Differences in the Lipolytic Function of Adipose Tissue Preparations From Black American and Caucasian Women

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The purpose of this study was to determine the potential causes of the lower lipolytic rates in obese Black American women compared to obese Caucasian women. Subcutaneous and omental adipose tissue were obtained from subjects during abdominal surgery, and hormone-sensitive lipase (HSL) mass, mRNA, and activity were determined. HSL mRNA levels did not differ between the Black American and Caucasian women in either subcutaneous or omental adipose tissue. However, HSL mass was approximately 35% lower ($P < .05$) in both subcutaneous and omental adipose tissue of the Black Americans. Because of these differences, we measured HSL activity in frozen subcutaneous and omental adipose tissue, and also measured basal and isoproterenol-stimulated lipolytic rates in tissue fragments. No racial differences were found in the activity of HSL in either subcutaneous or omental adipose tissue. However, basal lipolytic rates in the Black Americans were 53% and 44% lower ($P < .05$) in the subcutaneous and omental fat, respectively, compared to the Caucasian women, despite a lack of difference in cell size between the 2 groups. Interestingly, the degree of stimulation by isoproterenol was higher in both the subcutaneous and omental adipose tissue of the Black American than those of the Caucasian women, resulting in equal stimulation by isoproterenol in the 2 groups. These results indicate that despite the lower mass and lower basal HSL activity in the obese Black American women, stimulation of HSL results in equal activity of the enzyme in the 2 races. This suggests that the signaling pathway of HSL stimulation is more efficient in the Black American women.

OBESITY HAS REACHED epidemic proportions in the United States and is threatening to become a global health problem. According to the World Health Organization, 54% of US adults are overweight (body mass index [BMI] > 25 kg/m^2), 22% are obese (BMI > 30 kg/m^2), and 25% of US youth are overweight or obese.[1] The prevalence of obesity is higher among minority populations, particularly Black American women, than Caucasians. Among adult women, the incidence of obesity in Black American women is almost twice as high as that of Caucasian women. Obesity represents a serious health threat because of the increased risk of developing chronic diseases, and imposes a major impact on the economy in treatment costs and lost wages.

Obesity occurs when fat deposition chronically exceeds fat mobilization. Black American women gain weight at an earlier age and are heavier than Caucasians of similar age.[2] In addition to their propensity for a greater weight gain, weight control programs appear to be less effective in Black American than in Caucasian women. Obese Black American women lose less weight and at a slower rate than Caucasians do across a variety of treatments including conservative interventions,[3] very–low-calorie diets,[4,5] and surgery.[6-9] The causes of this decrease in the ability of Black American women to lose weight as efficiently as Caucasian women are not known. Explanations for the differences in the prevalence of obesity and the response to treatment have examined the influence of socioeconomic, behavioral, and cultural factors, including diet, physical activity, and standards of beauty.[10-13] Collectively, these studies showed that these factors are important, but they do not completely explain the basis for the increased obesity in Black American women. This suggests that there are additional yet-to-be identified biologic differences that contribute significantly to the prevalence of obesity in Black American women. It is possible that the capacity of adipose tissue of Black American women to mobilize the stored fat is lower than that of Caucasian counterparts.

The mobilization of fat from adipose tissue stores is mediated by the enzyme hormone sensitive lipase (HSL). HSL catalyzes the rate-limiting step of lipolysis in adipose tissue by hydrolyzing the stored triacylglycerols and diacylglycerols into fatty acids and glycerol. In the basal state, the rate of lipolysis is low because HSL is relatively inactive, but upon HSL activation, the rate of lipolysis is enhanced. Catecholamines bind the β-adrenergic receptors on adipocytes and activate HSL through the G-protein signaling cascade. Insulin counter-regulates lipolysis by activation of phosphodiesterase, which leads to a decrease in the concentration of the G-protein signaling cascade intermediate, cyclic adenosine monophosphate (cAMP).

