Characterization of the Insulin Resistance of Aging

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ABSTRACT To clarify the nature of the insulin resistance of aging we studied the dose response for insulin-induced glucose disposal and the binding of insulin to circulating monocytes in healthy young and old men. A total of 49 two-hour euglycemic insulin clamp studies were performed in 17 young and 10 old healthy nonobese subjects. While the old group had lower estimates of lean body mass and greater estimates of total body fat than the young group, these differences did not exceed 5% and did not reach statistical significance. Insulin was infused at 20 mU/m^2 per min (young = 8, old = 5); 80 mU/m^2 per min (young = 13, old = 9); 200 mU/m^2 per min (young = 9, old = 5). Increasing levels of hyperinsulinemia were associated with dose-dependent increases in steady-state glucose infusion rates in young and old. The maximal glucose infusion rates (milligrams per kilogram body weight per minute) were the same for young and old. However, the dose-response curve was shifted to the right in the old subjects. In the four individuals in each age group in whom studies were performed at each dose level, the K_m was 54±14 μU/ml in the young and 113±11 μU/ml in the old ($P < 0.02$). Correction of glucose infusion rate for lean body mass had no effect on comparisons between age groups. These data indicate an age-associated decline in sensitivity of peripheral tissues to insulin without a change in maximal tissue responsiveness. Studies of insulin binding with 14 young and 9 old subjects indicated no effect of age on the insulin binding to receptors on circulating monocytes (young = 5.25±0.35; old = 6.22±0.53% of ^{125}I-insulin bound/10^7 cells). These studies suggest that aging may be associated with a postreceptor defect in insulin action manifested by decreased whole-body tissue sensitivity to insulin without a change in tissue responsiveness.

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INTRODUCTION

For over 60 yr it has been recognized that normal human aging is associated with a progressive impairment in carbohydrate tolerance (1, 2). The carbohydrate intolerance of aging has been characterized by very modest increases in fasting glucose of ~1 mg/dl per decade (2, 3) and substantial elevations of glucose levels after oral or intravenous glucose challenge (2). Evaluation of the mechanisms underlying these changes have included studies of the influence of age on insulin release in response to a variety of stimuli, evaluation of the biological characteristics of circulating insulin with age, and studies of the response of peripheral tissues to insulin. While in vitro studies have generally indicated impairment in insulin release with advancing age (4–6) studies in intact animals and man have generally indicated that circulating insulin levels are either not influenced or are increased after glucose challenge with advancing age (7, 8). Studies using the euglycemic variant of the glucose clamp technique, which places circulating insulin levels under the control of the investigator, have yielded conflicting results regarding the influence of age on tissue responsiveness to insulin and have used only one insulin dose (8, 9). Defronzo (8) has reported that age has no effect on hepatic sensitivity to hyperinsulinemia. Studies of insulin receptors have generally shown no effect of age, although one report indicates an age-related decrease in receptors (10–16).

The present studies were undertaken to evaluate tissue sensitivity and responsiveness to insulin in healthy young and old individuals throughout a physiologic and supraphysiologic range of circulating insulin concentration and to evaluate the binding of insulin to circulating monocytes in the same subjects. Our results indicate that normal human aging is associated with impaired sensitivity to insulin in the absence of an effect on insulin responsiveness. There was no effect of age on monocyte insulin receptors.

METHODS

Study subjects. Subject selection is of crucial importance in gerontologic studies directed towards understanding changes in carbohydrate economy. The age-related increased prevalence of chronic illnesses, as well as the tendency to decreased physical activity, somewhat lower total caloric intake, and anthropometric changes, may impair carbohydrate tolerance. The 17 nonobese young male subjects (age range 22–37 yr) and 10 nonobese old male subjects (age range 63–77 yr) included in these studies were in good general health with no history of weight change over the previous 6 mo or renal, hepatic, or cardiovascular disease. No subject was taking medication on an acute or chronic basis. All subjects were fully ambulant and employed in mainly sedentary work. Daily carbohydrate intake as determined by dietician-obtained histories was ≧150 g in old subjects in the week before studies. Glucose tolerance testing using 100 g glucose drink was normal in all subjects (17). 2-h post glucose levels in the young subjects were 91.9±10 mg/dl and in the old group were 118±12 mg/dl.

