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Paradoxical rise in serum adiponectin concentration in the face of 13-*cis*-retinoic acid-induced insulin resistance

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Abstract *Aims/hypothesis:* We previously reported that treatment of acne with 13-*cis*-retinoic acid causes insulin resistance and disturbances in lipid metabolism resembling those of the insulin-resistance syndrome. It is not known whether this is associated with alterations in the concentrations of serum adiponectin, an insulin-sensitising hormone secreted by adipocytes. *Materials and methods:* Eleven men (age 24 ± 2 years, BMI 22.1 ± 0.9 kg/m²) received 13-*cis*-retinoic acid (Roaccutan) treatment for acne for an average of 5 months. The insulin sensitivity of the subjects and concentrations of serum adiponectin were measured before, during and 1 month after the treatment by a euglycaemic–hyperinsulinaemic clamp and ELISA, respectively. *Results:* There was a reversible reduction in whole-body insulin sensitivity during therapy with 13-*cis*-retinoic acid. This was associated with a transient 34% increase in serum adiponectin concentration (from 5.3 ± 0.9 to 7.1 ± 1.2 µg/ml, $p < 0.05$), with a return to pretreatment levels by 1 month after the end of therapy. In the pretreatment study, as well as in the study performed 1 month after the end of

therapy, there was a small yet significant decrease in serum adiponectin concentration during a 4-h euglycaemic–hyperinsulinaemic clamp. This decrease was not observed in the clamp performed during treatment with 13-*cis*-retinoic acid. *Conclusions/interpretation:* There is a paradoxical increase in fasting serum adiponectin concentration during the 13-*cis*-retinoic acid-induced reduction in insulin sensitivity.

Keywords Adiponectin · Dyslipidaemia · Insulin resistance · Retinoic acid · Vitamin A

Abbreviations PPAR: peroxisome proliferator-activated receptor · RAR: retinoic acid receptor · RXR: retinoic X receptor

Introduction

Adiponectin is a circulating adipose-derived cytokine, which ameliorates insulin resistance in rodent models by increasing skeletal muscle fatty acid oxidation, suppressing hepatic glucose production and increasing muscle glucose uptake [1]. Vitamin A (retinol) and its metabolites play a complex role in the regulation of insulin sensitivity. Certain retinoic acid isomers increase insulin sensitivity by activating peroxisome proliferator-activated receptor (PPAR)-γ-retinoic X receptor (RXR) heterodimer [2]. However, the retinol metabolite 13-*cis*-retinoic acid, an inhibitor of sebum production used widely to treat severe acne, reduces insulin sensitivity [3] and induces alterations in serum lipid concentrations reminiscent of the metabolic syndrome. Specifically, serum triglyceride concentrations increase and serum HDL cholesterol concentrations decrease during 13-*cis*-retinoic acid therapy [3].

Circulating adiponectin concentrations are reduced in insulin-resistant states such as coronary artery disease, hypertension, metabolic syndrome or type 2 diabetes in humans [1]. However, it is not known whether 13-*cis*-retinoic acid treatment, which causes insulin resistance [3], alters serum adiponectin concentrations. Given the central

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Fig. 1 Fasting serum adiponectin concentration before, during and 1 month after the end of treatment with 13-*cis*-retinoic acid. Error bars: SEM. * $p < 0.05$ vs before treatment. $n = 11$, except after treatment ($n = 10$)

role of adiponectin in glucose and lipid metabolism [1], we determined serum adiponectin concentrations, insulin sensitivity and serum lipid concentrations in 11 healthy men in response to 13-*cis*-retinoic acid treatment for acne.

Subjects, materials and methods

Patients

We have previously reported the effect of 13-*cis*-retinoic acid (Roaccutan) treatment on whole-body insulin sensitivity and serum lipid concentrations in the subjects of the current study [3]. Briefly, 11 healthy men (24 ± 2 years, BMI 22.1 ± 0.9 kg/m²) attending the outpatient clinic of the Department of Dermatology, Helsinki University Central Hospital, were chosen by the clinician (A. Remitz) to receive 13-*cis*-retinoic acid (~ 0.5 mg/kg, 30–60 mg/day) for treatment of their acne, and were asked to participate in the study after they had given their written informed consent. Whole-body insulin sensitivity was measured with a euglycaemic-hyperinsulinaemic clamp (insulin infusion rate 72 mU [m²]⁻¹ min⁻¹) before the start of treatment with 13-*cis*-retinoic acid, at 5 months (range 4–6 months) of

treatment, and 1 month (range 1–3 months) after the end of treatment [3]. The study protocol was approved by the Ethical Committee of the Helsinki University Central Hospital.

Adiponectin

Serum adiponectin concentrations were determined with an ELISA (R&D Systems, Wiesbaden-Nordenstadt, Germany) in blood samples taken in the fasting state and at the end of 240 min of euglycaemic hyperinsulinaemia.

Statistical analysis

Data are expressed as means $\pm$ SEM. Wilcoxon's test was used in the analysis of paired items. Correlation analysis was done with Spearman's test. A p value of < 0.05 was considered significant.

