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Interaction of fish oil and a glucocorticoid on metabolic responses to an oral glucose load in healthy human subjects

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Compared with saturated fat, *n*-3 long-chain PUFA-rich fish oil improves insulin sensitivity in rats. We studied whether *n*-3 long-chain PUFA could prevent insulin resistance induced by dexamethasone (a glucocorticoid) in healthy human volunteers. A group of eight subjects was studied twice after a 2 d dexamethasone treatment, before and after a 3-week supplementation with fish oil (providing daily doses of 1·1 g 20 : 5*n*-3 and 0·7 g 22 : 6*n*-3). The subjects were studied during the basal state and over the 6 h following an oral glucose load (1 g/kg). Plasma glucose fluxes were traced with [6,6-$^2H_2$]glucose and [^{13}C]glucose (naturally ^{13}C-enriched corn glucose). Substrate oxidation was obtained from indirect calorimetry. Following fish oil supplementation, plasma glucose fluxes and substrate oxidation were maintained despite a 17 % reduction ($P<0·05$) in the area under the curve of plasma insulin response, suggesting an insulin-sensitizing effect.

Eicosapentaenoic acid: Docosahexaenoic acid: Polyunsaturated fatty acids: Stable isotopes: Insulin resistance

In rats, fish oil substitution in a high-fat or a high-sucrose diet prevents insulin resistance induced by these diets (Storlien *et al.* 1987, 1991; Podolin *et al.* 1998; Taouis *et al.* 2002). In man, contrasting effects of dietary fish oil supplementation have been reported. In healthy subjects, fish oil supplementation (6 g/d over 3 weeks, providing daily doses of 1·1 g EPA (20 : 5*n*-3) and 0·7 g DHA (22 : 6*n*-3)) decreased the insulinaemic response to an oral glucose load by 40 % while plasma glucose response remained unaffected (Delarue *et al.* 1996). This suggested a sensitizing effect of fish oil on insulin action, since insulin secretion has been shown to be related to insulin sensitivity (Kahn *et al.* 2003). However, in patients with type 2 diabetes, fish oil does not reverse insulin resistance (Borkman *et al.* 1989; Puhakainen *et al.* 1995; Rivellese *et al.* 1996) and does not improve plasma glucose control (Montori *et al.* 2000). Taken together, these studies demonstrate that fish oil is able to prevent insulin resistance in rat models of dietary-induced insulin resistance and to improve glucose metabolism in healthy subjects, but for unclear reasons is probably unable to reverse insulin resistance once it is established (review in Delarue *et al.* 2004).

Short-term dexamethasone treatment (2 d) induces a reversible well-characterized insulin resistance in healthy subjects. Dexamethasone is a synthetic glucocorticoid used mainly for treatment of chronic inflammatory diseases and for exploration of the hypophyso–adrenal axis. Insulin resistance induced by dexamethasone translates into decreased insulin-mediated plasma glucose utilization during a euglycaemic hyperinsulinaemic clamp (Tappy *et al.* 1994; Willi *et al.* 2002) and by a larger increase in plasma insulin and glucose responses to an oral glucose load (Wajngot *et al.* 1992; Schneiter & Tappy, 1998; Willi *et al.* 2002). Dexamethasone decreases phosphatidylinositol 3′-kinase activity (Saad *et al.* 1993) and the translocation of GLUT4 glucose transporters in rat muscle (Dimitriadis *et al.* 1997; Weinstein *et al.* 1998), both abnormalities also present in muscle of patients with type 2 diabetes (Cusi *et al.* 2000; Ryder *et al.* 2000). Troglitazone, a pharmacological ligand of PPARγ, has been demonstrated to antagonize the metabolic effects of dexamethasone in healthy human subjects. This translates into both a marked reduction of the excessive plasma insulin responses to oral glucose and an increase in plasma glucose utilization during a euglycaemic hyperinsulinaemic clamp (Willi *et al.* 2002). Because 20 : 5*n*-3 is a natural ligand of PPAR and because fish oil prevents the decrease in phosphatidylinositol 3′-kinase and GLUT 4 content in muscle of rats fed a diet high in *n*-6 PUFA (Taouis *et al.* 2002), dietary fish oil supplementation could antagonize the metabolic effects of dexamethasone in healthy human subjects.

