Acute ω-3 Fatty Acid Enrichment Selectively Reverses High–Saturated Fat Feeding–Induced Insulin Hypersecretion But Does Not Improve Peripheral Insulin Resistance

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In rats fed a high–saturated fat diet, replacement of a small percentage of total fatty acids with long-chain ω-3 fatty acids from fish oil for the duration of high-fat feeding prevents the development of insulin resistance. We investigated the effect of acute (24-h) modulation of dietary fat composition on glucose-stimulated insulin secretion (GSIS) in rats made insulin resistant by high–saturated fat feeding for 4 weeks. Insulin secretion after an intravenous glucose challenge was greatly increased by high–saturated fat feeding. Glucose tolerance was minimally perturbed, demonstrating insulin hypersecretion compensated for insulin resistance. The effect of high–saturated fat feeding to enhance GSIS was retained in perifused islets, such that glucose stimulus-secretion coupling was potentiated. Acute replacement of 7% of dietary fatty acids with long-chain ω-3 fatty acids reversed insulin hypersecretion in vivo, and the effect of long-term high–saturated fat feeding to enhance insulin secretion by perifused islets was also completely reversed. Although a hyperbolic relationship existed between insulin secretion and action in the high–saturated fat and control groups, lowered insulin secretion in the acute fish oil–supplemented group was not accompanied by improved insulin action, and glucose tolerance was adversely affected. Our studies are important because they demonstrate that hyperinsulinemia can be rapidly reversed via the dietary provision of small amounts of long-chain ω-3 fatty acids. However, this "insulin sparing" action of acute dietary long-chain ω-3 fatty acids occurs in the absence of an acute improvement in insulin sensitivity and therefore at the expense of maintenance of glucose tolerance. *Diabetes* 53 (Suppl. 1):S166–S171, 2004

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ΔG, incremental blood glucose values integrated over the 30-min period after the injection of glucose; ΔI, incremental plasma insulin values integrated over the 30-min period after the injection of glucose; AGR, acute glucose response; AIR, acute insulin response; F-HIFAT, rats fed a high–saturated fat diet that was enriched with long-chain ω-3 fatty acids for the final 24 h; GSIS, glucose-stimulated insulin secretion; HIFAT, high–saturated fat–fed rats; IRI, insulin resistance index; ISI, insulin sensitivity index; LOFAT, control low-fat/high-carbohydrate–fed rats.

Environmental and lifestyle factors are established contributors to the development of insulin resistance (1). Among these, dietary fat plays an important role. Both the amount and type of fatty acids are important. Diets high in saturated fats (2,3) or rich in linoleic acid and ω-6 fatty acid (2) lead to insulin resistance, mainly because of the effects in oxidative muscle. The physiological alterations in metabolic flux induced by high–saturated fat feeding mimic those reported in patients with type 2 diabetes (4). However, the substitution of ω-3 long-chain fatty acids from fish oil for a small percentage (6–7%) of other types of lipids for the duration of high-fat feeding prevents the development of insulin resistance (5,6).

The peripheral insulin resistance evoked by the provision of increased dietary saturated fat can be accompanied by compensatory insulin secretion, such that glucose tolerance is maintained (7,8). However, the impact of dietary fatty acids on insulin secretion is less well defined. Epidemiological evidence suggests that insulin resistance in association with hyperinsulinemia is closely linked to the ingestion of saturated, rather than unsaturated, fat (9,10). During acute pancreas perifusion, the extent to which exogenous fatty acids augment glucose-stimulated insulin secretion (GSIS) is positively related to their chain length and degree of unsaturation (11). In addition, insulin responses during hyperglycemic clamps are augmented by the provision for 4 weeks of a diet enriched in saturated fat, but not a diet enriched in unsaturated fat (12).

In the present study, we investigated whether the acute (24-h) substitution of a small amount of dietary lipid with long-chain ω-3 fatty acids from fish oil modulates the action of antecedent high–saturated fat feeding to induce insulin resistance and elicit compensatory insulin hypersecretion. We used a diet moderately high in total and saturated fat, lying at the upper end of the typical fat intake for people in the Western world (9,13). In the rat, this high–saturated fat diet leads to the development of peripheral insulin resistance in conjunction with augmented GSIS, but not glucose intolerance, after 4 weeks (7). Holding the total lipid content of the diet constant, just 7% of the lipid was replaced by long-chain ω-3 fatty acids from fish oil (14). This modified high-fat diet, still containing predominantly saturated fat, was provided for only