Previous studies have shown that basal lipolysis is lower in Black American than Caucasian women, and that Black American women may be more responsive to the antilipolytic effect of insulin.[14] However, these studies did not address the underlying mechanisms that modulate the racial differences in lipolysis. The aim of the present study was to determine the potential causes of the decrease in lipolysis in subcutaneous and omental adipose tissue preparations from obese Black American and Caucasian women. Differences in these rates were determined before and after stimulation of lipolysis with isoproterenol and in the presence and absence of insulin. In addition, we determined the levels of HSL mRNA and protein,

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as well as HSL activity in the same fat depots from the same subjects. The results from these studies might shed light on the potential causes of the decrease in lipolysis that lead to the slower rate of weight loss in the Black American women.

MATERIALS AND METHODS

Subjects

Subcutaneous and omental fat samples were obtained from morbidly obese subjects undergoing gastric bypass surgery for the treatment of obesity. Subjects were instructed to fast overnight prior to surgery. Subjects participated in this study if they were free of vascular disease, diabetes, cancer, or emotional distress, and were not taking medications for hyperlipidemia. Black American women were included only if their parents and grandparents were of Black American descent. Body mass and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively, and BMI was calculated. Written consent was obtained from the participants after they were informed of the nature of the study. The Institutional Review Board of the University and Medical Center approved the protocols for these studies.

Determination of Adipocyte Cell Size

Adipocytes were isolated by collagenase digestion as described previously.[15] Diameters of approximately 200 cells were measured directly using a microscope and ocular micrometer according to the procedure of DiGirolomo et al.[16] The average cell volume, cell weight (assuming that the density of the lipids is that of triolein, 0.915 g/mL), and cell surface area were calculated from the mean cell diameters according to the formulas reported by Goldrick[17] and Zinder and Shapiro.[18] The total number of cells per milliliter of cell suspension was then calculated from the lipid content of the cell suspension divided by the mean fat cell weight.

Measurement of the Rates of Basal and Stimulated Lipolysis

The rates of lipolysis were determined in adipose tissue fragments using the procedure that was originally described by Edens et al.[19] Adipose tissue was obtained from the surgery and transported to the laboratory immediately in RPMI. The tissue was washed with phosphate-buffered saline (PBS), cleaned of connective tissue, minced into 100- to 200-mg pieces, and preincubated in Krebs-Henseleit bicarbonate buffer (4% albumin, 4 mmol/L glucose, pH 7.4) for 30 minutes at 37°C in a 95%O_2/5% CO_2 atmosphere. After preincubation, adipose tissue fragments (50 mg) were transferred to tubes containing 3 mL of the preincubation medium with or without isoproterenol (10^{-7} mol/L) and incubated, in triplicate. After 1 hour, samples of the media were collected for glycerol assay to determine the rate of lipolysis. Glycerol concentration was determined flourometrically, in triplicate, as described.[20] The concentration of isoproterenol used in the present study would not be rate-limiting, as the dose used was previously shown to be saturating.[19] Remaining tissue not used for the lipolysis experiments was cleaned, quick-frozen, and stored at −80°C in order to minimize degradation of mRNA, protein content, and protein activity.

Measurements of HSL Mass, mRNA, and Activity

HSL mass was determined by Western blot analysis as we have described earlier,[21] except that detection was by ECL plus (Amersham Pharmacia Biotech, Piscataway, NJ), and the blots were quantified on a Storm Phosphor imager (Molecular Dynamics, Piscataway, NJ). Measurement of HSL mRNA was by Northern blot analysis. We obtained the cDNA for HSL from Dr Cecilia Holm, Lund University, Sweden. All determinations for mRNA levels were normalized to β-actin that was applied to the same gel.

HSL activity was assayed essentially as described by Fredriksson et al,[22] with some modification. Instead of using 1(3) (^{3}H)-oleoyl- 2-O-oleoylglycerol, we used cholesterol-(^{14}C)-oleate as a substrate.[23] Adipocytes were homogenized in a buffer containing 0.25 mol/L sucrose, 1 mmol/L EDTA, 1 mmol/L dithiothreitol, and protease inhibitors. The homogenate was centrifuged at 100,000 × *g* at 4°C for 45 minutes. The fat cake was removed and the infranatant solution was assayed for HSL activity.

Statistics

Data are expressed as the mean ± SEM. All values with respect to basal, stimulated, and suppressed lipolysis, as well as HSL mass, mRNA, and activity, were compared with a 2-tailed nonpaired Student's *t* test. The level of statistical significance for these experiments was $P < .05$.

