0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism
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Vol. 83, No. 3
Printed in U.S.A.

Omental and Subcutaneous Adipose Tissues of Obese Subjects Release Interleukin-6: Depot Difference and Regulation by Glucocorticoid*

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ABSTRACT

The purpose of this study was to determine whether human adipocytes from different depots of obese subjects produce interleukin-6 (IL-6) and whether IL-6 release is regulated by glucocorticoids. Fragments of omental and abdominal sc adipose tissue released immunodetectable IL-6 into the medium during acute incubations. Omental adipose tissue released 2–3 times more IL-6 than did sc adipose tissue. Isolated adipocytes prepared from these tissues also released IL-6 (omental > sc), but this accounted for only 10% of the total tissue release. Culture of adipose tissue fragments for 7 days with the glucocorticoid dexamethasone markedly suppressed IL-6 production. These data show for the first time that substantial quantities of IL-6 (up to 75 ng/mL) accumulate in the medium during incubations of both adipocytes and adipose tissue. Although little is known about the effects of IL-6 on adipose tissue, one action is a down-regulation of adipose tissue lipoprotein lipase. The regulated production of this multifunctional cytokine may modulate regional adipose tissue metabolism and may contribute to the recently reported correlation between serum IL-6 and the level of obesity. (*J Clin Endocrinol Metab* **83:** 847–850, 1998)

ADIPOCYTES express a number of cytokines (1–4). Adipocyte production of tumor necrosis factor-α (TNFα) increases with fat cell enlargement in obesity and appears to function as a feedback inhibitor of adiposity by inducing cellular insulin resistance (5–7). Limited evidence indicates that adipose tissue also produces another ubiquitous cytokine, interleukin-6 (IL-6). IL-6 is a multifunctional cytokine produced by many different cell types, including immune cells, fibroblasts, endothelial cells, myocytes, and a variety of endocrine cells (8, 9). Like TNFα, IL-6 decreases adipose tissue lipoprotein lipase (LPL) activity and has been implicated in the fat wasting that occurs during cancer cachexia (10, 11). Interestingly, a recent study showed that serum IL-6 concentrations were positively correlated with the level of obesity as assessed by body mass index (BMI) (12).

Immunodetectable IL-6 accumulates in the medium of explant cultures of human mammary adipose tissue (13). Adipocytes (14, 15) or stromal-vascular cells (16) may be a source of this IL-6. No previous studies have examined whether the human adipocytes themselves produce IL-6 and whether there are differences between visceral and sc fat depots in IL-6 expression. Depot differences in cytokine expression would be expected based on an extensive literature demonstrating that visceral (including omental) and subcutaneous (sc) fat cells differ metabolically. For example, omental fat cells are more responsive to catecholamines and less sensitive to insulin (17). Thus, in the present study we examined IL-6 release by omental and sc adipose tissue and isolated adipocytes. Because glucocorticoids potently decrease IL-6 expression in a number of cell types (9), we also assessed the effect of dexamethasone on the IL-6 concentration in the medium of cultured adipose tissue.

Materials and Methods

Subjects

Subjects (n = 10; four men and six women) were severely obese, nondiabetic patients undergoing obesity surgery. The mean BMI was 52 ± 2 kg/m^2 (range, 44–68), and the mean age was 38 ± 3 yr. None was taking drugs that may affect adipocyte metabolism, such as steroids. Three subjects were taking antihypertensives (angiotensin-converting enzyme inhibitors, antidiuretics, and/or calcium channel blockers). One 52-yr-old woman was taking hormone replacement therapy, and the remainder were premenopausal. There were no gender-related differences in IL-6 release in this sample, so all data were pooled. All protocols were approved by the internal review boards of the University of Medicine and Dentistry of New Jersey and Rutgers University.