9 of the 10 old subjects were participants in the Normative Aging Study (NAS) of the Veterans Administration (18). Anthropometric and glucose tolerance testing (100 g) was available in these subjects with a minimum follow up of four examinations over 11 yr and a maximum of five examinations over 20 yr. The fasting glucose range in 37 studies over 128 subject yr in these nine subjects was 88–126 mg/dl. Fasting glucose was 110±2 mg/dl at initial examination and 106±4 mg/dl at final determination. The 2-h postprandial glucose range was stable over this longitudinal study period with only one of 37 values being >148 mg/dl. The mean 2-h postprandial glucose was 126±12 at the first examination and 118±12 at the last examination.

Our older subjects clearly represent a highly selected group in whom glucose tolerance, physical activity, and weight has been normal for between one and two decades. While this well-characterized select population may differ from elderly individuals included in other studies or seen clinically, studies in these subjects are likely to reflect changes associated with normal aging per se rather than physiologic alterations due to disease states or other age-associated phenomena, such as inadequate dietary intake and reduced activity.

Study protocol. The euglycemic clamp technique was used as previously described (19). Two basal samples for glucose and insulin were obtained before the start of the clamp study and at 5-min intervals for glucose and 30-min intervals for insulin thereafter. Crystalline porcine insulin was infused for 120 min in all studies. 4 min after the start of insulin infusion, glucose and water (20%) was administered at an initial empirical rate with subsequent adjustments in the rate to maintain basal glucose levels. Glucose was maintained at euglycemic levels for an additional 30 min after termination of the insulin infusion. Adequacy of euglycemia during the studies is indicated by the mean coefficients of variation (percent) for blood glucose levels by age group and insulin infusion level that were 20 mU: young 4.8, old 3.9; 80 mU: young 6.1, old 4.8; 200 mU: young 5.5, old 5.6 (Table II).

Insulin infusion studies were performed at three dose levels. Eight young and five old subjects received studies at insulin infusion of 20 mU/m^2 per min. 13 young and 9 old subjects received studies in which insulin was infused at 80 mU/m^2 per min. Nine young and five old subjects received studies in which insulin was infused at 200 mU/m^2 per min. Four young and four old subjects were included in the study group at all three infusion rates.

The volumes of blood removed and fluids infused were the same for both age groups and for the various levels of insulin infusion and were similar to those previously reported (20). The basal glucose levels were slightly, but not statistically significant, higher in old individuals (85.4±1.45 mg/dl) than in the young individuals (82.9±0.63 mg/dl).

Immediately before the initiation of the euglycemic clamp technique, blood samples were obtained for the determination of insulin binding to circulating monocytes on 14 young and 9 old individuals. Subjects were awake and supine throughout all studies. The protocols used were approved by the Committee on Clinical Investigation, New Procedures and New Forms of Therapy at the Beth Israel Hospital, and written informed consent was obtained from all subjects before study.

Analytical methods. Plasma glucose and serum insulin were determined as previously described (20). Insulin binding to circulating monocytes was performed as described by Bar et al. (21). Statistical comparisons between groups employed Student's *t* test.

Calculations. During the euglycemic insulin clamp studies, glucose infusion rate was expressed as the mean values observed during the 20–120-min and 80–120-min time periods after corrections for overfilling and underfilling the glucose space (19). Steady-state insulin concentration was calculated as a mean value from 20 to 120 min, and total kilograms of fat was calculated in 9 young and 10 old subjects utilizing the following modification of a previously reported formula (22): fat(kg) = −9.866 + 0.374 × weight (kg) + 1.755 × abdominal skin fold (cm) + 2.209 × triceps skinfold (cm) + 0.229 × abdominal circumference (cm) − 0.657 × elbow circumference (cm) − 0.003 × 24-h creatinine excretion. Lean body mass was calculated as weight minus kilograms fat. The body composition characteristics of young and old groups are shown in Table I. Although there was a clear trend for greater fat and less lean body mass in the old group, these differences were not statistically significant. Skin folds were measured using standard techniques with the aid of Lange skin fold caliper. Urine creatinine determinations were performed on 24-h urine specimens collected in the Clinical Research Center.