TABLE 1
Food intake and postabsorptive circulating insulin and glucose concentrations

	LOFAT	HIFAT	F-HIFAT
Food intake (kcal/day)	55.4 ± 8.6 (9)	78.0 ± 7.7 (9)	83.6 ± 9.3* (6)
Initial body weight (g)	237 ± 3 (9)	238 ± 6 (9)	234 ± 7 (6)
Final body weight (g)	264 ± 5 (9)	274 ± 6 (9)	272 ± 5 (6)
Plasma insulin (μU/ml)	16 ± 2 (9)	20 ± 3 (10)	15 ± 2 (6)
Blood glucose (mmol/l)	4.0 ± 0.3 (9)	4.3 ± 0.3 (9)	4.4 ± 0.2 (6)

Data are means ± SE with the numbers of rats in parentheses. Plasma insulin and blood glucose concentrations were determined using commercial kits. Statistically significant differences from LOFAT rats are indicated: *$P < 0.05$. There were no statistically significant effects of acute long-chain ω-3 enrichment of the high–saturated fat diet versus high-fat feeding.

24 h after an antecedent period of 4 weeks of high–saturated fat feeding. Studies of insulin secretion and glucose tolerance were conducted in the intact conscious animals, and, in addition, to identify persistent effects on the islet, studies of GSIS were conducted ex vivo using islet perifusions.

RESEARCH DESIGN AND METHODS

Materials. General laboratory reagents were purchased from Roche Diagnostics (Lewes, East Sussex, U.K.) or from Sigma (Poole, Dorset, U.K.). Kits for determination of insulin and glucose concentrations were purchased from Mercodia (Uppsala, Sweden) and Roche Diagnostics (Lewes, East Sussex, U.K.), respectively.

Animals. All studies were conducted in adherence to the regulations of the U.K. Animal Scientific Procedures Act (1986). Female albino Wistar rats (200–250 g) were purchased from Charles River (Margate, Kent, U.K.). Rats were maintained at a temperature of 22 ± 2°C and subjected to a 12-h light/12-h dark cycle. One group of rats was given free access to standard pelleted low-fat rodent diet purchased from Special Diet Services (Witham, Essex, U.K.) (52% carbohydrate, 15% protein, 3% lipid, and 30% nondigestible residue by weight) (the LOFAT group). High–saturated fat–fed rats (HIFAT) were given free access to a semi-synthetic diet high in saturated fat (7), henceforth referred to as high–saturated fat diet, for 4 weeks. The high-fat diet contained 34% carbohydrate, 19% protein, and 22% lipid (lard as the major source of lipid, together with corn oil [1.9 g/100 g diet] to prevent essential fatty acid deficiency) by weight (7). The lipid component of the high–saturated fat diet comprised 16% saturated fatty acids (mainly stearic, 18:0), 16% monounsaturated fatty acids (mainly oleic, 18:1), and 7% polyunsaturated fatty acids (mainly linoleic, 18:2) by energy. The second experimental high-fat diet was also lard/corn oil based, but ~7% of the dietary fatty acids were replaced with long-chain ω-3 fatty acids from marine oil (provided by Dr. D. Horrobin, Scotia Pharmaceuticals, Guildford, Surrey, U.K.). By gas liquid chromatography analysis, 49% of the long-chain ω-3 fatty acid was eicosapentaenoic acid (20:5) and 33% was docosahexaenoic acid (22:6). The high-fat diets were prepared at 3-day intervals using components supplied by Special Diet Services, with the exception of the saturated fat component (lard), which was purchased locally. Rats were maintained on the HIFAT diet for 4 weeks and then a subset of rats maintained on the HIFAT diet for 4 weeks were switched to the fish oil–enriched high–saturated fat diet for 24 h. These rats are referred to as the F-HIFAT group. In all experiments, rats were allowed ad libitum access to water.