Sleep apnea is reported to be independently associated with elevated serum IL-6 (12). Although documentation was not available, two subjects reported a diagnosis of sleep apnea, so we determined whether this factor influenced the results. One subject who reported sleep apnea was used for study of IL-6 secretion in incubated adipose tissue. His values [104 (omental) and 29 (sc) ng/g] were similar to the group mean (Fig. 1). Samples of sc adipose tissue from the other subject with sleep apnea were used for the time-course study, and his values also did not deviate from the mean of the group.

Tissue or cell incubations

Human omental or abdominal sc adipose tissue was obtained within 30 min after the start of surgery and processed as previously described (18). Aliquots of minced tissue fragments (5–10 mg each, total of 100 mg) were placed in 1 mL medium 199 containing 1% albumin (CRG-7, Intergen, Purchase, NY), pH 7.4, and incubated for up to 3 h under an

Received September 24, 1997. Revision received November 7, 1997. Accepted December 2, 1997.

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* This work was supported by grants from the New Jersey Agricultural Experiment Station and the American Diabetes Association (to S.K.F.) and the USDA (Contract 53–3KO6–5-10; to A.S.G.).

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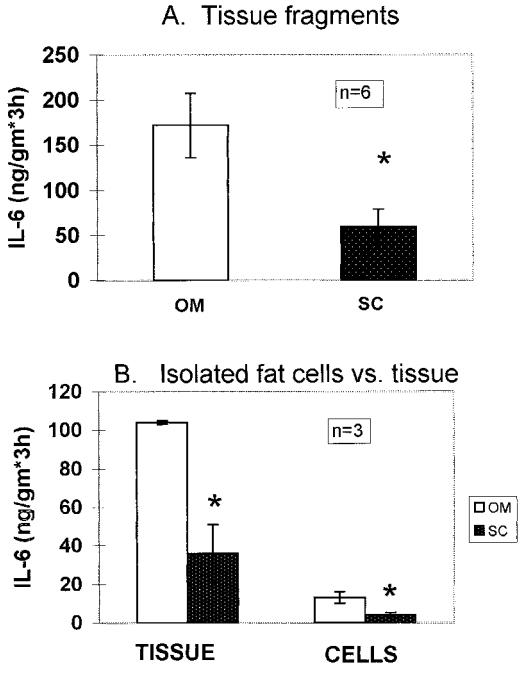

FIG. 1. IL-6 secretion from omental and sc adipose tissue. A, Adipose tissue from omental (Om) and sc depots of six subjects were minced and incubated for 3 h in medium 199 containing 1% BSA. The IL-6 concentration in the medium was determined by enzyme-linked immunosorbent assay. Data are the mean ± SEM of values for paired samples of omental and sc from six subjects (three men and three women). B, IL-6 secretion from tissue fragments and isolated fat cells prepared from paired omental and sc fat depots of three subjects. Isolated adipocytes were incubated for 3 h in medium 199 containing 1% BSA and 100 nmol/L phenylisopropyladenosine. *, $P < 0.05$, by paired t test.

atmosphere of 95% O_2-5% CO_2. At the end of the incubation, samples of the incubation medium were frozen at −80 C. Isolated cells were prepared by collagenase digestion as previously described (18). Phenylisopropyladenosine (100 nmol/L) was included in digestion, cell washing, and incubation steps to suppress lipolysis and to prevent cell lysis (19). Fat cell size and number were determined by measuring the diameter of at least 150 cells (20) or by osmium fixation and Coulter counting (Coulter Electronics, Hialeah, FL) (21).

Culture of adipose tissue

Minced adipose tissue fragments (~300–500 mg/15 mL) were placed in organ culture in serum-free medium 199 (without albumin) as previously described (18). Cultures were supplemented with or without 7 nmol/L insulin (Humulin) in the absence or presence of dexamethasone (2.5 or 25 nmol/L). Cultures were maintained for up to 7 days, with replenishment of medium with fresh hormones every 2–3 days. Samples of medium were collected, 24 h after medium was last exchanged, on days 1, 4, and 7 of culture and frozen at −80 C.