Results

Changes in serum substrate and hormone concentrations as well as insulin-stimulated glucose disposal rates have been reported in our previous publication [3]. Briefly, the rates of oxidative and non-oxidative glucose metabolism fell by 12% ($p < 0.05$) and 8% ($p = 0.05$) during the treatment with 13-*cis*-retinoic acid, respectively, and were back to baseline 1 month after the treatment was stopped. Similarly, the rate of whole-body glucose disposal fell by 8% ($p < 0.02$) during treatment and was back to baseline 1 month after the treatment was stopped. Fasting serum total cholesterol concentrations increased by 12% (from 3.8 ± 0.1 to 4.3 ± 0.2 mmol/l, $p < 0.02$) during treatment, whereas fasting serum HDL cholesterol concentrations fell by 11% (from 1.49 ± 0.10 to 1.32 ± 0.10 mmol/l, $p = 0.05$ vs baseline). Fasting serum triglyceride concentrations increased by 37% during treatment (from 0.68 ± 0.07 to 0.94 ± 0.10 mmol/l, $p < 0.02$) and fasting serum LDL cholesterol concentrations increased by 24% (from 2.05 ± 0.16 to 2.55 ± 0.22 mmol/l, $p < 0.02$).

Fig. 2 Serum adiponectin concentration was determined in the fasting state and in response to a 240-min euglycaemic-hyperinsulinaemic clamp. Determinations were performed before, during and 1 month after the end of treatment with 13-*cis*-retinoic acid. * $p \leq 0.05$ vs fasting, $n = 11$, except after treatment ($n = 10$)

Fasting serum adiponectin concentration increased by 34% (from 5.3 ± 0.9 vs 7.1 ± 1.2 $\mu\text{g/ml}$, $p < 0.05$, Fig. 1) during treatment, with a return to pretreatment levels by 1 month after the end of treatment. During a 240-min insulin infusion, there was a small yet significant decrease in serum adiponectin concentration in the studies performed before the start of (8% reduction, $p = 0.05$) and 1 month after the end of treatment (16%, reduction, $p < 0.05$), respectively (Fig. 2). The effect of insulin infusion on serum adiponectin concentration was not observed in the clamp performed during treatment. Fasting serum adiponectin correlated negatively with fasting serum triglyceride concentrations measured either before the start of (Spearman $r = -0.67$, $p < 0.05$) or during treatment (Spearman $r = -0.68$, $p = 0.02$).

Discussion

We report the first drug-induced dissociation of the relationship between adiponectin and insulin sensitivity. Interventions that increase insulin sensitivity such as therapy with thiazolidinediones [1, 4] or weight loss [5] usually result in increased serum adiponectin concentration. However, during 13-*cis*-retinoic acid treatment we observed a reduction in insulin sensitivity [3], and, paradoxically, a marked increase in fasting serum adiponectin concentration. Thus, serum adiponectin does not always reflect systemic insulin sensitivity. The dissociation between insulin sensitivity and adiponectin has been described previously in some physiological situations. For example, exercise training for 6 months augments insulin action but does not change plasma adiponectin concentration [5]. Moreover, pre-eclampsia, which is an insulin-resistant state, is characterised by increased, instead of reduced, serum adiponectin concentrations [6].

Insulin infusion for 240 min reduced serum adiponectin concentration by 8–16%. Interestingly, when the subjects had been on 13-*cis*-retinoic acid treatment for 5 months, there was no change in serum adiponectin concentration in response to insulin during the clamp study. Since insulin-stimulated glucose metabolism of the subjects was reduced at this time, our finding suggests a resistance to insulin regulation of adiponectin during treatment. Our observation that serum adiponectin concentration decreases during insulin exposure is in agreement with other groups who have also shown a ~20% decrease in circulating adiponectin concentrations by hyperinsulinaemia during clamp studies [4]. Collectively, reduced serum adiponectin concentration in insulin-resistant states such as obesity and type 2 diabetes may be a consequence of the chronic hyperinsulinaemia associated with these clinical entities.

The molecular basis of the increase in serum adiponectin concentration during 13-*cis*-retinoic acid therapy is unknown. The effects of vitamin A and its metabolites are mediated at least through two different kind of nuclear receptors: retinoic acid receptor (RAR) and RXR. Human adiponectin promoter contains a functional PPAR-response

element, and PPAR γ -RXR heterodimer transactivates human adiponectin promoter leading to increased adiponectin in response to PPAR γ agonism [7]. In contrast, a single dose of retinoic acid results in a 40% decrease in adiponectin mRNA in rat adipose tissue [8]. We observed an increase in serum adiponectin concentration in response to the vitamin A metabolite 13-*cis*-retinoic acid. Since 13-*cis*-retinoic acid binds to RAR with low affinity, while it does not bind to RXR [9], it is possible that 13-*cis*-retinoic acid competes with retinoic acid on RAR, thereby inhibiting the decrease of adiponectin that is effected by retinoic acid [8]. Clearly, such a hypothesis awaits experimental evidence from cell models. On the other hand, serum retinol-binding protein 4, the only specific transport protein for vitamin A, is increased in insulin-resistant animal models and obese or type 2 diabetic humans, and causes insulin resistance [10]. Future studies are needed to determine whether retinol-binding protein 4 plays a role in the insulin resistance induced by 13-*cis*-retinoic acid and in adiponectin metabolism.

In conclusion, treatment of acne with 13-*cis*-retinoic acid results in a paradoxical increase in fasting serum adiponectin concentrations in the face of the 13-*cis*-retinoic acid-induced reduction in insulin sensitivity. Given the insulin-sensitising action of adiponectin [1], the increase in serum adiponectin concentration might be viewed as a physiological adaptation to counteract alterations in systemic insulin sensitivity during therapy with 13-*cis*-retinoic acid.

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