Intravenous glucose challenge. Glucose was administered as an intravenous bolus (0.5 g glucose/kg body wt; 150 μl/100 g body wt) to conscious unrestrained rats (7). Glucose was injected via a chronic indwelling jugular cannula, and blood samples (100 μl) were withdrawn at intervals from the indwelling cannula, which was flushed with saline after the injection of glucose to remove residual glucose. Samples of whole blood (50 μl) were deproteinized with $ZnSO_4$/$Ba(OH)_2$ and centrifuged (10,000*g*) at 4°C, and the supernatant was retained for subsequent assay of blood glucose. The remaining blood sample was immediately centrifuged (10,000*g*) at 4°C, and plasma was stored at −20°C until assayed for insulin. The acute insulin response (AIR) was calculated as the mean of suprabasal 2- and 5-min plasma insulin values. The acute glucose response (AGR) was calculated as the mean of suprabasal 2- and 5-min blood glucose values. Insulin and glucose responses during the glucose tolerance test were used for calculation of the incremental plasma insulin values integrated over the 30-min period after the injection of glucose (ΔI) and the corresponding incremental integrated plasma glucose values (ΔG). The insulin resistance index (IRI) was calculated as the product of the areas under the glucose and insulin curves after the glucose challenge; the insulin sensitivity index (ISI) was calculated as the reciprocal of the IRI. The rate of glucose disappearance (k) was calculated from the slope of the regression line obtained with log-transformed glucose values from 2 to 15 min after glucose administration.

Islet isolation and perifusion. Rats were anesthetized by injection of sodium pentobarbital (60 mg/ml in 0.9% NaCl; 1 ml/kg body wt. i.p.), and, once locomotor activity had ceased, pancreases were excised and islets were isolated by collagenase digestion (15). Free islets were collected under a dissecting microscope with a 20-μl pipette into HEPES-buffered Hanks' balanced salt solution containing 5% BSA. Insulin release from freshly isolated islets was measured in a perifusion system as described by Hughes et al. (16). In this system, 50 islets were housed in small chambers on Millicell culture inserts. Islets were perifused in basal medium (Krebs-Ringer containing 20 mmol/l HEPES, pH 7.4, 5 mg/ml BSA, and 2 mmol/l glucose) for 60 min at a flow rate of 1 ml/min at 37°C before collection of fractions. Glucose concentrations were then modified as indicated. Fractions (2 ml) were collected at 2-min intervals and stored at −20°C before assay for insulin.

Analytical methods. Glucose concentrations were determined by a glucose oxidase method (Roche Diagnostic). Immunoreactive insulin concentrations were measured by enzyme-linked immunosorbent assay using rat insulin as a standard (Mercodia).

Statistical analysis. Results are presented as the mean ± SE, with the numbers of rats or islet preparations in parentheses. Statistical analysis was performed by ANOVA followed by Fisher's post hoc tests for individual comparisons or the Student's t test as appropriate (Statview; Abacus Concepts, Berkeley, CA). A P value of <0.05 was considered statistically significant.

RESULTS

Food intake and body weight gain. Although caloric intake was ~41% higher in the HIFAT group than in the LOFAT group (Table 1), the increase in caloric intake was not associated with an increase in body weight gain during the 4-week period of high-fat feeding compared with the low-fat group. Acute (24-h) long-chain ω-3 enrichment of HIFAT diet did not affect caloric intake compared with that of HIFAT rats or body weight gain (Table 1). Although we did not systematically measure physical activity, there were no obvious differences in physical activity between the dietary groups.

Effects of high–saturated fat feeding with or without acute long-chain ω-3 enrichment on GSIS in vivo in relation to indexes of insulin sensitivity. Postabsorptive plasma insulin concentrations in the HIFAT group were modestly, but not significantly, increased by 23% in comparison with the LOFAT animals (Table 1). This trend was no longer observed after acute long-chain ω-3 enrichment of the high–saturated fat diet (Table 1). The impact of dietary fat intake on GSIS was assessed using an intravenous glucose challenge in conscious unrestrained rats. The calculated AIR and AGR values after intravenous administration of glucose (0.5 g/kg) in LOFAT, HIFAT, and F-HIFAT rats are shown in Fig. 1. We confirmed previous findings (7) of increased insulin secretion after an intrave-

