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Effect of lipid oxidation on the regulation of glucose utilization in obese patients

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Abstract. The effect of changes in lipid oxidation on glucose utilization (storage and oxidation) was studied in seven nondiabetic obese patients. They participated in three protocols in which: (1) Intralipid (to raise plasma FFA concentrations), (2) β-pyridylcarbinol [a precursor of nicotinic acid, to lower plasma free fatty acids (FFA) concentrations], or (3) isotonic saline were infused over 2 h. Thereafter, these infusions were discontinued, and a 2-h euglycemic, hyperinsulinemic clamp was performed to measure glucose uptake. All studies were carried out in combination with indirect calorimetry to measure oxidative and nonoxidative glucose disposal (glucose storage). The high plasma FFA concentrations (1024±57 μmol/l) and lipid oxidation rates (1.1±0.1 mg/kg·min) found at the end of the Intralipid infusion and the low plasma FFA concentrations (264±26 μmol/l) and lipid oxidation rates (0.7±0.1 mg/kg·min) found at the end of the β-pyridylcarbinol infusions resulted in significantly different rates of total and nonoxidative glucose disposal during the insulin clamp. The values were 2.6±0.6 mg/kg·min after Intralipid and 4.1±1.0 mg/kg·min after β-pyridylcarbinol for total glucose disposal, and 0.4±0.4 and 1.6±0.8, respectively for nonoxidative glucose disposal. In conclusion, these observations show that changes in lipid oxidation rates preceding a glucose load influence glucose disposal and glycogen storage in obese subjects.

Key words: Obesity – Free fatty acids – Lipid oxidation – Glucose oxidation – Glucose storage – Glucose uptake

Introduction

Obesity, type 2 diabetes, and hypertriglyceridemia are often associated [1, 2]. Lately, Reaven proposed an insulin resistance syndrome as a common cause for this association [3]. Using a variety of techniques, many investigators have demonstrated that impaired insulin sensitivity is present in obesity and type 2 diabetes [4, 5]. Abnormalities commonly observed in obese and hypertriglyceridemic patients are elevation of the plasma free fatty acid (FFA) concentrations and increased lipid oxidation [6–8]. Several authors have shown that those abnormalities may explain, at least in part, the insulin resistance present under these conditions. Randle et al. [9–10] were the first to propose that an increase in FFA concentration, caused by an excessive fatty acid release from adipose tissue, may inhibit glycolysis and glucose transport in muscle through the preferential oxidation of lipids, thereby leading to glucose intolerance and insulin resistance. Since the initial observations of Randle, several authors have demonstrated that an increased plasma fatty acid concentration, as obtained after an infusion of triglyceride emulsion in man, induces a decrease in glucose oxidation and storage and causes insulin resistance during euglycemic, hyperinsulinemic clamps [11–13]. Measurements of substrate oxidation rates by indirect calorimetry demonstrated an inverse correlation between glucose oxidation and lipid oxidation under these conditions [11–14].

It was further postulated that such a mechanism may be responsible for insulin resistance in obese patients [15, 16]. Insulin resistance in obesity and diabetes is mainly due to a defect in glucose storage [15, 17, 18]. An impairment in glucose storage has also been demonstrated in nondiabetic obese patients during euglycemic clamp studies, although such a defect was not observed during oral glucose tolerance tests (OGTT), presumably because the rise in glycemia allows a normalization of the rate of glucose uptake and storage in muscles [15].

Several authors, however, have shown no correlation between fatty acid plasma levels and glucose storage [13, 14]. This suggests that a diminution of glucose storage in obesity does not directly result from a rise in plasma FFA concentration, but might be an indirect consequence of the metabolic changes which have occurred previously during the glucose-fatty acid interaction. The effect of increased basal lipid oxidation on subsequent insulin sensi-

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tivity has been studied in normal control subjects. Kleiber et al. [19] have shown that the rise in plasma FFA concentration during an Intralipid infusion was followed by a fall in both glucose uptake and storage, while the decrease in plasma FFA concentration during a β-pyridylcarbinol infusion was followed by a rise in glucose uptake and storage.

The purpose of the present study was to examine whether a lipid-glucose regulation mechanism still exists in obesity. In order to further delineate these glucose-lipid interactions, plasma FFA concentrations were altered in obese patients during a 2-h period prior to a 2-h euglycemic, hyperinsulinemic clamp. Plasma FFA levels were raised by means of an Intralipid infusion or lowered by means of a β-pyridylcarbinol infusion.