Determination of IL-6

Immunodetectable IL-6 was measured in aliquots of incubation or culture medium using a sandwich immunoassay [Cytokine Direct, Intergen (Purchase, NY) and R&D Systems (Minneapolis, MN)]. An antihuman monoclonal antibody was used for capture, and a rabbit antihuman IL-6 antibody was used for detection. Samples were diluted (up to 1:100) using the same buffer as culture/incubations, so that values fell within the linear range of the assay (6–500 pg/mL).

Statistical analysis

Paired t tests were used for within-subject comparison of the effect of depot (omental *vs.* sc) on rates of IL-6 release. The effects of time of culture (1 *vs.* 7 days) and hormone treatment were first determined for each depot by repeated measures ANOVA (2 × 4 design). As the main effects for time and hormone treatment were significant ($P < 0.05$), the effects of insulin and dexamethasone on day 1 or 7 of culture were analyzed by a 2 × 2 repeated measures ANOVA. *Post-hoc* paired t tests were used to compare different hormone treatments when main effects were significant by ANOVA ($P < 0.05$).

Results

IL-6 release into the incubation medium was 3-fold higher in omental than abdominal sc adipose tissue ($P < 0.015$; Fig. 1A). This difference could not be explained on the basis of fat cell size, which was, on the average, similar between depots in these subjects [0.9 ± 0.1 μg lipid/cell (omental) *vs.* 0.9 ± 0.1 (sc); n = 6; three men and three women]. To assess whether the source of the IL-6 released during tissue incubations was the fat cell, IL-6 release from collagenase-isolated omental or sc fat cells was determined in a subset of subjects. IL-6 release from isolated omental adipocytes was significantly greater than that from sc adipocytes (Fig. 1B). On a per lipid weight or per fat cell basis, only 10% of the amount of IL-6 released by intact adipose tissue fragments could be accounted for by release from isolated fat cells (Fig. 1B). Preliminary studies showed that the release of IL-6 from isolated adipocytes into the incubation medium was linear with time (not shown).

A time course for IL-6 release into the medium during culture of omental adipose tissue for up to 7 days is shown in Fig. 2. IL-6 release tended to fall over time in culture ($P < 0.02$, by ANOVA). Dexamethasone decreased the amount of immunodetectable IL-6 in the culture medium in the presence or absence of insulin ($P < 0.01$, by ANOVA). Culture with insulin had no effect on IL-6 release.

Samples of omental and sc adipose tissue from the same subjects were compared after culture for 1 or 7 days (Table 1). As expected from the depot difference noted in acute incubations of tissue, IL-6 release was markedly higher in

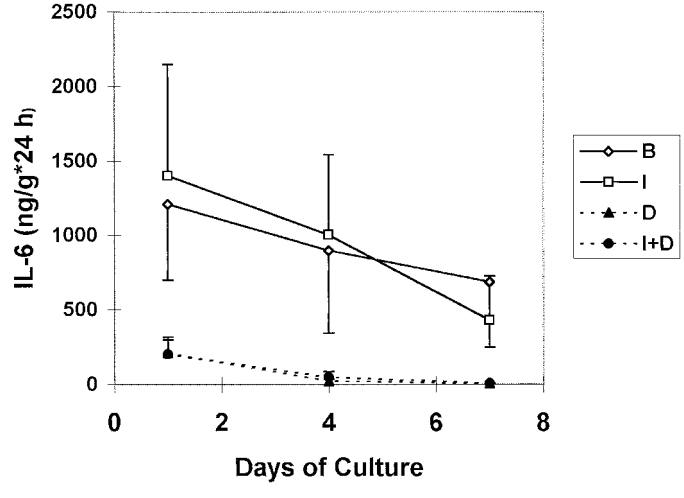

FIG. 2. Time course of IL-6 release from omental adipose tissue placed in organ culture. Omental adipose tissue from three subjects was placed in organ culture. The IL-6 concentration in the medium was determined on days 1, 3, and 7 of culture after medium was replenished 24 h previously. Repeated measures ANOVA demonstrated statistically significant effects of time (day of culture, $P < 0.02$) and dexamethasone ($P < 0.001$).