To verify this hypothesis, the aim of the present work was to determine whether a 3-week dietary fish oil supplementation (6 g/d, providing 1·1 g 20 : 5*n*-3 and 0·7 g 22 : 6*n*-3

Abbreviations: RaE, rate of appearance of exogenous plasma glucose; RaT, total rate of plasma glucose appearance; RdT, total rate of plasma glucose disappearance.

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daily) was able to prevent, at least in part, the metabolic alterations induced by a 2 d treatment with dexamethasone in healthy subjects following an oral glucose load (1 g/kg).

Subjects and methods

Subjects

Eight healthy subjects (six males, two females; mean age 25·4 (SE 0·2) years, mean weight 61·5 (SE 3·2) kg and mean BMI 20·7 (SE 1·2) kg/m^2) were studied. The subjects were in good health, non-smokers and were not taking any drugs. None had a personal or family history of diabetes or hypertension. The subjects did not regularly take part in any strenuous physical activity and had no history of endurance training. Female subjects were studied during the follicular phase of their menstrual cycle. The experimental protocol was approved by the Ethical Committee of Tours. Before participating in the study, each subject gave informed written consent.

Materials

The fish oil was kindly provided by Roche (Ropufa 30; Roche, Basel, Switzerland). Oral glucose from corn was purchased from Sigma-Aldrich Chimie (Lyon, France). Its isotopic enrichment in ^{13}C was 1·0974 at%. [6,6-$^2H_2$]Glucose (99 mol% excess) was purchased from Cambridge Isotopes Laboratory (Andover, MA, USA). Isotopic and chemical purity were checked by GC–MS (Hewlett-Packard 5971 series II instrument; Hewlett-Packard, Les Ulis, France). The [6,6-$^2H_2$]glucose was prepared as sterile pyrogen-free solutions in normal saline. The solution was filtered through a 0·22 μm Millipore filter (Millipore Corp., Bedford, MA, USA) during priming and intravenous infusion.

Study design

Each subject was studied twice, 3 weeks apart. At day −2 and day −1 of each of the two tests the subjects were given 2 mg dexamethasone per os (4 × 0·5 mg/d). Over the 3 weeks between the two tests, the subjects received a dietary supplementation with fish oil given as six capsules of 1 g each daily (two capsules at breakfast, two capsules at lunch and two capsules at dinner, providing total daily doses of 1·1 g 20 : 5*n*-3 and 0·7 g 22 : 6*n*-3 fatty acids).

All experiments began in the morning after an overnight fast. The diet consumed 2 d preceding the studies was standardized to provide 200 g carbohydrates/d. Subjects were asked to maintain their usual physical activity. Ethanol was excluded and coffee intake was restrained to one cup a day throughout the study. On the morning of each experiment, the subjects reported to the laboratory at 07.00 hours. After voiding, they were transferred to a bed where they remained quietly in a semi-recumbent position. An indwelling catheter was inserted in a vein of the right wrist for blood sampling. This vein was kept open by a slow infusion of isotonic saline. The right hand was maintained in a box heated at 56°C in order to achieve partial arterialization of venous blood. A second indwelling catheter was inserted in a deep vein of the contralateral arm for tracer infusion. At $t = -150$ min, a primed (5·6 mg/kg) constant (0·07 mg/kg per min) infusion of [6,6-$^2H_2$]glucose was started and maintained over 510 min. At $t = 0$ min, the subjects ingested a solution of naturally ^{13}C-enriched glucose, 1 g/kg, over a 5 min period. A blood sample was taken at $t = -150$ min for determination of plasma glucose enrichment in ^{2}H and ^{13}C before tracer infusion. Other blood samples were taken at $t = 0$ min, then every 30 min until $t = 240$ min and then every 60 min from $t = 240$ to 360 min for determination of isotopic enrichment in ^{2}H and ^{13}C of plasma glucose, and substrate and insulin concentrations. Gas exchange measurements were performed from $t = -60$ min to $t = 360$ min using a ventilated canopy, as described previously (Delarue *et al.* 1994). Urine was collected during experiments for determination of N excretion.

