Glucose Intolerance and Aging

Evidence for Tissue Insensitivity to Insulin

RALPH A. DEFRONZO

SUMMARY

The relative contributions of impaired insulin secretion and of impaired tissue sensitivity to insulin to the glucose intolerance of aging were examined in 84 healthy volunteers, ranging in age from 21 to 84 yr, employing the hyperglycemic and euglycemic insulin clamp techniques, respectively.

HYPERGLYCEMIC CLAMP. The blood glucose concentration was acutely raised and was maintained at 125 mg/dl above basal levels for 2 h. Since the glucose concentration was held constant, the glucose infusion rate was an index of glucose metabolism (M). In young subjects, M averaged 9.48 ± 0.40 mg/kg · min compared with 6.48 ± 0.28 in old subjects ($P < 0.001$). When all subjects were considered together, a progressive age-related decline in M was observed ($r = -0.665$, $P < 0.001$). The plasma insulin response (I) was biphasic, with an early burst within the first 6 min, followed by a phase of gradually increasing insulin concentration. No difference in either the early or late phases of insulin secretion was observed between young and old subjects. Consequently, the M/I (×100) ratio, an index of tissue sensitivity to endogenous insulin, decreased from 14.90 ± 1.01 to 10.98 ± 0.81 mg/kg · min per μU/ml ($P < 0.005$).

EUGLYCEMIC INSULIN CLAMP. The plasma insulin concentration was acutely raised and was maintained at about 100 μU/ml above basal levels by a primed continuous infusion of insulin. The blood glucose concentration was held constant at the basal level by a variable glucose infusion. M/I (×100), again, was a measure of tissue sensitivity to insulin (exogenous) and was decreased in old (4.95 ± 0.31 mg/kg · min per μU/ml) versus young (6.95 ± 0.45) subjects ($P < 0.001$). Hepatic glucose production was measured with tritiated glucose during the euglycemic clamp study; it declined similarly in young (to 0.13 ± 0.05 mg/kg · min) and old (to 0.09 ± 0.03 mg · min) subjects.

In conclusion, under the present experimental conditions, employing intravenous glucose and/or insulin, impaired tissue sensitivity to insulin is the primary factor responsible for the decrease in glucose tolerance observed with advancing age. Since hepatic glucose production is normally suppressed by insulin in old subjects, the site of insulin resistance must reside in peripheral tissues. Beta cell response to glucose, as determined by the hyperglycemic clamp technique, cannot account for the age-related decline in M. **DIABETES 28:1095–1101, December 1979.**

Impaired glucose tolerance has long been recognized to accompany advancing age. Spence[1] was the first to document that glucose tolerance was impaired in subjects over age 60, and, since this initial report, a progressive deterioration of all the commonly used diagnostic tests for diabetes has been repeatedly confirmed.[2] This decline starts in the third decade and continues through the entire adult life span.[2] Recently, Davidson[3] exhaustively summarized the English literature concerning the decline in glucose tolerance with age. He reported 62 papers employing the oral glucose tolerance test in older subjects, and all but three demonstrated a progressive deterioration in oral glucose tolerance as the population aged. Similarly, of 22 reports using the intravenous glucose tolerance test, 21 documented an age-related decrease in the K rate (percent glucose disappearance per minute), which averaged about 0.15–0.20 per decade of life.[2,3] However, despite this extensive literature documenting a progressive decline in glucose tolerance with age, the underlying mechanism(s) has(have) not been agreed on. Thus, the plasma insulin response to both oral and intravenous glucose has been reported to be increased,[4–14] normal,[15–21] or decreased.[22–26] Likewise, attempts to measure the presence of tissue insensitivity to insulin have yielded conflicting results.[27–33] In the present study, I employed the glucose clamp technique in combination with tritiated glucose to evaluate the relative contributions of impaired beta cell sensitivity to glucose, impaired tissue sensitivity to insulin, and abnormal hepatic glucose metabolism in the glucose intolerance of aging.

From the Department of Medicine, Yale University School of Medicine, New Haven, Connecticut 06510.

Received for publication 12 April and in revised form 6 August 1979.