Materials and methods

Subjects

Seven nondiabetic obese patients, 6 men and 1 woman, with an age range from 21 to 50 years (means±SEM 34±4), participated in the three protocols. Their body mass index (BMI) ranged from 30 to 50 kg/m^2 (37±3 kg/m^2). The mean absolute body weight was 108± 9 kg. All obese subjects had a glucose tolerance test within normal limits, and none was diabetic or had taken any medication. Two days prior to each study, they had to consume a diet containing at least 250–300 g of carbohydrate per day. No patient was excessively sedentary or participated in strenuous physical activity. Body weight had remained stable in all subjects for at least 3 months before the study, and no patient had any unusual dietary habit. All subjects were euthyroid as evidenced by normal plasma thyroid hormone levels. The nature, purpose, and risks of the study were explained to all subjects prior to participation, and their agreement was obtained. The experimental protocol was approved by the Human Investigation Committee of the Department of Medicine at the University of Lausanne, Switzerland.

Experimental protocol

All studies were performed in the recumbent position after a 10–12-h overnight fast. An intravenous catheter (Venflon) was inserted into an antecubital vein for infusing insulin, glucose and either (a) a 20% Intralipid (Vitrum, Stockholm, Sweden) to raise the plasma FFA levels; (b) β-pyridylcarbinol (Ronicol, Roche, Basel, Switzerland), a well-tolerated precursor of nicotinic acid to lower plasma FFA levels; or (c) isotonic saline as a control. A second catheter was placed in a contralateral vein for blood withdrawal and kept patent with an infusion of isotonic saline. To achieve arterialization of venous blood, the arm was kept in a heated box at 50°C. The glucose clamp was performed by a modification of the method of DeFronzo et al. [20]. Each participant was studied on three occasions, in random order, with an interval of at least 1 week between each test.

Intralipid+euglycemic, hyperinsulinemic clamp. After 30–45 min of baseline measurements, a 20% Intralipid infusion was administered at the rate of 1.0 ml/min for the next 120 min of the experiment (preclamp). Then the infusion was discontinued. A euglycemic, hyperinsulinemic clamp was started with a priming dose of human insulin (Actrapid HC, Novo Industry, Copenhagen, Denmark), given in a decreasing concentration over a period of 10 min. Insulin was then infused at a continuous rate of 40 mU/m^2·min for the remainder of the test. The plasma insulin level during the clamp was 85±3 μU/ml. A variable 20% glucose infusion was also started to keep the plasma glucose concentration at 5.0 mmol/l for the whole 120 min period of hyperinsulinemia. Samples for plasma glucose concentration were drawn every 5 min during the test. The plasma glucose concentration during the clamp was 5.6±0.6 mmol/l. The stability of the plasma glucose concentration is reflected by the coefficients of variation, which ranged from 2.1% to 4.3%.

β-pyridylcarbinol infusion + euglycemic, hyperinsulinemic clamp. After 30–45 min of baseline measurements, β-pyridylcarbinol was administered as an infusion for the next 120 min at the rate of 1.25 mg/m^2·min (preclamp). Then the infusion was discontinued, and the glucose clamp procedure was started as described following the Intralipid infusion. The plasma insulin concentration during the clamp was 92±9 μU/ml and the plasma glucose 5.2±0.5 mmol/l. The coefficients of variation ranged from 2.0% to 5.1%.

Control infusion + euglycemic, hyperinsulinemic clamp. After 30–45 min of baseline measurements, isotonic saline was infused for the next 120 min of the experiment (preclamp). The infusion was discontinued, and the glucose clamp procedure was started as described following the Intralipid infusion. The plasma insulin concentration during the clamp was 92±8 μU/ml and the plasma glucose 5.0±0.4 mmol/l. The coefficient of variation ranged from 1.9% to 3.9%.

Indirect calorimetry

All experiments were performed in combination with continuous indirect calorimetry. Urine was collected at the end of each test for nitrogen and glucose determination. During the 30–45 min baseline, the preclamp and the clamp periods, the O_2 uptake at standard temperature and pressure, dry (VO_2, STPD) and CO_2 production (VCO_2, STPD) were measured by an open-circuit technique [21]. This consists of a transparent plastic ventilated hood placed over the subject's head, a pump, a flowmeter, and a paramagnetic O_2 analyzer (Magnos 4G, Hartmann & Braun, Frankfurt, Germany). The analyzers and flowmeter outputs were connected to a desk computer (Hewlett Packard, 9835A) which continuously recorded calorimetry measurements integrated over 5-min intervals.