Sampling and analytical procedures

Blood samples were immediately spun at 4°C. The plasma was separated into aliquots and frozen at −80°C until time of assay. Urine samples were frozen at −80°C for later determination of total urinary N. Plasma glucose concentrations were measured by the glucose oxidase method using a Beckman glucose analyser 2 (Beckman Instruments, Fullerton, CA, USA). NEFA concentrations were measured by an enzymatic colorimetric method with the use of a commercial kit (NEFA C; Wako Chemicals, Freiburg, Germany). Lactate concentrations were determined using standard enzymatic methods (Bergmeyer *et al.* 1977). Plasma insulin (INS-IRMA; Biosource Europe SA, Nivelles, Belgium) and C-peptide (Riagnost; Hoechst Behring, Marburg, Germany) concentrations were measured by RIA. The urinary N concentration was determined using the Kjeldahl method (Hawk, 1977). The isotopic enrichment in ^{2}H of plasma glucose was measured by electron impact ionization on the pentaacetate derivative of glucose and the selective monitoring of ions of *m/z* 200 and 202 by GC–MS (Hewlett-Packard 5971, series II) as previously described (Delarue *et al.* 1996). The isotopic enrichment in ^{13}C of plasma glucose following ingestion of the naturally ^{13}C-enriched glucose was measured on the pentaacetate derivative of glucose using GC–isotope ratio MS as previously described (Delarue *et al.* 1993).

Computations

Absolute area under the curve was calculated using basal values of plasma glucose or insulin as baseline. The total rates of appearance (RaT) and disappearance (RdT) of plasma glucose were calculated in non-steady state using the equation of Steele *et al.* (1956) as modified by De Bodo *et al.* (1963). Plasma rate of appearance of exogenous glucose (RaE) was calculated by transposition of the Steele equation as proposed by Proietto *et al.* (1987) and validated by Tissot *et al.* (1990). Endogenous glucose production was calculated as RaT minus RaE. Metabolic clearance rate of plasma glucose was calculated as RdT/glycaemia. Total carbohydrate and fat oxidations were calculated from VCO_2, VO_2 and urinary N excretion using the equations of Livesey & Elia (1988).

Statistical analyses

All data are expressed as means with their standard errors. Comparison of values between the two periods used

Table 1. Basal plasma metabolites after 2 d treatment with dexamethasone, with and without chronic fish oil (FO) supplementation

(Mean values and their standard errors)

	Without FO		With FO		Statistical significance
	Mean	SE	Mean	SE	
Glucose (mmo/l)	5·1	0·1	5·1	0·2	NS
Insulin (pmol/l)	66·0	3·6	74·4	4·2	NS
Lactate (mmol/l)	1·26	0·13	0·93	0·07	NS
NEFA (μmol/l)	754	59	676	67	NS

two-way ANOVA with a *post hoc* test (paired *t* test). Statistical calculations were performed in Statview™ II (Abacus Concepts Inc., Berkeley, CA, USA) running on a Powerbook G4 (Apple, Cuppertino, CA, USA).

Results

Metabolites and insulin

Basal plasma metabolites and insulin concentrations are reported in Table 1. There was no effect of fish oil on plasma glucose concentrations (Fig. 1(a)) and area under the curve of glucose (439 (SE 17) *v.* 440 (SE 11) pmol/ml per 6 h, without *v.* with fish oil, respectively). Insulinaemia during oral load was significantly lower with fish oil supplementation than without fish oil supplementation (ANOVA, $P<0{\cdot}05$; Fig. 1(b)). Area under the curve of insulin was decreased by 17 % with fish oil *v.* without fish oil (15 220 (SE 1200) *v.* 18 280 (SE 1210) pmol/ml per 6 h, respectively; $P<0{\cdot}05$). There was no effect of fish oil on plasma C-peptide (Fig. 1(c)), lactate and NEFA concentrations during the oral glucose load (Fig. 2(a and b)).