TABLE I
Body Composition Characteristics of Young and Old Groups

	Relative weight*	Fat	Lean body mass
		kg	
Young	1.07±0.02‡ (17)	16.9±1.7 (9)	55.4±1.4 (9)
Old	1.12±0.04 (10)	19.2±1.8 (10)	52.5±1.3 (10)

* Relative weight calculated as the ratio of actual to desirable weight using the middle of the weight range for men of medium frame from the 1959 Metropolitan Life Insurance Company table for desirable weight.

‡ Data presented as mean±SEM, numbers in parentheses indicate number of subjects.

RESULTS

Euglycemic clamp studies. Within age groups and considering all insulin infusion levels there was no statistically significant relationship, in this nonobese study population, between steady-state glucose infusion rates and either relative weight (young $n = 30$, $r = 0.37$, P = NS; old $n = 19$, $r = -0.07$, P = NS) or percent fat (young $n = 30$, $r = -0.14$, P = NS; old $n = 19$, $r = -0.09$, P = NS).

As shown (Fig. 1 and Table II), increasing levels of hyperinsulinemia were associated with dose-dependent increases in glucose infusion rate in both young and old groups. As recently reported by two laboratories, insulin infusions at each dose level resulted in higher steady-state insulin levels in the elderly than in the young subjects that were not associated with age-related differences in creatinine clearance, indicating an age-related defect in insulin clearance (23, 24). While the maximal glucose infusion rates expressed as milligrams per kilogram body weight per minute were the same for both young and old groups, glucose infusion rates at low insulin levels were significantly lower in the old group than the young group. It can be seen from Fig. 1 that the curve describing the dose-response relation between insulin and glucose infusion rate was shifted to the right in older individuals. This finding is confirmed by the analysis of the individual dose-response curves in the four young and four old individuals on whom studies were performed at each level of insulin infusion. In the young individuals the maximal glucose infusion milligrams per kilogram body weight per minute) was 9.55±0.45 while the K_m (circulating insulin level at which half-maximal glucose infusion rate was achieved) was 54±14 μU/ml. In the four old individuals on whom individual dose-response curves were generated, the maximal glucose infusion rate was 9.12±0.50 mg/kg per min, similar to that seen in the young group, while the K_m was 113±11 μU/ml ($P < 0.02$ compared with the younger group). These data are consistent with an age-associated difference in sensitivity of peripheral tissues to insulin without a change in maximal tissue responsiveness.

When glucose infusion rates were corrected for lean body mass, which represents the body tissues most responsible for insulin-induced glucose uptake, the relation between glucose infusion rate and circulating