RESULTS

Table 1 shows the physical and biochemical characteristics of the subjects that participated in this study. The 2 groups were similar in age, BMI, and fasting plasma glucose and insulin concentrations.

Plasma free fatty acid and glycerol concentrations in Black American women were lower than those in Caucasian women ($P < .05$).

Table 2 shows the rates of lipolysis in the nonstimulated (basal) state and the isoproterenol-stimulated state in the presence and absence of insulin by adipose tissue preparations from a subset of the above subjects. The rate of glycerol production in the basal state in subcutaneous and omental adipose tissue fragments from Black American women was approximately 50% ($P < .05$) that of the corresponding preparations from the Caucasian women. Basal lipolysis was higher in the subcutaneous than omental fat in both groups of subjects. There were no differences in stimulated lipolysis, or insulin suppression of stimulated lipolysis, between Black American and Caucasian women, or between the 2 fat depots. However, there was a higher degree (fold) of stimulation of lipolysis in omental adipose tissue of Black American women than Caucasian women ($P < .05$), but no difference in the fold stimulation in subcutaneous adipose tissue between the 2 groups (Fig 1). The level of stimulation and the percent inhibition by insulin in the 2 groups were not different in either fat depot (Fig 1B).

Data for cell diameter and size, number of cells per gram of tissue, HSL mass, HSL activity, and HSL mRNA are presented in Table 3. Cell size, diameter, and cell numbers of the Black American women were not different from those of the Caucasian women. As has been shown by others,[24] cell diameter and

Table 1. Physical and Biochemical Characteristics of the Obese Subjects

	Caucasian	Black American
No.	27	23
Age (yr)	42 ± 2	40 ± 2
BMI (kg/m^2)	51 ± 2	52 ± 2
Glucose (mmol/L)	4.9 ± 0.2	4.2 ± 0.2
Insulin (μU/mL)	9.6 ± 1.3	11.4 ± 1.5
Glycerol (μmol/L)	166 ± 10	135 ± 7*
FFA (μmol/L)	758 ± 41	546 ± 48*

*Statistically significant ($P < .05$)

Abbreviations: BMI, body mass index; FFA, free fatty acids.

Table 2. Lipolysis in Adipocytes of Obese Subjects (μmol/glycerol/10^6 cells/h)

	Caucasian (n = 13)	Black American (n = 9)
Subcutaneous		
Basal	1.20 ± 0.22	0.63 ± 0.10*
Isoproterenol	2.20 ± 0.30	1.60 ± 0.16
Isoproterenol + insulin	1.90 ± 0.31	1.50 ± 0.18
Omental		
Basal	0.62 ± 0.13	0.27 ± 0.09*
Isoproterenol	1.70 ± 0.21	1.60 ± 0.16
Isoproterenol + insulin	1.60 ± 0.20	1.30 ± 0.28

*Statistically significant ($P < .05$).

size were lower in omental than subcutaneous fat. As a result, the number of cells per gram of tissue was higher in the omental than the subcutaneous depots. Although there were no differences in HSL activity or HSL mRNA level between the groups, HSL mass was lower in the omental adipose tissue of the Black American than Caucasian women ($P < .05$).

We could obtain adipose tissue from 23 individuals who were a subset of the 50 individuals presented in Table 1 (blood samples only). There was not sufficient sample (adipose tissue) volume to conduct each measure on adipose tissue from all individuals; hence the reason for the unequal number of subjects in Tables 2 and 3. There was no difference in the physical characteristics or blood parameters between the large group of subjects and the subsets presented in Tables 2 and 3.

DISCUSSION

We have found that the fasting plasma free fatty acid (FFA) and glycerol concentrations in obese Black American women were significantly lower than those of Caucasian women (Table 1). In the fasting state, plasma glycerol and FFA arise primarily from the lipolysis of fat stores and our findings indicate that lipid mobilization may be decreased in the Black American women. These in vivo studies are consistent with previous reports, which showed that the in vivo rate of lipolysis is lower in the Black American women than in the Caucasians.[14,25]