Plasma glucose fluxes

Basal RaT glucose was not different with and without fish oil supplementation (2·04 (SE 0·12) *v.* 2·14 (SE 0·12) mg/kg per min, respectively). Plasma glucose RaT, RdT and metabolic clearance rate (Fig. 3(a–c)) were not different with and without fish oil supplementation. RaE (Fig. 4(a)) and endogenous glucose production (Fig. 4(b)) were not different without and with fish oil.

Substrate oxidation

Basal carbohydrate oxidation was not different with and without fish oil supplementation (1·03 (SE 0·16) *v.* 1·24 (SE 0·1) mg/kg per min, respectively). Basal lipid oxidation was not different with and without fish oil supplementation (1·17 (SE 0·1) *v.* 1·10 (SE 0·07) mg/kg per min, respectively). Carbohydrate and lipid oxidations during oral glucose were not different without and with fish oil supplementation. (Fig. 5(a and b)).

Discussion

We have assessed the interaction between fish oil and glucocorticoids on the metabolic responses to oral glucose in healthy human subjects. Dexamethasone was chosen because it induces insulin resistance (Wajngot *et al.* 1992; Tappy *et al.* 1994; Schneiter & Tappy, 1998; Willi *et al.* 2002; Nicod *et al.* 2003).

Fish oil supplementation induced a modest but significant 17 % decrease in plasma insulin response without altering

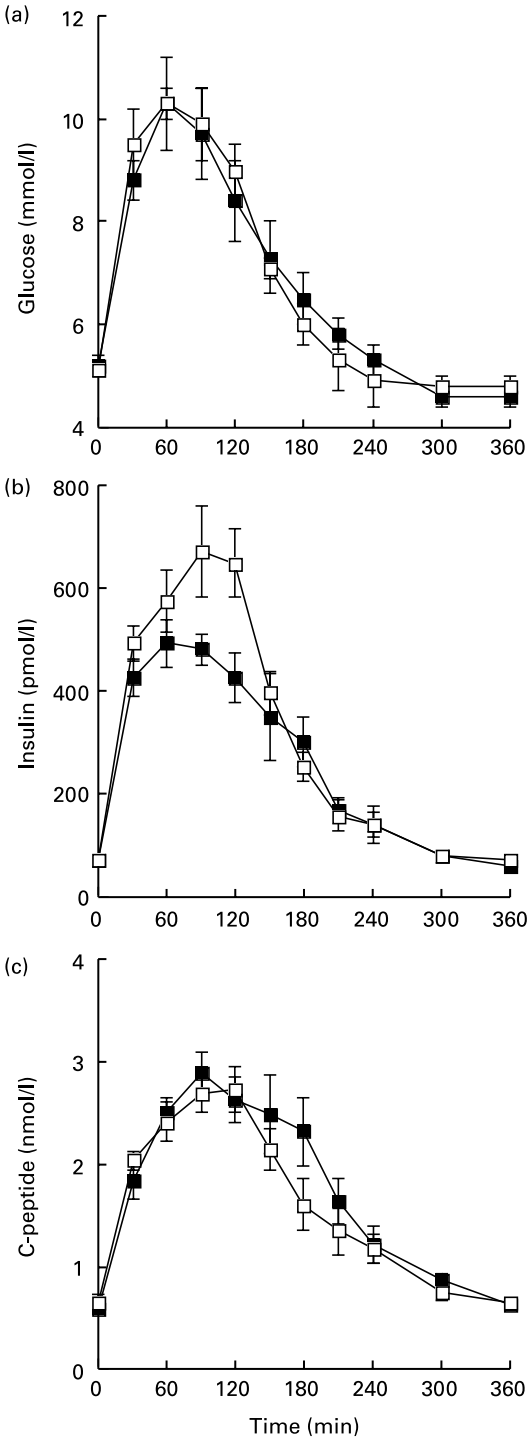

Fig. 1. Time course of plasma glucose (a), insulin (b) and C-peptide (c) in eight healthy subjects, pretreated with dexamethasone, without (□) or with (■) 3-week fish oil supplementation. Values are means with their standard errors shown by vertical bars. Fish oil supplementation had no statistically significant effect on glucose or C-peptide concentrations, but reduced insulin concentrations significantly compared with non-supplemented values ($P<0{\cdot}05$, ANOVA).