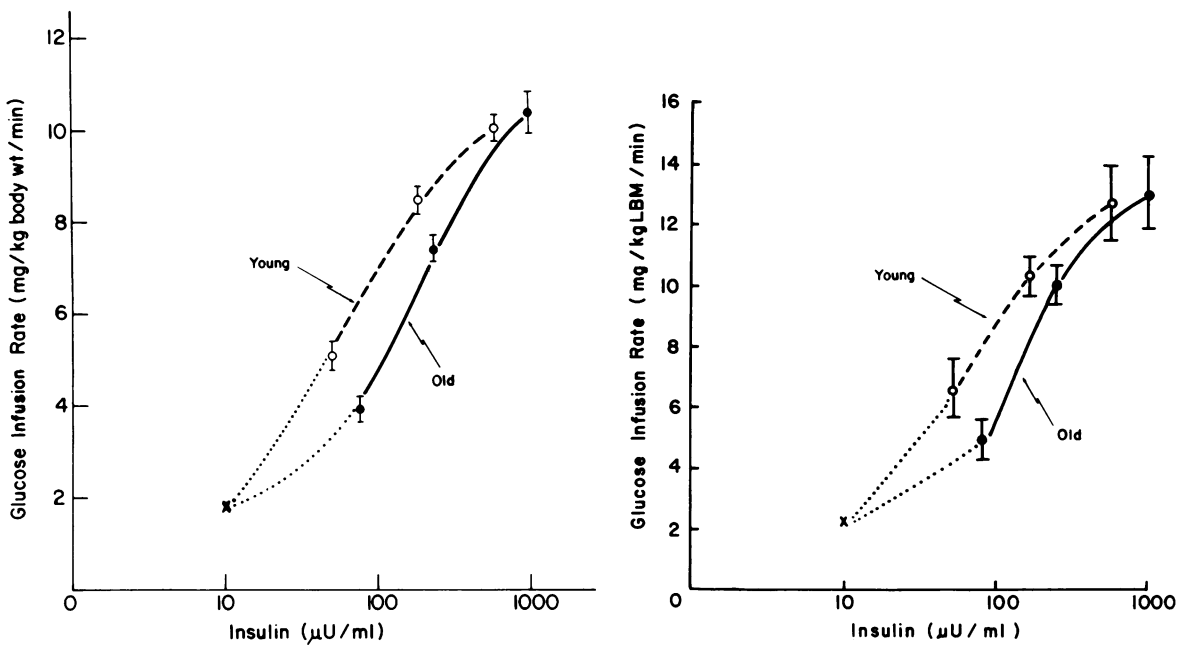

FIGURE 1 Dose-response curves for insulin-mediated whole body glucose infusion rates in young (- - -) and old (——) subjects. In the panel on the left, glucose disposal is expressed as milligrams per kg body weight. In the panel on the right, glucose infusion rates are normalized for lean body mass. Experimental data are extrapolated to known basal hepatic production rates for young and old subjects (8, 26, 27). Actual steady-state insulin values (microunits per milliliter) are 20 mU studies, young 52±2, old 81±4; 80 mU studies, young 193±15, old 251±17; 200 mU studies, young 609±52, old 1,023±83.

TABLE II
Results of Euglycemic Clamp Studies

	20 mU/m²/min		80 mU/m²/min		200 mU/m²/min	
	Young (n = 8)	Old (n = 5)	Young (n = 13)	Old (n = 9)	Young (n = 9)	Old (n = 5)
Mean glucose	82±1.8	83±4.1	79±0.9	85±2.2	80±1.0	81±1.7
Percent goal	97±0.4	98±0.5	97±0.2	98±0.2	98±0.3	98±0.4
CV	4.8±0.5	3.9±0.2	6.1±0.3	4.8±0.3	5.5±0.4	5.6±0.2
Glucose infusion rate *mg/kg/min*						
20–120 min	5.5±0.6	3.8±0.5*	8.6±0.4	7.4±0.5	10.1±0.5	10.3±0.9
80–120 min	6.6±0.7	4.6±0.7†	9.6±0.5	8.1±0.6	10.9±0.6	10.9±1.1
mg/kg LBM/min						
20–120 min	6.5±0.8	5.0±0.5	10.3±0.6	10.1±0.6	12.7±1.1	13.5±1.2
80–120 min	8.1±1.0	5.9±0.7	11.9±0.5	11.1±0.6	13.8±1.3	14.3±1.4

* $P < 0.05$ for difference between glucose infusion rate between young and old subjects.
† $P = 0.05$ for difference between glucose infusion rate between young and old subjects.
LBM, lean body mass.

insulin level was very similar to that seen before correction for body composition (Fig. 1). Comparison of the glucose infusion rates for the last 40 min of hyperinsulinemia (80–120 min) did not alter the findings based on the entire 20–120-minute period (Table II).

Insulin binding studies. There was no effect of age on the binding of insulin to receptors on circulating monocytes. Full insulin binding isotherms were generated in each patient. Specific insulin binding (percent of tracer ^{125}I-insulin bound/10^7 cells) was 5.25±0.35 (n = 14) in the young group and 6.22±0.53 (n = 9) in the old group (P = NS) (Fig. 2), as compared with the previously published level of 5.3±0.28 for young normals in our laboratory (25). The concentration of insulin that inhibits insulin binding by 50% is a convenient parameter for assessing receptor affinity, and this value did not differ significantly between young (4.58±0.55 ng/ml) and old (3.79±0.86 ng/ml) subjects. There was no statistically significant relation between glucose infusion rate and insulin receptor number in either the young or old subjects.

