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High saturated fatty acid intake induces insulin secretion by elevating gastric inhibitory polypeptide levels in healthy individuals

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ABSTRACT

Insulin resistance is central to the etiology of the metabolic syndrome cluster of diseases. Evidence suggests that a high-fat diet is associated with insulin resistance, which may be modulated by dietary fatty acid composition. We hypothesized that high saturated fatty acid intake increases insulin and gastric inhibitory polypeptide (GIP) secretion. To clarify the effect of ingested fatty acid composition on glucose levels, we conducted an intervention study to investigate the insulin and plasma GIP responses in 11 healthy women, including a dietary control. Subjects were provided daily control meals (F-20; saturated fatty acids/monounsaturated fatty acids/polyunsaturated fatty acids [S/M/P] ratio, 3:4:3) with 20 energy (E) % fat, followed by 2 isoenergetic experimental meals for 7 days each. These meals comprised 60 E% carbohydrate, 15 E% protein, and 30 E% fat (FB-30; high saturated fatty acid meal; S/M/P, 5:4:1; F-30: reduced saturated fatty acid meal; S/M/P, 3:4:3). On the second day of the F-20 and the last day of F-30 and FB-30, blood samples were taken before and 30, 60, and 120 minutes after a meal tolerance test. The plasma glucose responses did not differ between F-20 and FB-30 or F-30. However, insulin levels were higher after the FB-30 than after the F-20 ($P < .01$). The GIP response after the FB-30 was higher than that after the F-30 ($P < .05$). In addition, the difference in the incremental GIP between FB-30 and F-30 correlated significantly and positively with that of the insulin. These results suggest that a high saturated fatty acid content stimulates postprandial insulin release via increased GIP secretion.

Abbreviations: F-20, control meal (20% fat calorie content and S/M/P ratio of 3:4:3); F-30, reduced saturated fatty acid experimental meal (30% fat calorie content and S/M/P ratio of 3:4:3); FB-30, high saturated fatty acid experimental meal (30% fat calorie content and S/M/P ratio of 5:4:1); GIP, gastric inhibitory polypeptide; MTT, meal tolerance test; S/M/P, saturated fatty acids/monounsaturated fatty acids/polyunsaturated fatty acids ratio; ΣC-peptide, sum of C-peptide at 0, 30, 60, and 120 minutes of meal tolerance test; ΣGlucose, sum of glucose at 0, 30, 60, and 120 minutes of meal tolerance test; ΣGIP, sum of GIP at 0, 30, and 120 minutes of meal tolerance test; ΣInsulin, sum of insulin at 0, 30, 60, and 120 minutes of meal tolerance test.

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1. Introduction

The number of diabetes patients in Japan has increased dramatically due to an increase in insulin resistance [1], which is most likely induced by stress, lack of exercise, and the Westernization of dietary habits. Moreover, insulin resistance carries a risk for atherosclerotic disease, and the risk of the onset of atherosclerotic disease is compounded by the existence of other disease conditions [2]. Therefore, both the prevention and management of insulin resistance are extremely important.

In our previous clinical epidemiologic study, multiple regression analysis revealed positive regression in the sum of insulin (Σinsulin) levels at 0, 30, 60, and 120 minutes during a 75-g oral glucose tolerance test. It also revealed a slight but positive correlation with the log of 24-hour urinary norepinephrine excretion and decreased blood pressure achieved through a weight loss program [3]. These findings support the conclusions by Reaven [1]. Our published data also support their finding that this mechanism may improve insulin sensitivity, as measured using ∑IRI as an index of insulin resistance due to weight loss. Furthermore, we found that insulin resistance, as identified by Σinsulin levels during the 75-g oral glucose tolerance test, is associated with saturated fatty acid intake, rather than calorie intake, and improvements after blood pressure reduction were noted [4]. The significant correlation between insulin resistance and saturated fatty acid intake was valid, even after adjusting for total fat intake [4].