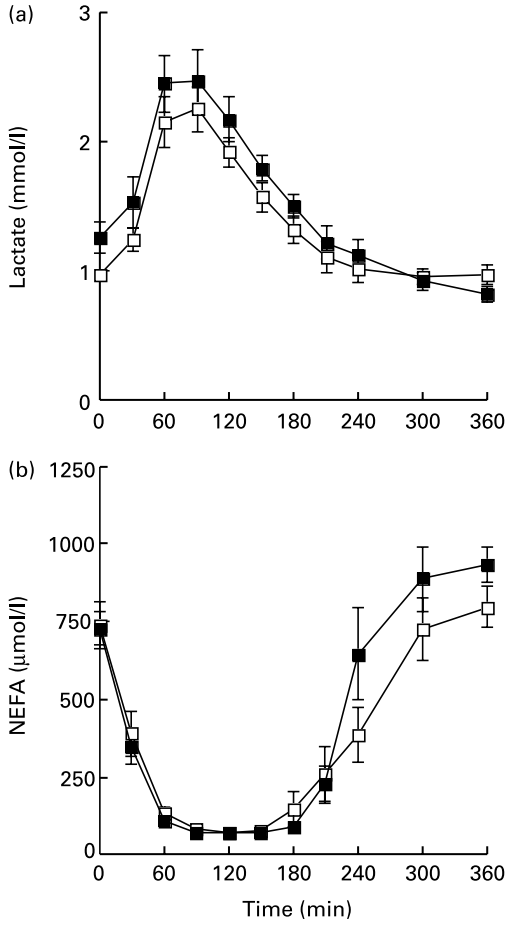

Fig. 2. Time course of plasma lactate (a) and NEFA (b) in eight healthy subjects, pretreated with dexamethasone, without (□) or with (■) 3-week fish oil supplementation. Values are means with their standard errors shown by vertical bars. Fish oil supplementation had no statistically significant effect on lactate or NEFA concentrations.