The present in vitro studies were initiated in order to determine the differences in the lipolytic process in adipose tissue of Black American and Caucasian women. This effort was undertaken to gain insight of the potential underlying causes of the decreased lipolysis in vivo. In order to approximate the in vivo tissue architecture, we used adipose tissue pieces for the determination of the rates of basal lipolysis isoproterenol-stimulated lipolysis, and insulin suppression of lipolysis in Black American and Caucasian women. The use of tissue pieces allows for a better understanding of the influence of the stroma and other in vivo architecture on fat cell function.[26] It should be noted here that some caution should be used when directly comparing lipolysis in vivo and in vitro studies because the in vitro studies are conducted under optimal conditions that do not necessarily replicate the in vivo situation. We also compared mRNA, mass, and activity of hormone sensitive lipase in frozen omental and subcutaneous adipose tissue from the same subjects in whom we determined rates of lipolysis. The present study provided the following novel findings: (1) there were measurable differences in the rates of in vitro lipolysis between the races; (2) there were no major differences in HSL expression, or activity between the races; and (3) there was a decrease in HSL mass in the adipose tissue of the Black Americans.

In Vitro Lipolytic Differences Between the Races

Basal lipolysis was lower in both subcutaneous and omental adipose tissue of Black American than Caucasian women. The lower rates of basal lipolysis that we observed in this study (Table 2) are consistent with in vivo findings from our laboratory and others.[14,25] These in vitro findings were not due to differences in cell size, since cell size in either fat depot was not different between Black American and Caucasian women. A possible cause of the decrease in basal lipolysis is the relatively lower HSL mass that was observed in both adipose tissue depots (Table 3). The mass of HSL was approximately 35% lower in both the subcutaneous ($P < .05$) and omental ($P < .05$) adipose tissue of the Black American than those of the Caucasian women. The lower HSL mass in the adipose tissue of the Black American women occurred despite the lack of difference in HSL mRNA or activity. The similarity in total

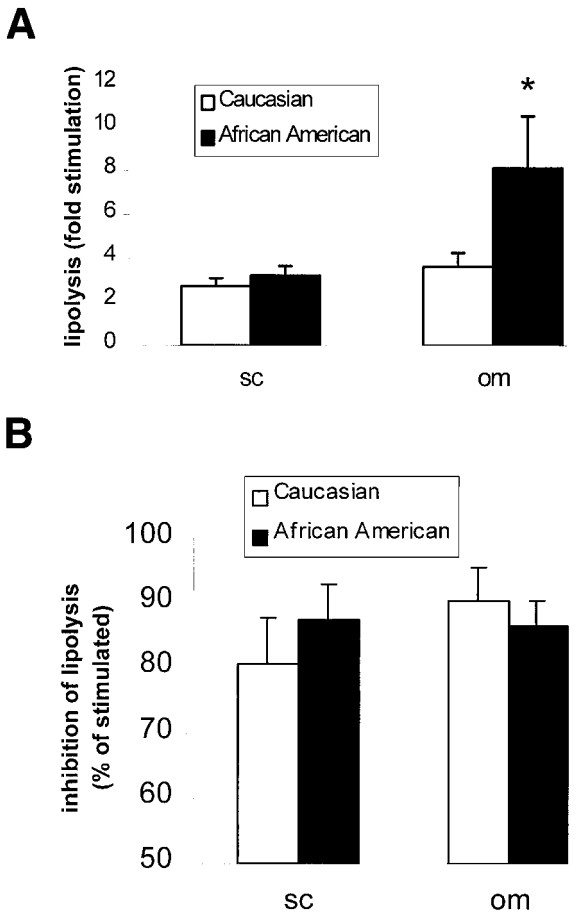

Fig 1. (A) Subcutaneous (sc) and omental (om) adipose tissue lipolysis presented as fold-stimulation upon simulation with isoproterenol. (B) Subcutaneous and omental adipose tissue lipolysis presented as percent inhibition by insulin after stimulation with isoproterenol. *Statistically significant ($P < .05$).