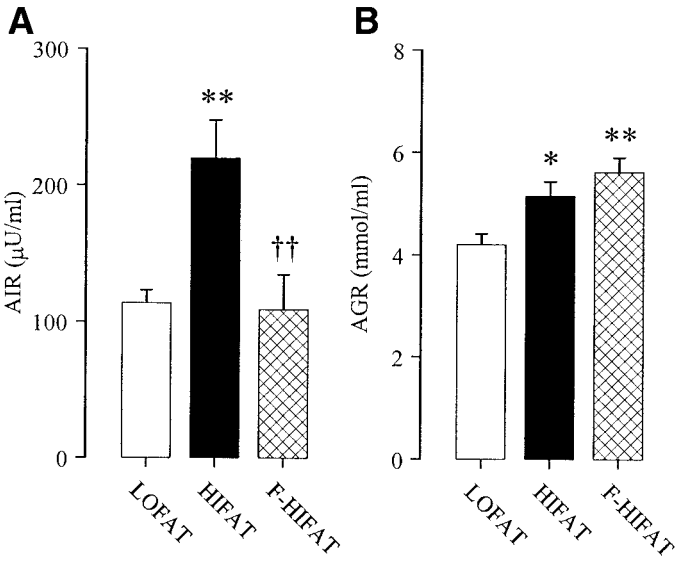

FIG. 1. Acute (24-h) long-chain ω-3 enrichment markedly lowers glucose-stimulated hypersecretion of insulin after an intravenous glucose challenge in high-fat-fed rats. Glucose was administered as an intravenous bolus (0.5 g glucose/kg body wt) to the LOFAT, HIFAT, or F-HIFAT group. Studies were undertaken in conscious unrestrained rats in the postabsorptive state. Blood samples were withdrawn at intervals for measurement of plasma insulin and blood glucose using commercial kits. AIR values were calculated as the mean of suprabasal 2- and 5-min plasma insulin values. AGR values were calculated as the mean of suprabasal 2- and 5-min blood glucose values. Results are means ± SE for seven LOFAT rats, ten HIFAT rats, or six F-HIFAT rats. Statistically significant differences from LOFAT rats are indicated: *$P < 0.05$; **$P < 0.01$. Statistically significant effects of acute (24-h) enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids are indicated: ††$P < 0.01$.

nous glucose challenge as a consequence of high–saturated fat feeding for 4 weeks. High–saturated fat feeding for 4 weeks elicited a 1.9-fold increase in AIR ($P < 0.01$) (Fig. 1*A*), together with a 23% increase in AGR ($P < 0.05$) (Fig. 1*B*). Although the period of marine oil enrichment of the high–saturated fat diet was only 24 h, the relative response of insulin to a rapid increase in glycemia elicited by intravenous glucose challenge was greatly attenuated in the F-HIFAT group compared with the HIFAT group (Fig. 1*A*). This effect was reflected by a substantial decrease in AIR (50%; $P < 0.01$) compared with the HIFAT group (Fig. 1*A*). Consequently, the effect of antecedent high–saturated fat feeding to increase AIR was completely reversed. However, the AGR remained significantly higher (34%; $P < 0.01$) than that observed in the LOFAT group (Fig. 1*B*).

Enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids for 24 h impairs glucose tolerance. Postabsorptive blood glucose concentrations were modestly increased in both the HIFAT and F-HIFAT groups in comparison with the LOFAT group, although these increases did not achieve statistical significance (Table 1). Indexes of glucose tolerance, together with ΔI values, are shown for the three dietary groups in Fig. 2. The significant 1.9-fold increase ($P < 0.01$) in ΔI elicited by high-fat feeding (Fig. 2*A*) was accompanied by a significant increase in the integrated glucose area (ΔG) (33%; $P < 0.001$) (Fig. 2*B*). However, the 40% decline in ΔI due to an effect of marine oil enrichment of the high–saturated fat diet (Fig. 2*A*) was accompanied by a 23% increase in ΔG compared with the HIFAT group (Fig. 2*B*). As a consequence, the ΔG value in the F-HIFAT group was 64% higher ($P < 0.001$) compared with the ΔG value in the LOFAT group (Fig. 2*B*). Although high–saturated fat feeding resulted in an increase in ΔG, the *k* values for rates of glucose disappearance over the first 15 min after glucose challenge did not differ significantly between the LOFAT and HIFAT groups (Fig. 2*C*). This indicates that insulin hypersecretion can compensate for impaired insulin action in the high–saturated fat–fed group. Marine oil enrichment of the high–saturated fat diet elicited a 28% decline ($P < 0.05$) in the *k* value for glucose disappearance compared with the HIFAT group (Fig. 2*C*). As a conse-