METHODS

Subjects. Eighty-four healthy adult volunteers comprised the study population, and they were divided into three groups on the basis of age. The young group (N = 39) included 24 men and 15 women aged 21 to 29 yr (mean = 25 ± 1 yr), the middle-aged group (N = 15) included nine men and six women aged 30 to 49 (mean = 43 ± 1 yr), and the old group (N = 30) included 14 men and 16 women aged 50 to 74 yr (mean = 60 ± 1 yr). Hyperglycemic clamp studies were performed on 20 young subjects (mean age = 24 ± 1 yr), 15 middle-aged subjects (43 ± 1 yr), and 13 old subjects (54 ± 1 yr). The euglycemic insulin clamp studies were performed on 19 young subjects (mean = 26 ± 1 yr) and 17 old subjects (64 ± 2 yr).

All subjects were in good general health with no history of endocrine, renal, hepatic, or cardiovascular disease, and none had a history of diabetes mellitus. They were all within 13% of ideal body weight based on the Metropolitan Life Insurance Tables, 1959. The mean ideal body weights for the young, middle, and old groups were 1.03 ± 0.01, 1.07 ± 0.01, and 1.05 ± 0.01, respectively. All subjects were consuming a weight-maintaining diet containing at least 200 g carbohydrate per day for 3 days before study, and none were taking any medications for at least 4 wk before study. All tests were performed in the postabsorptive state at 8 a.m. after a 12-h overnight fast. The purpose and potential risks of the study were carefully explained to all subjects, and written voluntary consent was obtained before their participation.

Hyperglycemic clamp. Before each study, a polyethylene catheter was inserted into a forehand vein under local Xylocaine anesthesia, and the patency was maintained with a slow infusion of normal saline. The subject's hand was placed in a box heated to 70 ± 2°C to ensure arterialization of venous blood.[34] A second catheter was inserted into an antecubital vein for glucose administration. After a 30-min equilibration period, four baseline samples were drawn at 5-min intervals for plasma glucose and insulin determination. A priming infusion of a 20% glucose solution was then administered over 15 min to acutely raise the plasma glucose concentration to either 40 mg/dl or 125 mg/dl above the basal level. The plasma glucose concentration was subsequently measured at 5-min intervals, and a variable glucose infusion was adjusted to maintain the plasma glucose concentration constant at +125 mg/dl for a period of 2 h. The adjustment of the glucose infusion rate is based on a servocontrol negative feedback principle.[28] Blood samples for insulin were obtained at 2-min intervals for the first 10 min and at 5–10-min intervals for the remaining 110 min. Under these steady state conditions of constant hyperglycemia, the amount of glucose infused (mg/kg · min) minus urinary losses (mg/kg · min) is a measure of the glucose metabolized (M). The amount of M divided by the plasma insulin response (I) provides a measure of tissue sensitivity to endogenously secreted insulin.

Euglycemic insulin clamp. Polyethylene catheters were inserted into a forehand vein and an antecubital vein as previously described. After collection of four baseline blood samples, a prime plus continuous infusion of crystalline porcine insulin (Eli Lilly, Indianapolis) was administered to obtain a plateau of constant hyperinsulinemia.[35] The priming dose was administered in a logarithmically falling manner over 10 min, at which time the continuous insulin infusion was begun. The total amount of insulin infused during the priming period was twice that infused during subsequent 10-min intervals. The continuous infusion (42.6 mU/m² surface area/min) was maintained for 110 min. To prevent insulin adsorption to both glassware and the plastic infusion apparatus, infusates were prepared with the addition of 2 ml of the subject's whole blood per 50 ml of infusate. The plasma glucose level was maintained at basal preinfusion levels by determination of the plasma glucose concentration every 5 min and the periodic adjustment of a variable infusion of a 20% glucose solution as described for the hyperglycemic clamp technique. Under these steady state conditions of constant euglycemia, all the glucose infused (M) is taken by cells and, thus, serves as a measure of the body's sensitivity to the infused insulin.