Table 3. HSL Mass, mRNA, and Activity Levels in Subcutaneous and Omental Fat of Obese Black American and Caucasian Women

	Subcutaneous		Omental	
	Caucasian	Black American	Caucasian	Black American
No.	10	10	10	10
Cell diameter (μm)	125 ± 2.8	123 ± 3.0	112 ± 4.5	112 ± 2.7
Size (μg lipid/cell)	0.931 ± 0.015	0.887 ± 0.013	0.657 ± 0.045	0.657 ± 0.094
No. of cells/g	7.1×10^5	7.4×10^5	1.1×10^6	1.0×10^6
HSL mass*	0.93 ± 0.11	0.61 ± 0.14§	1.31 ± 0.15	0.83 ± 0.15§
HSL mRNA†	3.0 ± 0.37	3.7 ± 0.38	3.3 ± 0.30	3.3 ± 0.60
HSL activity‡	0.21 ± 0.04	0.17 ± 0.02	0.25 ± 0.03	0.22 ± 0.05

NOTE. Values are expressed as mean ± SEM.

*Mass is expressed in arbitrary units that were normalized to one value obtained from including the same sample on all gels.

†mRNA values are expressed in arbitrary units after normalization of values to β-actin.

‡Enzymes activity is expressed as mmol ^{14}C-labeled cholesterol ester hydrolyzed/mg cell protein/h.

§Denotes statistically significant difference at $P < .05$ in the same tissue between the races.

HSL activity between the 2 races despite the decrease in HSL mass in the Black American women suggests that HSL in the Black American women is relatively more active than that in the Caucasians. These observations also suggest that there could be differences in translation or degradation of HSL that result in a lower HSL protein content that was observed in Black American women (Table 3).

Stimulated Lipolysis

In vitro stimulation of lipolysis by isoproterenol resulted in similar absolute rates of lipolysis in both adipose tissue depots in the Black American and the Caucasian women. However, when presented as fold-stimulation (Fig 1), there was a higher degree of stimulation in the Black American than the Caucasian women because basal lipolysis was lower in the Black American women. The differences in fold-stimulation could be due to: (1) differences in the individual steps of the lipolytic cascade such as adenylate cyclase or protein kinase A; (2) a higher number of β-adrenergic receptors, which would result in a higher maximal binding capacity, in adipose tissue of Black American women; and/or (3) enhanced affinity (lower K_d) of the β-adrenergic receptors to ligands in adipose tissue of Black American women. Clearly, these issues need to be investigated in future studies.

Considering the higher fold-stimulation of in-vitro lipolysis in Black American compared to Caucasian women, the question arises as to why in vivo lipolysis is not higher in the Black American women, particularly during the fasted state when the levels of catabolic hormones are high. A potential cause of these differences in lipolysis between Black American women and Caucasian women may be related to the presence of an endogenous inhibitor(s) of in vivo lipolysis. The most obvious of such inhibitors would be insulin, which has a well-documented antilipolytic effect. However, the data that we have obtained (Fig 1B) showed that insulin's antilipolytic effect is not different between Black American and Caucasian women in either adipose depot. Differential stimulation of the adrenergic receptors in-vivo is another possible explanation for the lower lipolytic rate in Black American than Caucasian women. We investigated lipolysis in vitro with isoproterenol, a nonselective reversible adrenoceptor agonist. Stimulation of the α_2-adrenoceptors suppresses lipolysis; therefore, it is possible that there is a greater activation of the α_2-adrenoceptors in Black American women in vivo. A difference in α_2-adrenoceptor density between Black American and Caucasian women has not been investigated, but there is no difference in plasma norepinephrine concentration between Black American and Caucasian women.[27] The possibility and extent to which other endogenous inhibitors, ie, nitric oxide,[28] are responsible for the lower rates of in vivo lipolysis remains to be investigated. Endothelial nitric oxide synthase, the rate-limiting enzyme for nitric oxide production, has been detected in adipose tissue.[28,29] Furthermore, nitric oxide has recently been shown to suppress lipolysis in vivo[30]. There are likely other yet-to-be identified in vivo regulators of lipolysis that need to be investigated further.

In summary, fasting plasma FFA and glycerol concentrations are lower in Black American than in Caucasian women. In vitro lipolytic rate is lower in the basal state in abdominal omental and subcutaneous adipose tissue in Black American than Caucasian women. Isoproterenol-stimulated in vitro lipolysis is similar in absolute terms between Black American and Caucasian women, although fold-stimulation of lipolysis is greater in both abdominal omental and subcutaneous adipose tissue in Black American than Caucasian women. Understanding the exact causes between the differences in lipolysis in vitro and in vivo would provide new insights into the differences in the rate of weight loss between Black American and Caucasian women.

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