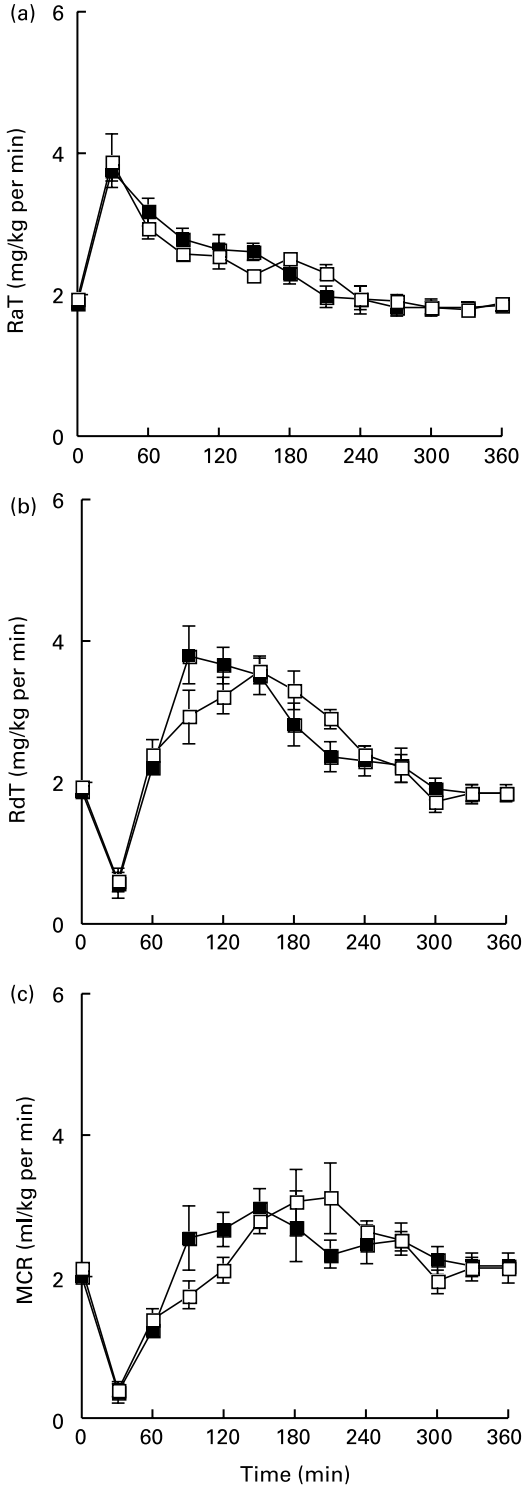

Fig. 3. Time course of plasma glucose total rate of appearance (RaT; a), disappearance (RdT; b) and metabolic clearance rate (MCR; c) in eight healthy subjects, pretreated with dexamethasone, without (□) or with (■) 3-week fish oil supplementation. Values are means with their standard errors shown by vertical bars. Fish oil supplementation had no statistically significant effect on RaT, RdT or MCR.

other metabolic parameters. The maintenance of plasma glucose disappearance and of substrate oxidation despite the significant decrease in plasma insulin response suggests an insulin-sensitizing effect of fish oil. The lack of effect of fish oil on plasma C-peptide response and on the molar ratio of plasma C-peptide : insulin argues against an effect on insulin secretion or insulin clearance. We have previously reported a 40% decrease in plasma insulin response after the same amount of fish oil supplementation in healthy subjects not pretreated with dexamethasone (Delarue *et al.* 1996). This larger effect of fish oil without dexamethasone can be explained mainly by the potent negative impact of dexamethasone on insulin sensitivity, preventing fish oil from exerting its full positive effect. Willi *et al.* (2002) have previously reported that the insulin-sensitizer troglitazone totally prevented the deleterious effect of dexamethasone on insulin sensitivity. In comparison, fish oil in the present study decreased postprandial insulin response, suggesting that it indeed prevented some of the metabolic effects of dexamethasone. However, the lowering of insulin concentration was less than with fish oil alone (Delarue *et al.* 1996), suggesting that fish oil did not completely prevent the effects of dexamethasone. Careful analysis of the data reported by Willi *et al.* (2002) similarly suggests that troglitazone only partially corrected the effect of dexamethasone, since the postprandial insulin responses remained higher after dexamethasone + troglitazone than after troglitazone alone.