Endogenous glucose production. During the insulin clamp, the effect of hyperinsulinemia on hepatic glucose production was examined in 18 young and 16 old subjects by infusing [3-^{3}H]glucose.[38] For 3 h before initiating the insulin infusion, each subject's glucose pool was labeled by a primed continuous insulin infusion of [3-^{3}H]glucose (New England Nuclear, Boston). The labeled glucose was administered as an initial intravenous priming dose (25 μCi) followed immediately by a continuous intravenous infusion at a rate of 0.25 μCi/min. Plasma samples for determination of glucose-specific activity were taken at 30-min intervals for the first 2 h and at 10–15-min intervals for the subsequent hour. A steady state plateau of glucose-specific activity was achieved in all subjects during the third hour of [3-^{3}H]glucose infusion, and this plateau value was used to calculate basal hepatic glucose production. After 3 h of continuous [3-^{3}H]glucose infusion, the insulin infusion was begun and the [3-^{3}H]glucose was continued at the same rate. During the insulin infusion, plasma samples for glucose-specific activity were drawn every 15 min for the first 90 min and every 5–10 min thereafter.

Calculations. During the hyperglycemic clamp studies, the glucose infusion rate was determined by calculating the mean value observed from 20 to 120 min. M was calculated by subtracting the mean urinary glucose excretion rate during the 2-h study period from the mean glucose infusion rate. To calculate the steady state plasma glucose concentration during the period of sustained hyperglycemia, the mean of values from 20 to 120 min was used. The early plasma insulin response was calculated as the mean of values from 0 to 10 min and the late plasma insulin response as that from 10 to 120 min.

During the insulin clamp studies, the glucose infusion rate (M) was determined by calculating the mean value observed from 20 to 120 min. To calculate the steady state plasma glucose and insulin concentrations during the insulin infusion, the mean of the values from 20 to 120 min was employed. The metabolic clearance rate (MCR) of insulin was calculated by dividing the continuous insulin infusion rate (42.6 mU/m² per minute) by the mean increment above basal in plasma insulin concentration during the 20–120-min time period.

Glucose production in the basal state was determined by dividing the [3-^{3}H]glucose infusion rate (counts per minute) by the steady state plateau of [3-^{3}H]glucose-specific activity achieved during the last hour of the preinsulin infusion con-

trol period. Because renal glucose production is negligible in the postabsorptive state, the rate of glucose appearance was assumed to be equal to the rate of hepatic glucose production. After the insulin-glucose administration (euglycemic insulin clamp), a nonsteady state condition in glucose-specific activity exists, and hepatic glucose production was calculated by Steele's equations in their derivative form,[37] which permits the evaluation of continuous changes in the rates of glucose turnover. The value of 0.65 was used as the pool fraction in the present calculations.[38] The determination of glucose turnover by the primed constant infusion and pool fraction techniques has recently been validated for both steady and nonsteady states.[39] The rate of endogenous production was calculated by subtracting the glucose infusion rate (M) from the rate of glucose appearance (Ra) as determined by the isotopic tracer technique. All calculations were performed with a program written in BASIC on a desk computer (Hewlett-Packard Co., Palo Alto, California).

All data are presented as the mean ± SEM. All statistical comparisons between groups were calculated by unpaired *t*-test analysis.[40] Coefficients of correlation were determined by standard procedures.[40]

Analytic procedures. Plasma glucose was determined by the glucose oxidase method (Glucostat, Beckman Instruments). Methods for the determination of plasma immunoreactive insulin[41] and the specific activity of plasma glucose[36] have previously been described.

RESULTS

Hyperglycemic clamp. The fasting blood glucose concentrations in the young (92 ± 1 mg/dl), middle (95 ± 2), and old (96 ± 2) age groups were not significantly different: during the period of sustained hyperglycemia, the mean glucose concentrations were 214 ± 2, 218 ± 2, and 218 ± 2 mg/dl, respectively. The stability of the plasma glucose concentration during the period of hyperglycemia is reflected by the coefficient of variation, which averaged 4.2 ± 0.3%, 3.9 ± 0.2%, and 3.6 ± 0.3%, respectively.