Substrate oxidation rates were calculated as previously described [21]. The nonprotein respiratory quotient (NPRQ) was calculated from calorimetric values and urinary nitrogen. The basal carbohydrate oxidation rates were calculated from indirect calorimetric data by averaging the values obtained during the 30 min preceding the preclamp infusion (Intralipid, β-pyridylcarbinol, or isotonic saline). In the preclamp state they were calculated by averaging the values for the 30 min preceding the euglycemic, hyperinsulinemic clamp. The insulin-stimulated carbohydrate oxidation rates were calculated by averaging the values for the last 60 min of the glucose clamp. The carbohydrate storage rate was calculated by subtracting the carbohydrate oxidation from the total glucose infusion during the clamp.

Analytical methods

Plasma glucose concentrations were determined by the glucose oxidase method with a Beckman Glucose Analyzer II (Beckman Instrument, Fullerton, Calif.). Urinary nitrogen concentrations were measured by the method of Kjeldahl [22]. Plasma FFA were extracted using the method of Dole and Meinertz [23] and determined according to Heindel et al. [24]. Plasma immunoreactive insulin (IRI) was determined by radioimmunoassay as described by Herbert et al. [25].

Table 1. Lipid oxidation, glucose oxidation, storage, and uptake after Intralipid and β-pyridylcarbinol (*β-PC*) administration

	Basal			Preclamp			Clamp		
	NaCl	Intralipid	*β-PC*	NaCl	Intralipid	*β-PC*	NaCl	Intralipid	*β-PC*
Free fatty acid (μmol/l)	730 ± 37	754 ± 46	706 ± 46	799 ± 61	1024 ± 57	264 ± 26	293 ± 31	366 ± 44	359 ± 26
Lipid oxidation (mg/kg · min)	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	0.7 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.2
Glucose oxidation (mg/kg · min)	1.7 ± 0.2	1.8 ± 0.2	1.8 ± 0.4	1.5 ± 0.2	1.3 ± 0.1	2.2 ± 0.4	2.5 ± 0.3	2.2 ± 0.4	2.5 ± 0.5
Glucose storage (mg/kg · min)							1.0 ± 0.8	0.4 ± 0.4	1.6 ± 0.8*
Glucose uptake (mg/kg · min)							3.5 ± 1.0	2.6 ± 0.6	4.1 ± 1.0**

*$P<0.05$; **$P<0.01$ (*β-PC* compared with Intralipid infusion)

Statistics

Data are presented as group means±SEM. Parameters were measured in the same individual under the three experimental conditions. Consequently, a repeated-measures analysis of variance with randomized blocks was performed. Statistical differences between the three different protocols were considered significant when P value was ≤0.05 using Fischer and Scheffe tests [26].

Results

The basal plasma FFA concentration was similar before the three infusions (Table l, Fig. 1). At the end of the period preceding the clamp, the plasma FFA concentrations increased to 1024±57 μmol/l after Intralipid and decreased to 264±26 μmol/l after β-pyridylcarbinol, vs 799±61 μmol/l in the control group (both $P< 0.01$ vs control). At the end of the 2-h clamp procedure, FFA concentrations were low under all three conditions, with values of 293±31, 366±44, and 359±26 μmol/l after saline, Intralipid, and β-pyridylcarbinol, respectively. Basal lipid oxidation was similar in the three experimental protocols (0.9±0.1, and 0.8±0.1, and 0.8±0.1 mg/kg·min) before the NaCl, Intralipid, and β-pyridylcarbinol infusions, respectively (Table 1). Lipid oxidation rose to 1.1±0.1 mg/kg·min after Intralipid ($P< 0.01$ vs basal) vs 0.9±0.1 mg/kg·min in the control study (NS). It fell to 0.7±0.1 mg/kg·min after the β-pyridylcarbinol infusion (NS) (Fig. 1). At the end of the clamp, lipid oxidation was similar in the three experimental protocols (0.5±0.1, 0.6±0.1, 0.6±0,2 mg/kg·min in the NaCl, Intralipid, and β-pyridylcarbinol protocols, respectively).