DISCUSSION

There is general agreement that advancing age, in the absence of disease, is associated with a progressive impairment in carbohydrate tolerance (2). Previous studies using the euglycemic glucose clamp technique to evaluate glucose uptake in response to steady-state hyperinsulinemia in man have yielded discordant results. Defronzo (8) using a 40-mU/m² per min insulin infusion for 2 h, which yielded steady-state insulin levels in the range of 100–120 μU/ml, showed a statistically significant reduction in insulin-mediated glucose infusion rates between 19 young subjects (age 26±1 yr) and 17 old subjects (age 64±2 yr). Fink et al. studied 11 nonobese elderly and 21 young subjects, using the euglycemic insulin clamp and demonstrated a 35% decrease in glucose infusion rate during similar steady-state hyperinsulinemia at levels ~100 μU/ml (26). Andres et al. (9) failed to detect a difference in insulin action in a comparison of 12 young (mean age 26), 11 middle-aged (mean age 52), and 11 older (mean age 72) individuals during 80-min insulin infusions. In this study we have used steady-state infusions of insulin for 2 h at three dose levels in healthy young and old individuals. Our studies indicate an approximate doubling of the K_m for insulin-mediated glucose infusion rate in the elderly (decreased insulin sensitivity) with no change in the maximal glucose infusion rate (insulin responsiveness).

During euglycemic insulin clamp studies total body glucose disposal is equal to the glucose infusion rate plus hepatic glucose production. Since hepatic glucose output has been shown in other studies to be >90% suppressed in both young and old subjects in the range of insulin levels obtained in our studies (8, 26, 27), our glucose infusion rates reflect total body glucose disposal rates. However, the effect of age on insulin-induced suppression of hepatic glucose output has not

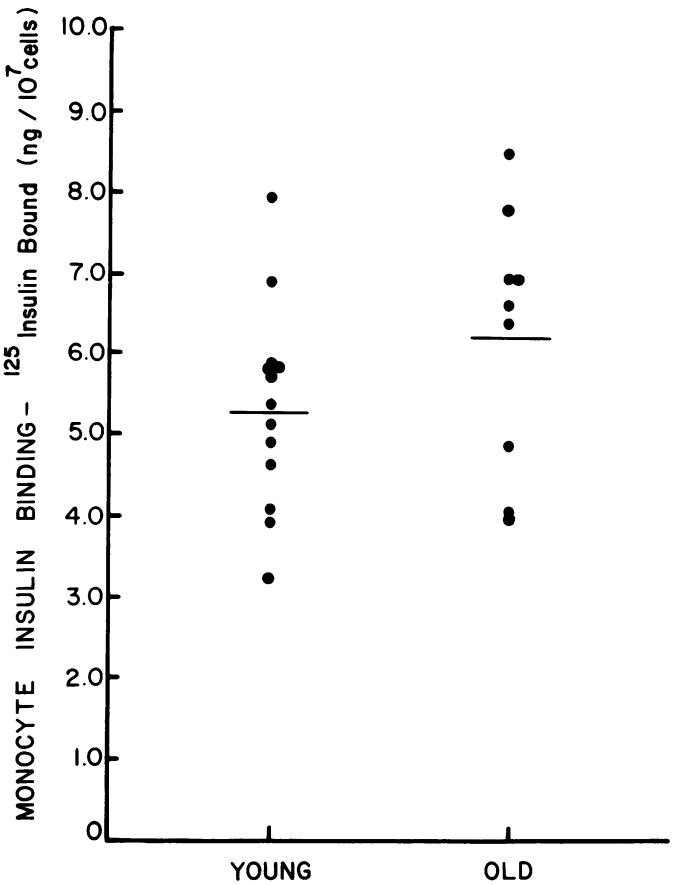

FIGURE 2 Insulin receptor number on circulating monocytes from 14 young and 9 old subjects.

been reported at insulin levels below those achieved in our studies. If hepatic glucose suppression is less complete at low insulin levels in old subjects than in young subjects, the curve extrapolating our results to basal glucose production (Fig. 1) may overestimate the degree of insulin resistance in the elderly. While our results indicate an age-related impairment in insulin action during hyperinsulinemia, prior studies (8, 26, 22) have failed to show an age difference in circulating insulin or whole body glucose disposal under basal conditions. This is probably due to the fact that, under basal conditions, noninsulin-dependent glucose disposal accounts for a substantial portion of whole body glucose disposal, thus blunting the capacity to detect age differences in insulin action. Our findings, thus, suggest an age-related difference in the sensitivity of muscle, the tissue contributing most to the uptake of glucose. The reduction in insulin sensitivity observed in the present studies is consistent with prior clinical studies of young and old individuals that have used the standard oral and intravenous glucose tolerance techniques, since the circulating insulin levels in those studies would be on that part of the dose-response curve at which insulin action is reduced. Our studies confirm the findings of Defronzo (8) and Fink et al. (26) of an age-related insulin resistance and further characterize this defect as a decrease in insulin sensitivity with no change in insulin responsiveness.

