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A human model of dietary saturated fatty acid induced insulin resistance

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ABSTRACT

Background. Increased consumption of high-fat diets is associated with the development of insulin resistance and type 2 diabetes. Current models to study the mechanisms of high-fat diet-induced IR in humans are limited by their long duration or low efficacy. In the present study we developed and characterized an acute dietary model of saturated fatty acid-enriched diet induced insulin resistance.

Methods. High caloric diets enriched with saturated fatty acids (SFA) or carbohydrates (CARB) were evaluated in subjects with normal and impaired glucose tolerance (NGT or IGT). Both diets were compared to a standard eucaloric American Heart Association (AHA) control diet in a series of crossover studies. Whole body insulin resistance was estimated as steady state plasma glucose (SSPG) concentrations during the last 30 min of a 3-h insulin suppression test.

Results. SSPG was increased after a 24-h SFA diet (by 83 ± 74% vs. control, n = 38) in the entire cohort, which was comprised of participants with NGT (92 ± 82%, n = 22) or IGT (65 ± 55%, n = 16) (all $p < 0.001$). SSPG was also increased after a single SFA breakfast (55 ± 32%, $p = 0.008$, n = 7). The increase in SSPG was less pronounced after an overnight fast following a daylong SFA diet (24 ± 31%, $p = 0.04$, n = 10), and further attenuated 24 h after returning to the control diet (19 ± 35%, $p = 0.09$, n = 11). SSPG was not increased after a 24-h CARB diet (26 ± 50%, $p = 0.11$, n = 12).

Conclusions. A short-term SFA-enriched diet induced whole body insulin resistance in both NGT and IGT subjects. Insulin resistance persisted overnight after the last SFA meal and was attenuated by one day of a healthy diet. This model offers opportunities for identifying early mechanisms and potential treatments of dietary saturated fat induced insulin resistance.

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Abbreviations: CARB, high-carbohydrate diet; GIR, glucose infusion rate; IGT, impaired glucose tolerance; IST, insulin suppression test; MUFA, monounsaturated fatty acids; NEFA, non-esterified fatty acids; NGT, normal glucose tolerance; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; SSPG, steady-state plasma glucose.

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1. Introduction

Insulin resistance is an early and major metabolic abnormality underlying development of type 2 diabetes [1]. It is also closely linked with a variety of conditions, including dyslipidemia, hyperglycemia, hypertension and inflammation which increase the risk for cardiovascular disease. Excess caloric intake, in concert with insufficient physical activity, is a major driver of obesity and insulin resistance [2]. Although excessive intake of all macronutrients can lead to obesity, there has been particular attention paid to the ability of high fat diets to induce insulin resistance.

In addition to the nearly 2-fold higher energy density of fat, elevated circulating free fatty acids have been identified as one of the principal mechanisms of obesity-induced impairment of insulin action [3–5]. Consistent with this hypothesis, short-term infusions of fatty acid emulsions for 3–6 h induces insulin resistance [5–8] while pharmacologically lowering plasma free fatty acids levels improves insulin action [9,10].

Although free fatty acids are important players in the development of insulin resistance, appropriate models to study dietary fatty acid-induced insulin resistance in humans are lacking. While weeks to months of *isocaloric* high fat diets reproducibly induce insulin resistance in animal models [11,12], even modest overfeeding with high-fat diets in humans has had mixed or at best modest effects on insulin resistance [13–15]. It generally takes weeks of a substantial *hypercaloric* high-fat diet to begin to increase plasma glucose, insulin or insulin resistance in humans [16–18]. Such studies are almost universally associated with weight gain, which makes distinguishing the effects of nutrient content vs. weight gain nearly impossible. In addition, there are ethical concerns related to such long-term overfeeding studies.

While lipid infusion can rapidly reduce insulin action in skeletal muscle and lower whole body glucose disposal, this is achieved by acutely raising plasma fatty acid levels 2–3 fold, which does not normally occur after oral fat intake. In fact, fatty acid levels usually decline with mixed meals containing carbohydrates due to insulin-mediated suppression of adipose tissue lipolysis. Furthermore, it has been shown that plasma fatty acids are only modestly elevated even in individuals with substantial insulin resistance [19]. Moreover, the typical emulsions for IV use contain primarily polyunsaturated fatty acids (PUFA), whereas typical Western diets (and consequently, plasma and tissue lipids) are greatly enriched in SFA. This may be particularly important as it has become increasingly clear that SFA and unsaturated fatty acids may have very different effects on cellular inflammation and function [20,21].

A model of rapid diet induced insulin resistance in humans would have several important advantages and could serve as a valuable tool for studying mechanisms of insulin resistance in humans. A short term diet would allow investigation of signaling events and tissue changes accompanying the earliest events associated with development of insulin resistance. It would also allow the study of events in the absence of weight gain and thereby remove, or greatly lessen, the resulting effects of changes in adipose tissue on insulin action-thereby permitting a more direct investigation of the mechanisms of FFA-induced insulin resistance. Using an oral route of nutrient administration also better mimics normal dietary physiology than does the IV infusion model. For example, nutrient ingestion engages typical gastrointestinal incretin hormones and can include a broader range of fatty acids, not just PUFA [22]. We therefore set out, in the present series of studies, to develop and test an acute, hypercaloric high fat-diet model of insulin resistance in humans.

2. Methods

2.1. Participants

Healthy male and female participants were recruited from the Phoenix Veterans Affairs Health Care System. Inclusion criteria included: age 40–75 years, body mass index (BMI) 25–35 kg/m^2, fasting triglycerides levels <5.65 mM, stable weight in the last 3 months, absence of diabetes based on history and a fasting plasma glucose <7 mM, a hemoglobin A_{1c} <6.5% (47.5 mmol/mol), and a 2-h glucose <11.1 mM on a standard 75-g oral glucose tolerance test. Exclusion criteria included acute medical problems, use of medications or current/planned dietary (e.g., hypocaloric or restrictive diets) or life-style behavior changes (e.g., exercise) known to interfere with glucose metabolism. The protocol was approved by the Phoenix VA Medical Center institutional review board and adhered to the Declaration of Helsinki and Joint Commission National Patient Safety Goals. All participants provided an informed written consent.

2.2. Research Design

A series of crossover studies compared in random order the effects of experimental diets to a nutritionally balanced (American Heart Association based) control diet. All experimental diets (described below) were provided by the Phoenix VA Medical Center Nutrition Department.

The high saturated fatty acid (SFA) diet consisted of high caloric liquid shakes with fat supplying about 80% of calories (15% carbohydrates and 5% proteins). The foundation of shakes was “heavy cream” supplied with sugar, chocolate syrup, and nonfat skim milk – with taste and consistency based on prior participant feedback. The fatty acid composition of the diet was ~63% SFA (42% palmitic acid), ~29% MUFA (primarily oleic acid from canola oil) and ~4% PUFA. The amount of fat was 65 g/m^2 of body surface area (BSA) for breakfast, lunch and dinner meals, and 32.5 g/m^2 BSA for the bedtime snack. For the primary study diet comparison subjects consumed the SFA diet for 24 h (SFA24) including breakfast, lunch, dinner, and a bedtime snack (all at home), and breakfast the next morning upon arrival in the clinical research center. In several smaller crossover studies exploring the temporal onset and duration of the SFA-diet effects on insulin action, patients consumed (a) a single SFA-breakfast (SFA-B, n = 6), (b) a daylong SFA diet (breakfast to bedtime snack, SFA-D, n = 7) or (c) a daylong SFA diet followed by a daylong control diet (SFA-D/C, n = 6).