Basal glucose oxidation was similar before the control (1.7±0.2 mg/kg·min), Intralipid (1.8±0.2 mg/kg·min) and β-pyridylcarbinol (1.8±0.4 mg/kg·min) infusions (Table 1). At the end of the preclamp period, glucose oxidation fell to 1.3±0.1 mg/kg·min ($P< 0.05$ vs basal) after Intralipid infusion and rose to 2.2±0.4 mg/kg·min after β-pyridylcarbinol, vs 1.5±0.2 mg/kg·min after isotonic saline ($P< 0.05$ vs NaCl) (Fig. 1). During the second hour of the clamp, the rate of glucose oxidation rose to 2.5±0.3, 2.2±0.4, and 2.5±0.5 mg/kg·min after saline, Intralipid, and β-pyridylcarbinol, respectively. Glucose uptake (exogenous glucose infusion) was lower after Intralipid than after saline, with values of 2.6±0.6 vs 3.5±1.0 mg/kg·min and higher after β-pyridylcarbinol with a value of 4.1±1.0 mg/kg·min ($P< 0.01$ between Intralipid and β-pyridylcarbinol) (Fig. 1, Table 1). Similarly, glucose storage was lower after Intralipid than after saline, with values of 0.4±0.4 vs 1.0±0.8 mg/kg·min, and higher after β-pyridylcarbinol, with a value of 1.6±0.8 mg/kg·min ($P< 0.05$ between Intralipid and β-pyridylcarbinol) (Fig. 2, Table 1).

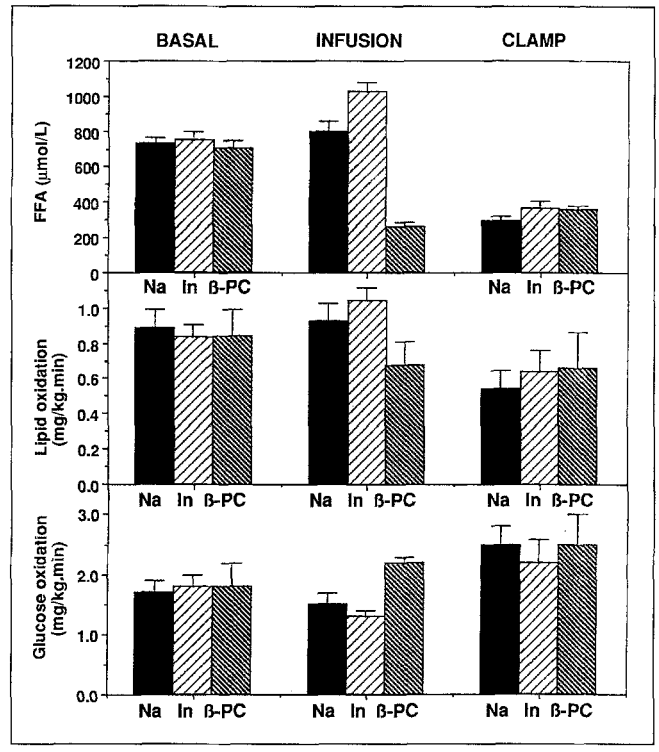

Fig. 1. Plasma free fatty acid (FFA) concentration, lipid oxidation rate, and glucose oxidation rate in the basal state, after the end of the infusions of saline (*Na*), Intralipid (*In*) and β-pyridylcarbinol (*β-PC*), and during the second hour of the glucose-insulin clamp

Discussion

In the present study, the sequence of events shows the inhibitory effect of the lipid infusion given before the clamp procedure on glucose uptake and storage and, inversely, the stimulatory effect of the fatty acid-lowering agent β-pyridylcarbinol. The changes in plasma FFA concentrations and in lipid oxidation rates resulting from these infusions are followed by modifications of the rates of glucose storage during the subsequent euglycemic, hyperinsulinemic clamp. The effect is similar to that reported in

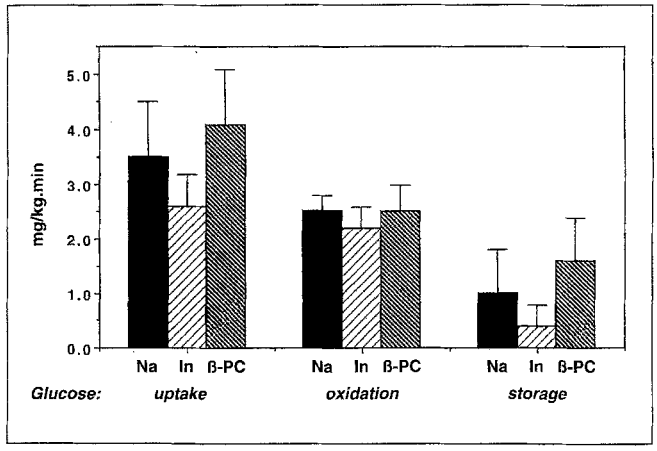

Fig. 2. Glucose uptake, oxidation, and storage rates measured during the second hour of the glucose-insulin clamp after the infusion of NaCl (*Na*), Intralipid (*In*) and β-pyridylcarbinol (*β-PC*). There were significant differences in glucose storage ($P< 0.05$) and glucose uptake ($P< 0.01$) between Intralipid and β-pyridylcarbinol

