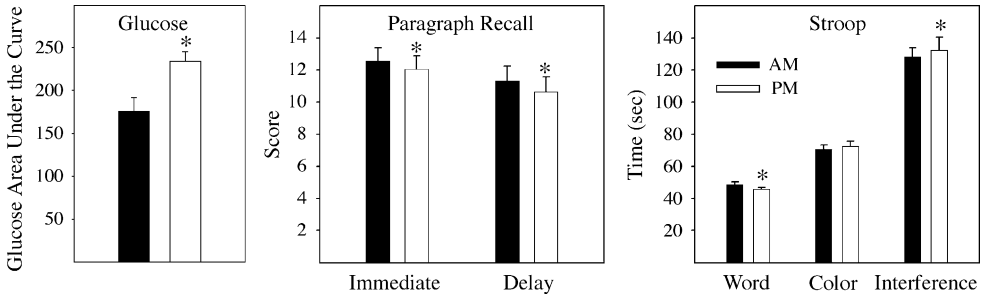

Fig. 1. Circadian changes in glucose tolerance and cognitive performance in healthy older adults. * Significant differences between morning and afternoon measures ($p < 0.05$).

Collectively, these data suggest that declining glucose-regulatory status is associated with poorer cognitive function and that even a minor decline in glucose-regulatory status contributes to a loss of cognitive function.

4. Insulin resistance, type 2 diabetes and response to glucose

Previous studies indicate that glucose enhances cognitive function and that this enhancement is most notable in individuals with lower levels of cognitive function, including older adults, and in tasks associated with hippocampal function (reviewed in [12,14,31]). Paradoxically, more robust response to glucose is observed in individuals with declining glucose-regulatory status compared to those with better glucose tolerance (see e.g. [23]). Such a parallel is observed in our animal studies, where rats fed high-fat diets showed improved performance on a variable interval delayed alternation task following glucose injections, with the most memory demanding components of the task demonstrating the greatest response to glucose administration; yet, this glucose-induced enhancement was absent in rats fed normal laboratory chow [16].

Interestingly, this beneficial effect of glucose ingestion in those with poor glucose control is no longer evident in those with DM2. Rather, acute hyperglycemic episodes in adults with DM2 result in transitory cognitive dysfunction. Specifically, hyperglycemia induced by either ingestion of 50 g of carbohydrate as a high-glycemic index carbohydrate meal [15] or implementation of a hyperinsulinemic/hyperglycemic clamp [43] result in transitory cognitive dysfunction. Even normal hyperglycemic fluctuations experienced throughout the day in adults with DM2 have a negative impact on cognitive performance [30]. Thus, glycemic variations typically experienced in individuals with DM2, especially during the postprandial period, can be of sufficient magnitude to cause deterioration in cognitive function.

Collectively, the results suggest that mild increases in blood glucose levels are associated with cognitive enhancement. However, once glucose levels rise beyond a certain critical level, the benefits of glucose ingestion are not only absent, but frank declines in function are apparent. Numerous mechanisms have been proposed to explain the association between glucose ingestion and cognitive enhancement, all of which relate, on at least one level, to enhanced neuronal metabolism and transmission, be it through provision of energy, precursors for acetylcholine synthesis, or increased insulin signaling [7,13,31,47]. Yet, the mechanisms underlying the glucose-induced deficits in cognitive function in those with diabetes are still under investigation (reviewed in [30]). Hyperglycemia is associated with numerous events which could negatively impact on brain within the timeframe associated with meal ingestion. This includes a glucose-induced increase in oxidative stress, which in turn can lead to increased inflammatory cytokine [10,37] and/or cortisol release [25,37,45]. Since many adults with DM2 already have elevated levels of inflammatory cytokines [44] and/or cortisol [42], the additional hyperglycemia-induced surge in these factors may be sufficient to suppress cognitive function [29,41]. Alternatively, our results [49] and those from others [11] in obese Zucker rats provide evidence that hippocampal insulin signaling is impaired, at least in this animal model. The degree to which impaired insulin signaling may contribute to the underlying cognitive deficit in the face of diabetes is under investigation [39,40], and indeed may also contribute to deficits associated with glucose-stimulated insulin secretion.

5. Summary

Results from both rodent and human studies provide evidence that chronic consumption of high-fat diets is associated with increased risk of cognitive decline and dementia. One mechanism potentially linking high-fat diets to cognitive deficits is the development of insulin resistance and/or DM2. In turn, the myriad of endocrine abnormalities apparent in those with insulin resistance or DM2 can adversely affect cognitive function, both under chronic situations and in response to meal ingestion. Given the increasing North American prevalence not only of DM2, but more importantly of the metabolic syndrome, unless public health measures to improve health status are effectively undertaken, incidence rates of cognitive deficits and dementia may rise.

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