While the carbohydrate intolerance of aging is generally recognized to be independent of specific disease processes, there is controversy regarding the contributions of age-related differences in diet, exercise, and especially the decreases in lean body mass and increases in total body fat that accompany normal human aging (2). In this study, which used carefully screened nonobese subjects, we did not detect any influence of fatness estimated by either relative weight or percent fat, on insulin sensitivity within age groups. In addition, correction of total body glucose infusion rate for lean body mass did not alter the relation between age and insulin-induced glucose infusion rates. Thus, while changes in body composition, especially

marked obesity, may play a role in the carbohydrate intolerance of some nondiabetic elderly, the present results would indicate that there is a decrease in insulin sensitivity associated with normal aging independent of changes in body composition.

Our failure to detect an effect of age on insulin receptor number and affinity is consistent with the bulk of previous reports in rodents and man. Sorrentino and Florini (10) reported no effect of age on insulin receptors in mouse liver membranes. Olefsky and Reaven (11) found no difference in insulin binding of adipocytes from young adult and senescent rats. Studies in human fibroblast cultures from young and old donors have shown either no change with age (12) or an age-related increase in insulin receptors (13). Helderman (14), studying insulin binding to transformed lymphocytes, failed to show a difference between cells from young and old subjects. Jackson et al. (15) studied monocyte insulin receptor binding in six young (30–45 yr) and four old (70–83 yr) subjects and found no difference in insulin receptor binding or 50% inhibition concentrations. Pagano (16), studying adipocytes of elderly surgical patients, has reported a decline in insulin receptor binding in the elderly.

What is the meaning of our finding that the dose response for insulin-mediated glucose infusion rates in older individuals is shifted to the right with normal maximal effect at very high insulin concentrations? Kahn (28) has discussed the use of complete dose-response curves to distinguish between changes in hormone sensitivity and hormone responsiveness. This analysis was based on in vitro studies, but similar analysis has been applied to in vivo insulin response data, as obtained with the euglycemic clamp technique (28). Because of the complexity of in vivo dose-response physiology, mechanistic interpretations should be performed with caution. However, such an analysis has been applied to human obesity. It has been shown that the dose-response for insulin-mediated glucose infusion rate is shifted to the right with normal maximal insulin effect in many obese patients with mild to moderate insulin resistance. This dose-response pattern could have several explanations. First, it is the predicted consequence of a reduced number of receptors in a system in which spare receptors exist (i.e., in which submaximal receptor occupancy elicits a maximal biologic effect). Alternatively, a similar pattern could result from a modest reduction in receptor affinity or from an altered coupling efficiency between hormone receptor occupancy and a subsequent signalling step. In obesity, the right shift in dose-response studies has correlated well with the reduction of insulin receptor concentration on adipocytes (29). In contrast, the right-shifted insulin dose-response curve that we have observed in older individuals was not accompanied by significant changes in either the number or affinity of monocyte insulin receptors. It is possible that with aging, unlike obesity (20, 29, 30), monocyte insulin receptors fail to mirror insulin receptors in other important target tissues for insulin action. Alternatively, the right-shifted dose-response curve (i.e., diminished insulin sensitivity) of aging could be a consequence of a cellular defect beyond the binding function of the receptor, leading to impaired signalling of the insulin message consequent to formation of the hormone-receptor complex. The observation of a right-shifted dose-response curve with preserved maximal responsiveness in the presence of unchanged receptor numbers has been documented in several other aspects of insulin physiology. Rizza et al. (31), studying the insulin resistance induced by 24-h cortisol infusion in man demonstrated a decrease in both hepatic and extrahepatic sensitivity to insulin with preserved maximal responsiveness, occurring in the presence of unchanged monocyte and erythrocyte insulin receptor concentrations. Olefsky (32) studying the dose response of insulin on glucose uptake in rat adipocytes during incubation with dexamethasone reported a similar pattern of findings. During dexamethasone treatment, glucose uptake was decreased at low insulin concentrations, but unchanged at high insulin concentrations in the face of unchanged adipocyte insulin receptor binding (32). Although clarification of this issue will require further studies, aging could well be an important model for postbinding defects in insulin action.

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