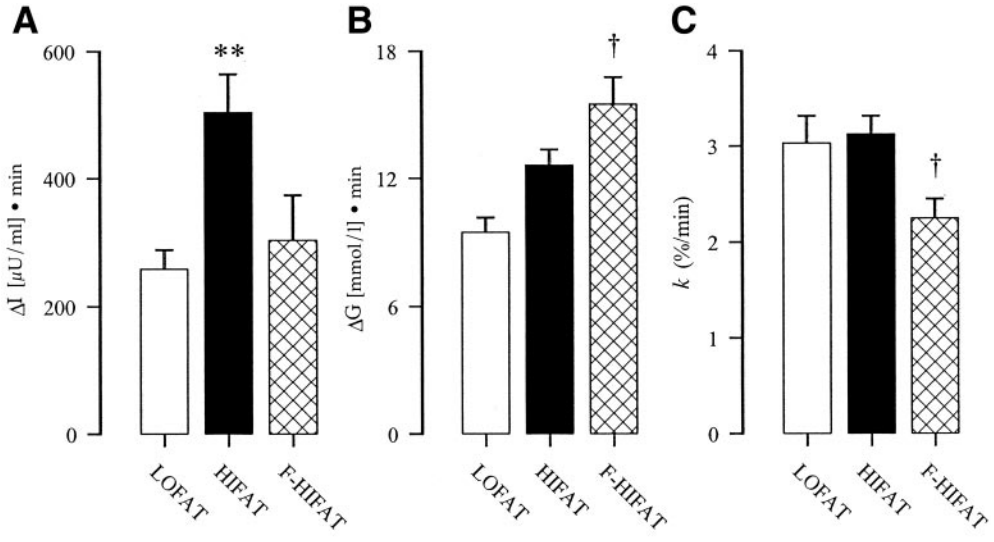

FIG. 2. Acute (24-h) long-chain ω-3 enrichment impairs glucose clearance after intravenous glucose challenge in high-fat–fed rats. Insulin and glucose responses during the glucose tolerance test were used for calculation of the incremental plasma insulin (ΔI; *A*) and blood glucose (ΔG; *B*) values integrated over the 30-min period after the injection of glucose, which are shown in *A* and *B*, respectively. Rates of glucose disappearance (*k*), calculated from the slopes of the regression lines obtained with log-transformed glucose values from 2 to 15 min after glucose administration and expressed as percent per minute, are shown in *C*. Further details are provided in the legend to Fig. 1. Results are means ± SE for seven LOFAT rats, ten HIFAT rats, or six F-HIFAT rats. Statistically significant differences from LOFAT rats are indicated: **$P < 0.01$. Statistically significant effects of acute (24-h) enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids are indicated: †$P < 0.05$.

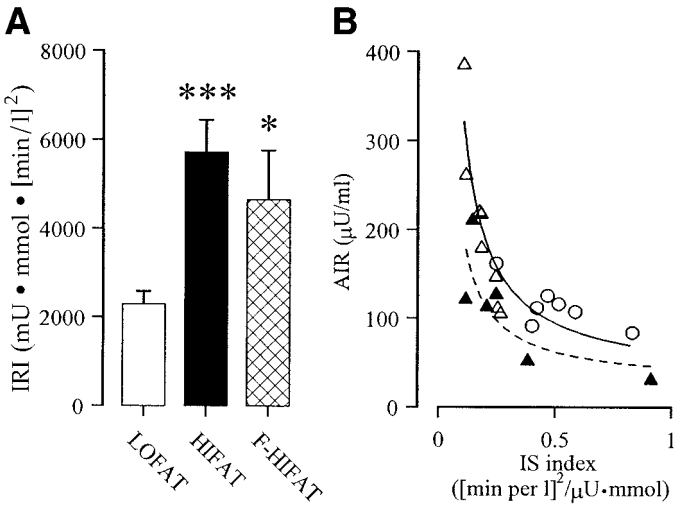

FIG. 3. Acute (24-h) long-chain ω-3 enrichment in vivo does not reverse insulin resistance elicited by high-fat feeding. The IRI, calculated as the product of the areas under the glucose and insulin curves after glucose challenge in the postabsorptive state, is shown in *A*. The relationship between AIR and ISI, the reciprocal of the IRI, in LOFAT rats (○), HIFAT rats (△), or F-HIFAT rats (▲) in the postabsorptive state is shown in *B*. Results are means ± SE for seven LOFAT rats, ten HIFAT rats, or six F-HIFAT rats. Statistically significant differences from LOFAT rats are indicated: *$P < 0.05$; ***$P < 0.001$. There were no statistically significant effects of acute (24-h) enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids compared with high-fat-fed rats.

quence, the k value was significantly lower (by 26%; $P < 0.05$) in the F-HIFAT group compared with the LOFAT group, indicating that insulin secretion in the former group is inadequate to maintain rates of glucose disposal, and thus compensatory insulin secretion is impaired.

Enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids for 24 h does not ameliorate high fat–induced insulin resistance in vivo. The IRI, the product of the areas under the glucose and insulin curves after glucose challenge, significantly increased after high–saturated fat feeding by 2.5-fold ($P < 0.001$) compared with the LOFAT group, indicating the development of insulin resistance (Fig. 3*A*), as has been demonstrated previously using the euglycemic-hyperinsulinemic clamp (3). Despite the markedly lowered ΔI, the IRI after enrichment of the high–saturated fat diet with marine oil was only modestly (19%) and not significantly lowered compared with the HIFAT group and was twofold higher ($P < 0.05$) than that in the LOFAT group. Increasing evidence indicates that changes in insulin sensitivity in healthy individuals are compensated for by inverse changes in β-cell responsiveness such that the product of insulin sensitivity and insulin secretion, termed the "disposition index," remains unchanged. Thus, a hyperbolic relationship exists between insulin sensitivity and secretion (17,18). Figure 3*B* demonstrates that a strong hyperbolic relationship exists ($r = 0.93$) between AIR and insulin sensitivity (assessed as the reciprocal of the IRI) for the LOFAT and HIFAT groups. Thus, enhanced insulin secretion in the HIFAT group is able to compensate for decreased insulin sensitivity. Although a similar hyperbolic relationship existed between insulin sensitivity and secretion in the F-HIFAT group ($r = 0.76$), there was a significant leftward shift in the curve, suggesting that the insulin secretory response to glucose is inappropriately low for the reduction in insulin sensitivity.

Long-chain ω-3 enrichment of a high–saturated fat diet exerts a rapid effect to lower insulin secretion by perifused islets. Additional experiments were undertaken to evaluate insulin release from perifused islets to eliminate any acute influences that in vivo variables, such as altered islet lipid delivery, might exert on insulin responses. Overall patterns of insulin release were measured during stepwise glucose perifusion designed to generate a steady rise in perifusate glucose concentrations to a target concentration of 8 mmol/l for 16 min. After this, the perifusate glucose concentration was increased to a target concentration of 16 mmol/l for a further 16 min, then lowered to basal levels over a total 2-h perifusion period. Rates of insulin release by islets isolated from LOFAT rats and perifused with 8 mmol/l glucose were not significantly higher than basal levels (Fig. 4*A*). However, raising the perifusate glucose concentration to 16 mmol/l led to a significant increase in rates of insulin release to peak rates (~97 μU/min) (Fig. 4*A*). Rates of insulin release then steadily declined toward basal once perifusate glucose concentrations returned to basal levels of ~2 mmol/l. Basal rates of insulin release by perifused islets isolated from HIFAT rats were significantly higher (by 59%; $P < 0.01$) compared with rates of insulin release by LOFAT perifused islets (Fig. 4). Although raising the perifusate glucose concentration to 8 mmol/l did not significantly increase rates of insulin release by perifused islets from HIFAT rats, insulin release rates were significantly higher than corresponding rates from perifused LOFAT islets. Raising the perifusate glucose concentration to 16 mmol/l resulted in more rapid increases in and higher rates of insulin release (by 2.8- to 4.3-fold; $P < 0.05$) compared with LOFAT islets. Peak rates of insulin release by perifused islets from HIFAT rats (153 μU/min) were 58% higher ($P < 0.01$) than corresponding peak rates of insulin release by perifused LOFAT islets. Although rates of insulin release by perifused islets from HIFAT rats steadily declined toward basal values once perifusate glucose concentrations returned to basal levels, they remained ~1.9-fold higher than corresponding LOFAT values.

Holding both the period of high–saturated fat feeding (4 weeks) and the total lipid content constant, the replacement of 7% of the dietary fat with long-chain ω-3 fatty acids for only 24 h resulted in a significant decrease in insulin release from perifused islets under conditions of glucose stimulation (Fig. 4*C*). Although acute (24-h) long-chain ω-3 enrichment of the HIFAT diet (F-HIFAT group) did not significantly affect insulin release rates by perifused islets at basal or mid-glucose concentrations (compare Fig. 4*B* and *C*), rates of insulin release by islets from F-HIFAT rats perifused at higher glucose concentrations were significantly and consistently lower (by 59%; $P < 0.05$) than those of islets of the HIFAT group. Decreased insulin release by perifused islets from F-HIFAT rats compared with HIFAT rats resulted in a 50% decline ($P < 0.05$) in the incremental area under the curve for insulin secretion during the 2-h perifusion period (HIFAT, 1,888 ± 357 μU/min per l [$n = 6$]; F-HIFAT, 949 ± 187 μU/min per l [$n = 6$]), such that it was similar to that of perifused islets from LOFAT rats. Thus, our data demonstrate, for the first