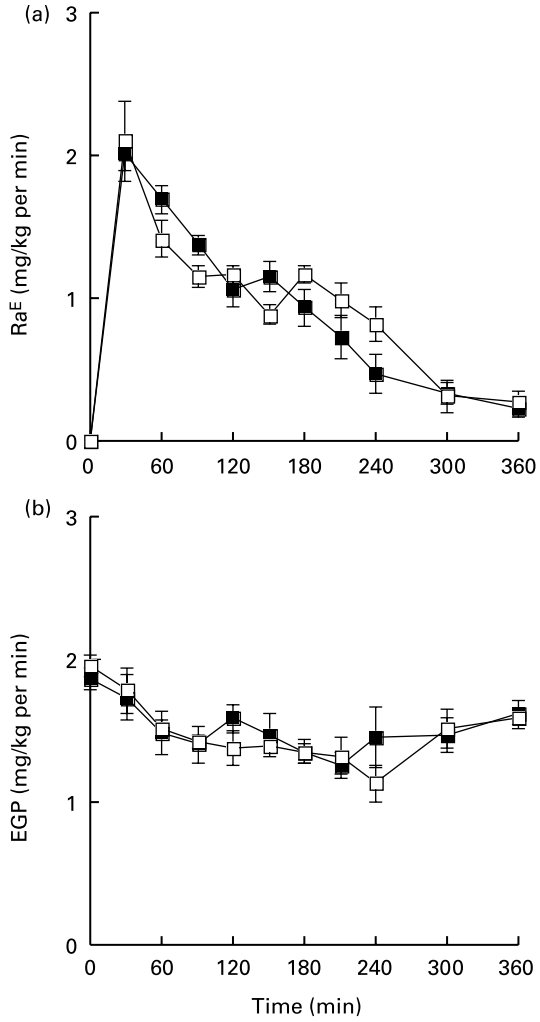

Fig. 4. Time course of rate of exogenous plasma glucose appearance (RaE; a) and endogenous glucose production (EGP; b) in eight healthy subjects, pretreated with dexamethasone, without (□) or with (■) 3-week fish oil supplementation. Values are means with their standard errors shown by vertical bars. Fish oil supplementation had no statistically significant effect on RaE or EGP.

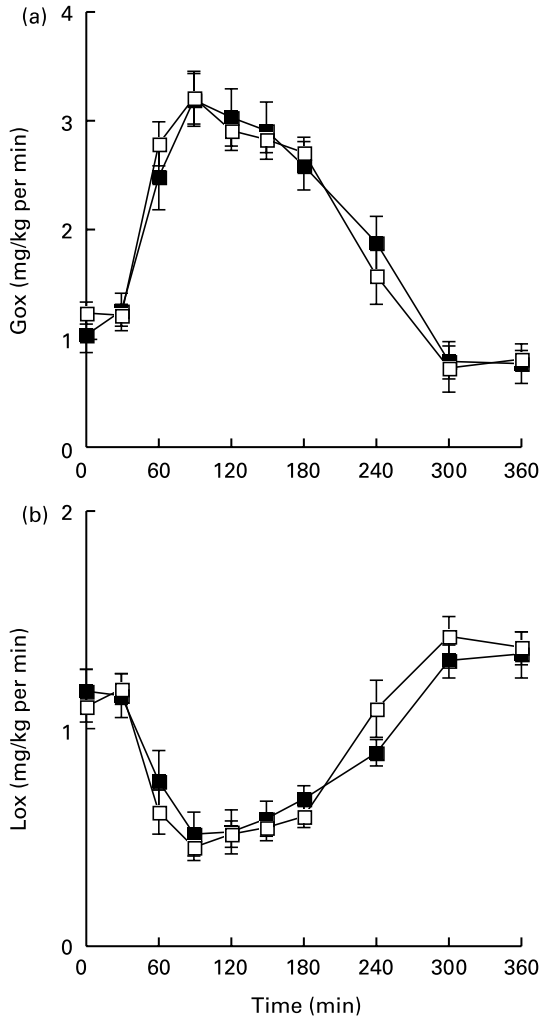

Fig. 5. Whole-body carbohydrate oxidation (Gox; a) and lipid oxidation (Lox; b) in eight healthy subjects, pretreated with dexamethasone, without (□) or with (■) 3-week fish oil supplementation. Values are means with their standard errors shown by vertical bars. Fish oil supplementation had no statistically significant effect on Gox or Lox.

The lack of randomization of fish oil intake in our study is an unlikely explanation for its effect on plasma insulin response. A cross-over study would have been an ideal design, but incorporation of 20 : 5*n*-3 and 22 : 6*n*-3 into membranes has been reported to take as long as 18 weeks (Endres *et al.* 1989), so that the two experiments should have been performed at least 18 weeks apart. During such a long period other confounding factors could appear. Subjects had very similar basal plasma metabolites and insulin concentrations, as well as basal plasma glucose fluxes and substrate oxidations, on the day of each of the two experiments, which demonstrates a similar metabolic state. Moreover, we have previously checked (data not shown), in a group of healthy subjects, that mean plasma glucose and insulin responses to an oral load of 1 g glucose/kg were similar over a 3-week interval.

In conclusion, the present study shows that a 3-week fish oil supplementation (1·8 g 20 : 5*n*-3 + 22 : 6*n*-3 daily) given prior to induction of insulin resistance by a 2 d dexamethasone treatment did not alter plasma glucose utilization and substrate oxidation despite a significant decrease (−17 %) in plasma insulin response to an oral glucose load. This suggests an insulin-sensitizing effect of fish oil, which could be of potential interest in subjects predisposed to insulin resistance.

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