The amount of glucose metabolized (M) during the 20–120-min period of sustained hyperglycemia (+125 mg/dl hyperglycemic clamp) was significantly greater in the young (9.48 ± 0.40 mg/kg · min) compared with the middle (6.95 ± 0.44; $P < 0.02$) and old (6.48 ± 0.28; $P < 0.001$) age groups (Figure 1). If the amount of glucose metabolized (M) is plotted against age (Figure 2), a highly significant inverse correlation ($r = -0.665$; $P < 0.001$) is found. The decrease in M was similar in men (9.05 ± 0.39 to 7.00 ± 0.45 mg/kg · min) and women (10.72 ± 0.86 to 6.16 ± 0.34).

The fasting plasma insulin concentration was slightly less in old (12 ± 1 μU/ml) compared with both middle (14 ± 1) and young (15 ± 1) subjects. In response to the sustained hyperglycemia, the plasma insulin response was biphasic, with an early burst of insulin within the first 6 min followed by a gradually increasing phase of insulin release that lasted until the end of the study (Figure 3). There were no differences in the early (0–10 min), late (10–120 min), or total (0–120 min) insulin responses between any of the three age groups ($P > 0.50$).

Tissue sensitivity to insulin (M/I × 100) in the young group (14.90 ± 1.01 mg/kg · min per μU/ml) was significantly greater than in both the middle (10.39 ± 0.40; $P < 0.001$) and old (10.98 ± 0.84; $P < 0.005$) groups (Figure 1). There was no difference in M/I between the middle and old groups.

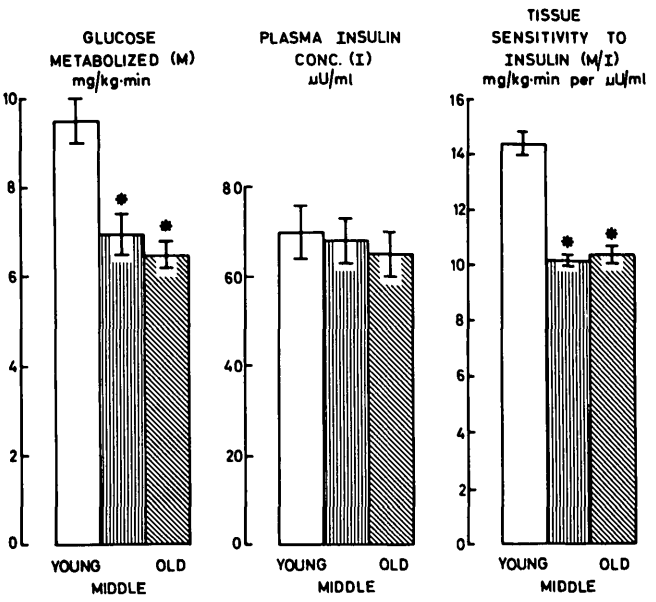
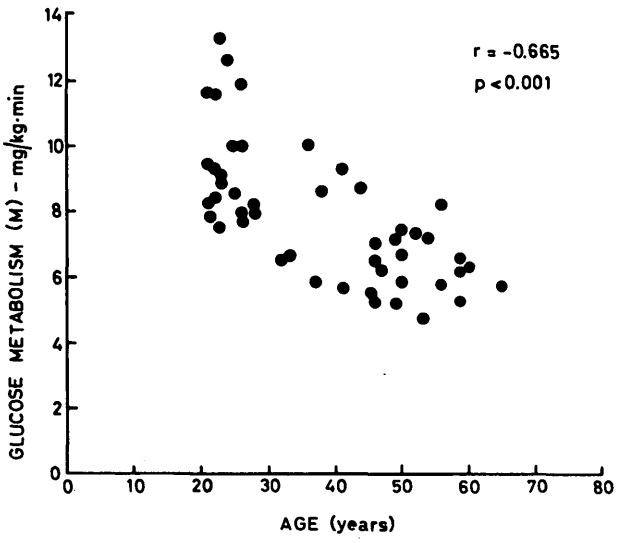


Figure 1. Glucose metabolism (M), plasma insulin response (I), and tissue sensitivity to insulin (M/I × 100) during the hyperglycemic clamp study in young, middle, and old subjects. Mean values ± SEM are displayed.