Since the association between insulin resistance and fat intake was first investigated by Himsworth [5] in 1935, many studies have assessed insulin resistance in small animals and humans. In recent years, Borkman et al [6] reported a positive correlation between insulin sensitivity and the proportion of polyunsaturated fatty acids in the total fat of skeletal muscles. This phenomenon might suggest that higher levels of saturated fatty acids are related to increased insulin resistance and that dietary fat, especially fatty acid composition, might play a significant role in insulin resistance. Epidemiologic studies on insulin resistance report that a high intake of saturated fatty acids induces hyperinsulinemia and increases the risk of diabetes in humans [7–12]. Storlien et al [13–15] showed that insulin resistance is promoted by unsaturated fat, n-6 fatty acids, and saturated fat, but it is improved by n-3 fatty acids, thus suggesting a significant association with obesity. However, impaired insulin activity is also frequently observed in nonobese individuals, and the relationship between insulin resistance and dietary fatty acid composition has never been investigated in an intervention study with a dietary control in humans.

It is well known that nutrients, such as oral glucose, promote the secretion of incretin hormones in the digestive tract and insulin secretion from β cells. Glucagon-like peptide 1 is chiefly secreted by L cells and gastric inhibitory polypeptide (GIP) from K cells. Gastric inhibitory polypeptide secretion is associated with high fat intake, but the way in which its secretion relates to differences in fatty acid composition has not been adequately clarified. In a previous observational study, after adjusting for differences in total fat intake, we found that saturated fatty acid intakes had an effect on insulin resistance. Based on these findings, we hypothesized that insulin and GIP concentrations would increase in response to high saturated fatty acid levels. To test this hypothesis, we performed an interventional dietary control study. For 7 days, 11 healthy young women consumed either of 2 meals that were supplemented with different amounts of fatty acids (high saturated fatty acids meal or reduced saturated fatty acid meal).

If the results indicate that the intake of a high amount of saturated fatty acids induced elevated insulin and GIP secretion in this intervention study, it would indicate the effectiveness of recommending a suitable intake of saturated fatty acids for diabetes prevention.

2. Methods and materials

2.1. *Subjects and study protocol*

The subjects were 11 healthy, nondiabetic (fasting plasma glucose, <7.0 mmol/L) Japanese women with a mean ± SE age of 23.6 ± 1.7 years, a body mass index of 22.1 ± 0.69 kg/m^2, and a fasting plasma glucose level of 4.83 ± 0.07 mmol/L.

The study protocol is shown in Fig. 1. For 1 day, the subjects were provided control meals (F-20) that had a fat calorie content of 20% and a saturated fatty acids/monounsaturated fatty acids/polyunsaturated fatty acids (S/M/P) ratio of 3:4:3. The meal tolerance test (MTT) was performed by the test meal for F-20 (F-20-TM) the next morning. Subsequently, the subjects were given a reduced saturated fat experimental meal (F-30) that had a fat calorie content of 30% and an S/M/P ratio of 3:4:3, for 7 days. The MTT was performed by the test meal for F-30 (F-30-TM) at the last morning of the F-30 phase. The control meals (F-20) and F-30 experimental meals were prepared to the same calorific value, with identical levels of protein, simple carbohydrates, and dietary fiber. After a 3-week washout period to synchronize the menstrual cycles of the subjects, control meals (F-20) were provided for 1 day, and MTT was performed by F-20-TM the next morning, as done previously. Thereafter, high saturated fat experimental meals (FB-30; S/M/P ratio of 5:4:1) were provided for the next 7 days, and MTT was performed by the test meal for FB-30 (FB-30-TM) on the last morning of the FB-30 phase. The compositions of the control meal (F-20) and the experimental meals (F-30 and FB-30) are shown in Table 1, and those of the test meals used for MTT (F-20-TM, F-30-TM and FB-30-TM) are shown in Table 2.

The 3 experimental test meals were isoenergenic and were as follows: reduced saturated fatty acid (F-30; 30% energy from fat, 16% energy from protein, and 54% energy from carbohydrate, S/M/P ratio 3:4:3), high saturated fatty acid (FB-30; 30% energy from fat, 16% energy from protein, and 54% energy from carbohydrate, S/M/P ratio 5:4:1), and low-fat (control (F-20; 20% energy from fat, 16% energy from protein, and 64% energy from carbohydrate, S/M/P ratio 3:4:3). The experimental meals and test meals for MTT were standard Japanese meals. The recipes for both experimental meals (F-30 and FB-30) were essentially the same, except for the use of cooking oil. Specifically, FB-30 used 47 g butter and F-30 used 40 g soybean oil, with both having the same calorie content. The experimental meals and test meals were delivered by a dietitian. We calculated the composition of fatty acids as follows: saturated fatty acids (S) included