lean subjects [19] using the same protocol with, however, a difference in the amplitude of the changes, both inhibitory and stimulatory. When compared with lean individuals, the obese subjects have a lower amount of glucose stored according to the control studies and a smaller amplitude of the changes subsequent to the Intralipid and the β-pyridylcarbinol infusions. The changes in glucose uptake are similar to those observed in glucose storage, as the modifications in glucose uptake essentially reflect the variations in glucose storage [27]. The hypothesis can be put forward that the preliminary treatment of subjects with Intralipid or β-pyridylcarbinol decreased or increased the oxidation of glucose released from glycogen stores in the preclamp period and, as a consequence, affected the size of glycogen stores available at the beginning of the clamp. As a function of the size of glycogen stores, during the subsequent insulin clamp, glycogen synthesis would be diminished or increased.

Plasma FFA concentrations and lipid oxidation rates did not differ between the three treatments (Intralipid, β-pyridylcarbinol, and NaCl) during the clamp (Fig. 1). Plasma FFA concentrations and lipid and glucose oxidation rates were essentially affected by the glucose-insulin infusion, independently of the changes induced by the different plasma FFA levels preceding the clamp. In spite of these similar responses, there were marked differences in glucose storage. The latter are not associated with the changes occurring during the glucose-insulin clamp, but depend on the changes which preceded the clamp, i.e. those related to the infusions of Intralipid or β-pyridylcarbinol. Changes in glucose storage occurred when the changes in glucose oxidation tended to disappear. This is in line with the studies of Bonadonna et al. [14], Kleiber et al. [19], and Boden et al. [28], who demonstrated a delayed effect of a lipid infusion on the inhibition of glucose storage. In their study, Boden et al. [28] contrasted the rapid effect of Intralipid (raising lipid oxidation and lowering glucose oxidation) to the delayed effect on the inhibition of glucose storage.

Comparing the effects of hyperglycemia with either Intralipid to raise plasma FFA concentration and lipid oxidation rates or β-pyridylcarbinol to lower the same parameters, Felley et al. [29, 30] demonstrated the absence of interaction between the two treatments (hyperglycemia on one side, rise or fall in FFA on the other) on insulin-mediated glucose disposal. These observations suggest that the effects of hyperglycemia and the changes in lipid metabolism occur through two different metabolic pathways.

Plasma FFA may significantly affect hepatic glucose production [31]. If hepatic glucose production was differently suppressed following saline, Intralipid, or β-pyridylcarbinol, glucose disposal might be different. However, although hepatic glucose production was not measured in the present study, since a 40 $mU/m^2 \cdot min$ insulin infusion was used, it is likely that residual hepatic glucose production was negligible and that glucose infusion equalled glucose disposal. It is interesting to observe that plasma FFA increased after β-pyridylcarbinol treatment was discontinued and the insulin clamp initiated. This suggests that the inhibition of FFA release by β-pyridylcarbinol is stronger than that by insulin.

Increase in lipid oxidation is a typical feature of obesity [32]. It is more specifically associated with obesity than a rise in plasma FFA concentration [6]. The present work, by modulating lipid oxidation in a group of obese subjects, confirms the importance of changes in lipid oxidation on glucose metabolism, in particular glucose storage and uptake. These changes are at the basis of the insulin resistance which characterizes obesity [32]. Glucose storage is the main route of glucose disposal, and impaired glucose storage is a direct cause of glucose intolerance [18]. Impaired glucose tolerance, which is frequently observed in obesity, is a consequence of a decrease in glucose uptake and can be modified by changes in lipid oxidation, as previously reported [33]. The observation that the defect in glucose utilization and storage is reversed by the β-pyridylcarbinol infusion suggests that such a defect may be, at least in part, due to an acquired abnormality related to the increased lipid metabolism in obesity. As for the improvement of glucose uptake and storage following weight loss in obese subjects [34, 35], this is an argument for the hypothesis of a metabolic origin of the insulin resistance observed in obesity [36].

In conclusion, this study confirms the importance of changes in lipid metabolism on glucose uptake and storage in obesity: an increase in lipid oxidation induces impairment of glucose metabolism and insulin sensitivity, whereas a decrease in lipid oxidation improves these parameters.

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