Sixteen young, seven middle, and eight old subjects also received a +40 mg/dl hyperglycemic clamp. The amount of glucose metabolized during the 20–120-min period of sustained hyperglycemia was significantly less in old (2.58 ± 0.11 mg/kg · min) than in middle (3.18 ± 0.17 mg/kg · min; $P < 0.05$) or young (3.99 ± 0.16 mg/kg · min; $P < 0.001$) subjects. A highly significant inverse correlation ($r = -0.771$, $P < 0.001$) was observed between age and glucose metabolism (Figure 4). Although both the early (22 ± 3 versus 27 ± 2 μU/ml) and late (24 ± 3 versus 29 ± 2 μU/ml) insulin responses were slightly less in old than in young subjects, these differences were not statisti-

Figure 2. Correlation between age and the amount of glucose metabolized (M) during the +125 mg/dl hyperglycemic clamp study. A highly significant inverse correlation was observed ($r = -0.665$, $P < 0.001$).



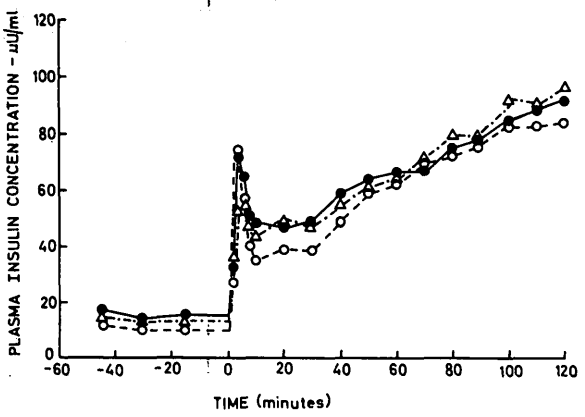


Figure 3. Time course of the plasma insulin response during the hyperglycemic clamp study in young (●——●), middle (△—·—△), and old (○——○) subjects.

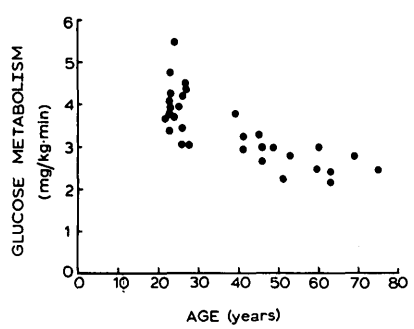
cally significant. The peak insulin response, which occurred at 4 min, was significantly greater in young (39 ± 3 μU/ml) than in old (28 ± 4 μU/ml) subjects ($P < 0.05$). The M/I (×100) ratio was reduced 23% in old (11.36 ± 0.78 mg/kg · min per μU/ml) compared with young (14.75 ± 1.22) subjects ($P < 0.025$).

Euglycemic clamp. The fasting plasma glucose concentration was slightly lower in the young (89 ± 1 mg/dl) than in the old (93 ± 2) subjects ($P < 0.05$). During the period of hyperinsulinemia, the plasma glucose concentration was maintained at 88 ± 1 and 93 ± 1 mg/dl, respectively. The stability of the plasma glucose concentration during the sustained hyperinsulinemia is reflected by the coefficient of variation, which was 4.7 ± 0.2 and 3.8 ± 0.2, respectively.

The fasting plasma insulin concentration was similar in young (15 ± 1 μU/ml) and old (14 ± 1) subjects. The steady state (20–120 min) plasma insulin concentration in young and old subjects during the constant insulin infusion was 112 ± 4 and 119 ± 4 μU/ml (Figure 5) with coefficients of variation of 9.3 ± 0.7% and 8.8 ± 0.6%, respectively. The calculated metabolic clearance rate of insulin was not different in the young (450 ± 19 ml/m² · min) and old (410 ± 15) groups.