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TABLE 1. Comparison of IL-6 release from omental and sc adipose tissue during organ culture

	IL-6 release (ng/g·day)			
	Basal	Ins	Dex	Ins + Dex
Subcutaneous				
Day 1	17 ± 2	24 ± 10	6.6 ± 1	7.9 ± 1
% of control			37 ± 13	53 ± 34
Day 7	3.8 ± 1.1	9.7 ± 1.4	0.4 ± 0.2[a]	0.1 ± 0.1[b]
% of control			1 ± 1	1 ± 1
Omental				
Day 1	642 ± 476[c]	1245 ± 1060[c]	57 ± 12[b,c]	57.3 ± 6.1[c]
% of control			28 ± 13	29 ± 20
Day 7	333 ± 232[c]	208 ± 77[c]	0.6 ± 0.3[a]	2.0 ± 1.5[b]
% of control			13 ± 1	1 ± 0

Adipose tissue from the omental and sc fat deposits of three subjects was cultured with no additions (basal), 7 nmol/L insulin (Ins), 25 nmol/L dexamethasone (Dex), or Ins plus Dex for 1 or 7 days. Medium was replenished on days 1, 3, and 6 of culture. Thus, the values for day 7 represent the amount of IL-6 (mean ± SEM) accumulating in the culture medium during the final day of culture. The main effects of depot and of Dex were significant by ANOVA ($P < 0.05$). Significance was determined by *post-hoc* two-tailed paired *t* tests. % of control refers to the comparison of basal *vs.* Dex or insulin *vs.* Ins + Dex calculated for each subject.

[a] $P = 0.055$, effect of Dex *vs.* appropriate control, with or without insulin.

[b] $P < 0.05$, effect of Dex *vs.* appropriate control, with or without insulin.

[c] $P < 0.05$, omental *vs.* sc under same hormone condition and day.

cultured omental compared to sc adipose tissue under each culture condition on day 1. This depot difference persisted after culture for 7 days under basal conditions or insulin alone. However, dexamethasone decreased IL-6 release by omental and sc adipose tissue to similarly low levels after 7 days of culture. In both depots, dexamethasone decreased IL-6 accumulation in the medium by up to 100-fold. The absolute concentrations of IL-6 in the medium after 1 day of culture without dexamethasone ranged from 1–75 ng/mL and were decreased to less than 100 pg/mL after 7 days of culture with dexamethasone.

Discussion

Increasing evidence points to the importance of locally produced cytokines in the regulation of adipocyte metabolism (4, 5). The present results demonstrate that IL-6 is released from human adipose tissue of obese subjects. Omental adipose tissue produces 3-fold more IL-6 than sc adipose tissue. Adipocytes isolated from the omental depot also secrete more IL-6 than those from the sc depot. Although it is clear that adipocytes themselves secrete IL-6, they account for only 10% of the total tissue production. Thus, other cells within adipose tissue must also contribute to the high release of IL-6. This result is not surprising because IL-6 production in stromal-vascular cells isolated from human mammary adipose tissue has been previously demonstrated (13, 16), and endothelial cells as well as fibroblasts are known to express IL-6 (22). Thus, IL-6 may be both an autocrine and a paracrine regulator of adipocyte function. Regardless of the cellular source of IL-6 within adipose tissue, the present results raise the possibility that adipose tissue is an important source of the elevated serum IL-6 levels noted in obesity and suggest that different adipose depots may make different contributions to the serum pool. Furthermore, depot differences in the IL-6 concentration may contribute to depot differences in adipose tissue metabolism.