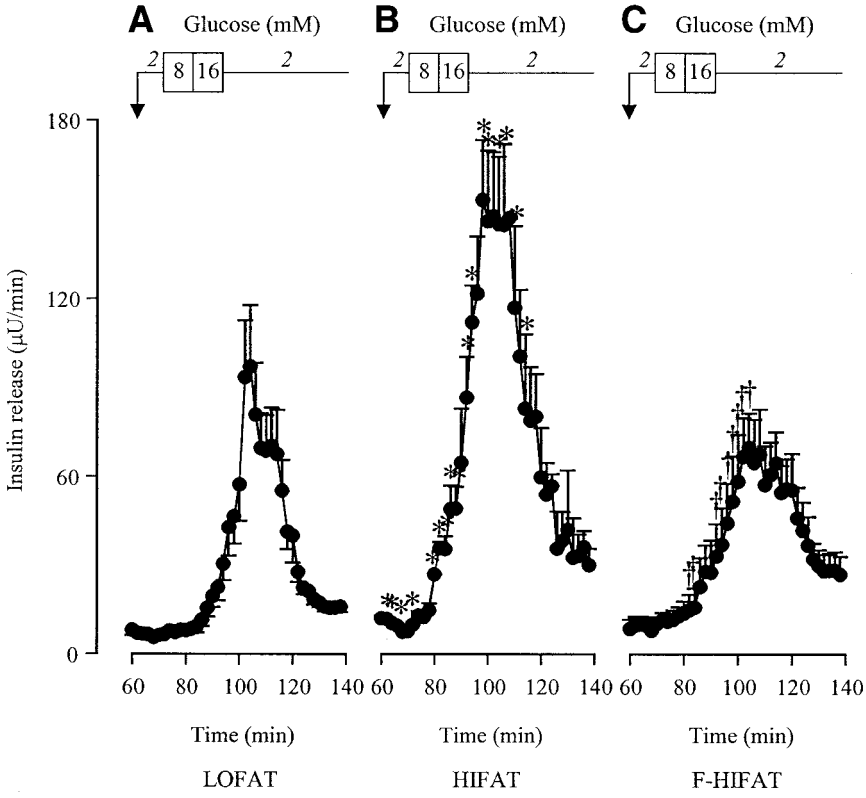

FIG. 4. Effects of chronic (4-week) high–saturated fat feeding or acute (24-h) long-chain ω-3 enrichment on insulin release by perifused islets. Islets isolated from LOFAT (*A*), HIFAT (*B*), or F-HIFAT (*C*) rats were perifused in basal medium containing 2 mmol/l glucose for 60 min at a flow rate of 1 ml/min at 37°C before collection of fractions. Glucose concentrations were then modified as indicated. Fractions (2 ml) were collected at 2-min intervals and stored at −20°C before assay for insulin using a commercial kit. Results are means ± SE for seven LOFAT rats, six HIFAT rats, or six F-HIFAT rats. Statistically significant effects of high–saturated fat feeding are indicated: *$P < 0.05$. Statistically significant effects of acute (24-h) enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids are indicated: †$P < 0.05$. Statistical symbols are placed above the relevant error bar.

time, that acute long-chain ω-3 enrichment of a high–saturated fat diet for only 24 h reverses the effects of antecedent long-term high–saturated fat feeding to enhance insulin secretion by perifused islets ex vivo.

DISCUSSION

The present study demonstrates that acute (24-h) enrichment of a high–saturated fat diet with long-chain ω-3 fatty acids attenuates insulin hypersecretion in vivo by rats previously provided with a high–saturated fat diet for 4 weeks and reverses the effects of long-term (4-week) high–saturated fat feeding to enhance insulin secretion by perifused islets. The substitution of only 7% of total dietary lipid with long-chain ω-3 fatty acid was adequate to provoke these effects; a high rate of delivery of saturated fat to the islet was maintained throughout. Our data therefore indicate that marine oil enrichment directly alters β-cell responses as insulin secretion by perifused islets is modified. Importantly, these effects were observed even though long-chain ω-3 enrichment failed to alleviate insulin resistance, resulting in an acute action of long-chain ω-3 enrichment to impair glucose tolerance after intravenous glucose challenge. The studies are important because they stress the labile nature of high–saturated fat–induced insulin hypersecretion and suggest that relatively acute (24-h) long-chain ω-3 enrichment could exert a diabetogenic effect, at least in the short term, by suppressing hyperinsulinemia without enhancing insulin sensitivity in insulin-resistant states via direct modulation of β-cell function. Thus, they demonstrate that altered insulin responses evoked by acute marine oil enrichment of a saturated fat diet do not simply reflect compensatory adaptations to differences in whole-body insulin sensitivity, but act directly at the level of the β-cell to modify insulin responsiveness to glucose.