The amount of glucose infused (M) to maintain euglycemia was significantly higher in the young (7.60 ± 0.35 mg/kg · min) than in the old (5.80 ± 0.31) groups ($P < 0.001$; Figure 5). Since comparable steady state plasma insulin levels were achieved in both groups, the M/I (×100) ratio (Figure 5) was likewise higher in young

Figure 4. Correlation between age and the amount of glucose metabolized (M) during the +40 mg/dl hyperglycemic clamp study. A highly significant inverse correlation was observed ($r = -0.771$, $P < 0.001$).



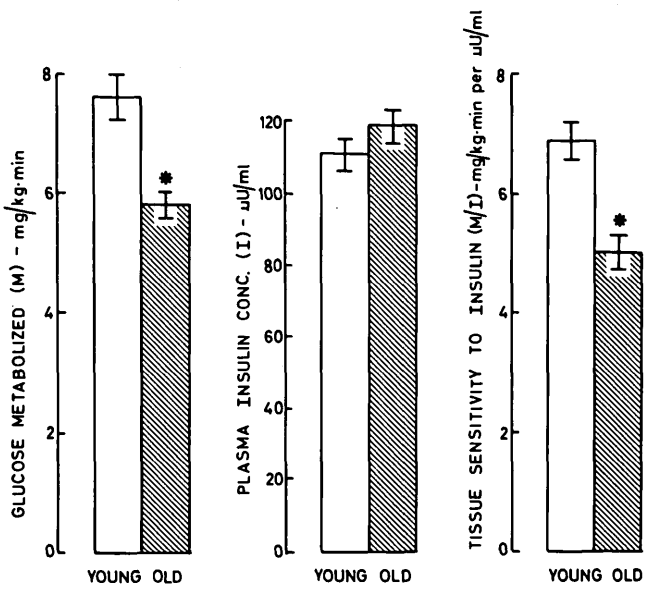


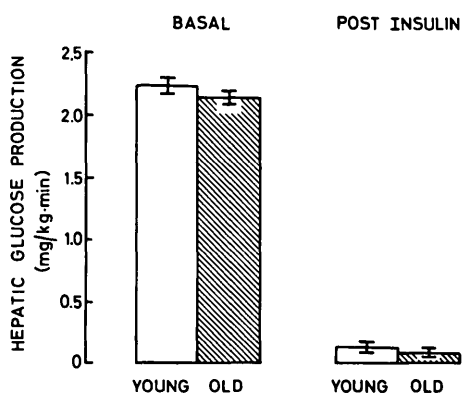
Figure 5. Glucose metabolism (M), steady state plasma insulin concentration (I), and tissue sensitivity to insulin (M/I × 100) during the euglycemic insulin clamp study in young and old subjects. Mean values ± SEM are displayed.

(6.94 ± 0.45 mg/kg · min per μU/ml) than in old (4.95 ± 0.31; $P < 0.001$) subjects. The decrease in M was similar in men (7.72 ± 0.52 to 5.81 ± 0.54 mg/kg · min) and women (7.43 ± 0.48 to 5.79 ± 0.32).

Endogenous glucose production. Basal glucose production (Figure 6), measured in 18 young and 16 old subjects, was 2.14 ± 0.06 and 2.24 ± 0.06 mg/kg· min, respectively. After insulin administration, a prompt decline in hepatic glucose production occurred, which reached near maximal suppression within 30 min and remained suppressed throughout the study. During the 80–120-min time period, basal glucose production fell by about 95%, to 0.13 ± 0.05 and 0.09 ± 0.03 mg/kg · min in young and old groups, respectively.

Relationship between obesity index and glucose metabolism. No correlation between M ($r = -0.257$) or M/I ($r = -0.216$) and obesity index was observed during the hyperglycemic clamp studies. Likewise, no significant correlation between obesity index and either M ($r = -0.152$) or M/I ($r = -0.084$) was demonstrable during the euglycemic insulin clamp. Even when the M/I ratios from both the hy-

Figure 6. Effect of insulin (euglycemic clamp) on hepatic glucose production in young and old subjects. Mean values ± SEM are displayed.



perglycemic and euglycemic clamp studies were combined and plotted against the obesity index, a significant correlation ($r = 0.113$) could not be demonstrated.