In the present study we examined adipose tissue solely from severely obese subjects. Previous studies have demonstrated much higher rates of TNFα production in adipose tissue from obese than lean subjects (37). It will clearly be important to compare the rates of IL-6 production in subjects with varying levels of adiposity and as a function of adipose tissue distribution. In addition, sleep apnea, which is commonly associated with severe obesity, is reported to be an independent correlate of serum IL-6 (12). Values for the two subjects reporting sleep apnea did not differ from the group means, but further investigation of this issue appears warranted.

The amount of IL-6 produced by adipose tissue is equal to or greater than that reported for a variety of other tissues and cells (23, 24). The concentrations of IL-6 that accumulate in adipose tissue or cell incubations (up to 75 ng/mL) are well within a range that can elicit biological effects (11, 25). IL-6 produced by adipose tissue may act in a paracrine manner in addition to possible effects on other tissues. IL-6 is considered to be an inflammatory mediator as well as a stress-induced cytokine (26). It has pleiotropic effects on a variety of tissues (8, 27, 28), including down-regulation of adipocyte LPL (14), stimulation of acute phase protein synthesis, and stimulation of the hypothalamic-pituitary axis. Because the venous drainage from omental adipose tissue flows directly into the liver, the metabolic impact of IL-6 release from omental adipose tissue may be of particular importance. For example, IL-6 increases hepatic triglyceride secretion (29) and may, therefore, contribute to the hypertriglyceridemia associated with visceral obesity.

IL-6 is secreted from adipose tissue under basal conditions, *i.e.* without additions to the medium. It is possible that adipose tissue TNFα, whose expression is increased in obesity, induces adipocyte and nonadipocyte IL-6 expression. TNFα produces a 60-fold increase in IL-6 production in differentiated 3T3-L1 adipocytes (30). It will also be important to examine potential modulators of IL-6 expression in different fat depots, such as catecholamines (31).

IL-6 production tended to decline over days of culture, even in the absence of glucocorticoids. The decline in IL-6 over time is not a nonspecific consequence of a compromise in function of adipose tissue in organ culture. We have previously noted that adipose tissue LPL activity and messenger ribonucleic acid levels are greater than the initial values after 1 week of culture (18) (our unpublished observations).

Results from organ culture studies showed that adipose tissue production of IL-6 was regulated by glucocorticoid, but that insulin had no effect. The effect of dexamethasone was present as early as 24 h of culture and persisted for 7 days. These data suggest that cortisol may act physiologically to modulate IL-6 production by adipose tissue.

Increased cortisol turnover is a feature of the obese state and is exaggerated in upper body (usually visceral) obesity (32). Recent studies indicate that IL-6 directly stimulates adrenal cortisol release in addition to stimulating hypothalamic CRH and pituitary ACTH release (33–35). Adipose tissue IL-6 may, therefore, act as a feedforward regulator of hypo-

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thalamic-pituitary axis function. Cortisol suppression of adipose IL-6 production may serve as a feedback inhibitor of this regulatory loop. Adrenal cortisol production could be influenced by IL-6 originating from perirenal adipose tissue surrounding the adrenal gland itself.

The metabolic effects of IL-6 on adipose tissue have not been extensively studied. IL-6, like TNFα, appears to have potent effects on adipose tissue, as demonstrated by the fact that neutralization of either cytokine decreases the loss of adipose tissue in cachexia (10, 36). It seems unlikely that this effect is mediated solely by the documented ability of IL-6 to down-regulate LPL activity, implying that IL-6 has multiple effects on adipocyte metabolism. The present data demonstrate a high rate of IL-6 production in adipose tissue of obese subjects, particularly in the omental depot, and suggest that IL-6 is an important autocrine and paracrine regulator of regional adipose tissue metabolism. Adipose tissue production of IL-6 may also underlie the observed correlation between serum IL-6 and BMI (12).

Acknowledgments

We thank Colleen Russell, Sue Rosenbaum, and Judy Storch for comments on the manuscript.

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