Obesity is the most common cause of insulin resistance in humans (19). There is an inverse relationship between insulin sensitivity and insulin secretion, which is indicative of β-cell compensation for insulin resistance (17,18,20). The overall sensitivity of the β-cell to glucose has been thought to reflect the sensitivity of peripheral tissues to the action of insulin. Thus, insulin-resistant subjects have higher insulin levels and AIR to glucose than insulin-sensitive subjects (17,21). In a high proportion of obese subjects, β-cell compensation is able to maintain normal glucose tolerance for several decades, preventing the development of overt type 2 diabetes.

High–saturated fat feeding is a nongenetic factor that affects insulin sensitivity, but the factors that determine the ability of the β-cell to compensate for insulin resistance, and the mechanisms involved, remain largely unknown. Although it has been suggested that prolonged increased exposure to fatty acids through a lipotoxic effect on the β-cell could precipitate β-cell failure (20,22), this is not necessarily the case. Both our own and previous studies (12) do not favor the concept that prolonged exposure to excess saturated fatty acids inevitably impairs GSIS. Dobbins et al. (12) found that a soy oil–based diet resulted in insulin secretion rates both in vivo and in vitro that were lower than those found in control rats maintained on low-fat/high-carbohydrate diet. This led to the suggestion that the polyunsaturated fatty acids found in soy oil, predominantly linoleate (18:2), might elicit a diminished insulin response. Our studies indicate that, even under conditions of a sustained increase in saturated fatty acid delivery to the islet, the dietary provision of a small quantity of long-chain ω-3 fatty acids—eicosapentaenoate

(20:5) and docosahexaenoate (22:6) in the present study—rapidly (over 24 h) reverses the much more long-term (4-week) effects of high–saturated fat feeding to augment GSIS. Our data imply that the β-cell response to high–saturated fat feeding is both readily reversible and labile, rather than a pathological chronic and rigid adaptation of the β-cell to hypersecrete insulin.

Previous studies have shown that peripheral (but not hepatic) insulin resistance is ameliorated if the composition of a high-fat diet contains predominantly stearate (18:0) plus oleate (oleate > stearate) rather than predominantly linoleate plus oleate (18:1) (linoleate > oleate) (12). In addition, replacement of only 6% of fatty acids with long-chain ω-3 fatty acids from fish oil prevents the development of insulin resistance in rats fed a high–saturated fat diet (5). High–saturated fat–induced insulin resistance can also be ameliorated by acute dietary lipid withdrawal or by a single bout of exercise (23). Both the unsupplemented and ω-3 fatty acid–enriched HIFAT diets that we used in this study contained a similar total lipid content (47% of calories) and approximately equal quantities of saturated and monounsaturated fatty acids. However, fish oil enrichment resulted in a modest increase in linoleate and addition of both eicosapentaenoic and docosahexaenoic fatty acids at the expense of approximately equal quantities of saturated and monounsaturated fatty acids. Contrasting with previous studies, we observed that acute effects of fish oil enrichment to attenuate glucose-stimulated insulin hypersecretion in vivo and reverse glucose-stimulated insulin hypersecretion with perifused islets were not accompanied by an acute improvement in insulin sensitivity, and as a consequence, glucose tolerance was significantly impaired. It can thus be concluded that the islet response to fish oil–enriched high-fat diets does not represent a direct physiological response to attenuated peripheral insulin resistance. Rather, as supported by the data with perifused islets, saturated and ω-3 unsaturated fatty acids exert disparate effects directly on the islet, because insulin secretion is suppressed by acute ω-3 fatty acid enrichment without alleviation of insulin resistance, implying that, at least in the short term, these fatty acids exert a diabetogenic effect. Further studies are required to determine the molecular mechanisms that might be involved.

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