DISCUSSION

The present results clearly document that glucose tolerance declines with age. The decline is most marked between ages 20 and 45 yr and tends to level off thereafter. Previously reported results[3] suggest that the age-related decline in glucose tolerance persists throughout life. Why I did not observe a more striking decline in glucose tolerance from ages 45 to 75 is not clear. All subjects were on a weight-maintaining diet, rich in carbohydrate, before the study, and all were healthy, physically active community dwellers. It is possible that better nutrition and/or differences in physical activity tended to offset the decline in glucose metabolism that occurs with age.

The impairment in glucose metabolism cannot be explained by a decrease in insulin secretion. During the +125 mg/dl hyperglycemic clamp study, both the early and late phases of insulin secretion were similar in young, middle, and old subjects (Figure 3), yet the amount of glucose metabolized by the latter two groups decreased by 27%–32%. Likewise, during the +40 mg/dl hyperglycemic clamp study, the amount of glucose metabolized by old subjects was reduced by 35%, although the plasma insulin response was not significantly diminished.

Previous studies, employing the OGTT and IVGTT to evaluate insulin secretion, yielded varied results.[2–26] During both the OGTT[4–13,15–19] and IVGTT,[14,20,21] most authors have reported either increased or normal plasma insulin levels with aging despite a decrease in glucose tolerance. Five studies, however, have documented an impairment in early insulin secretion in elderly subjects, although the late insulin response was normal.[22–26] What relationship this impairment in early insulin release has to the decrease in glucose tolerance observed in these same subjects is unknown at present. During the hyperglycemic clamp studies, the glucose concentration is presented to the beta cell as a square wave. This results in a biphasic pattern of insulin release, in which the early peak is related to insulin stored within the beta cell and the late peak primarily reflects insulin synthesis.[35] This technique, therefore, allows one to examine the early and late phases of insulin secretion independently. During the +125 hyperglycemic clamp study, no defect in the early releasable phase could be demonstrated (Figure 3). Likewise, during the +40 hyperglycemic clamp study, the early (0–10-minute) phase of insulin release was not significantly reduced in old subjects. However, the peak insulin response, which occurred at 4 min, was significantly greater in young (39 ± 3 μU/ml) than in old (28 ± 4 μU/ml) subjects ($P < 0.05$). These data suggest that, at lower hyperglycemic plateaus, older subjects may have mild impairment in the early phase of insulin release.

Both the hyperglycemic (+125 and +40 mg/dl) and euglycemic insulin clamps consistently showed an age-related decline in the M/I ratio, indicating that impaired insulin action is the primary factor responsible for the decreased glucose metabolism in elderly subjects. Previous studies, which have attempted to examine insulin action as a function of age, have yielded conflicting results. Himsworth[27] and Silverstone[28] were the first to provide evidence for the existence of impaired tissue sensitivity to insulin in elderly subjects. These authors compared the difference in glucose area in subjects given an oral glucose load alone and in combination with insulin, and they found much smaller differences between the two studies in the older age group. In contrast, both the rate of decline and the nadir in blood glucose concentration are reported to be normal in old subjects during the insulin tolerance test.[29–33] However, the interpretation of this test is clouded by the complex neuroendocrine response elicited by hypoglycemia. Himsworth and Silverstone, by not allowing the blood glucose concentration to drop, would have avoided the release of catecholamines, growth hormone, cortisol, and glucagon, which are known to impair the action of insulin.

The euglycemic insulin clamp technique offers significant advantages over these previously used techniques for assessing the insulin sensitivity: (1) by maintaining the glucose concentration constant after insulin administration, the complex neuroendocrine response to hypoglycemia is avoided; (2) because the plasma insulin concentration is raised, on the average, to the same level in all subjects, the insulin delivery to all experimental groups is similar; (3) since the plasma glucose is maintained constant at the basal level, the amount of glucose infused to maintain euglycemia (plus that produced endogenously) must equal the amount of glucose metabolized by all tissues of the body; (4) by combining the insulin clamp with tritiated glucose, endogenous glucose production can be quantitated and the contribution of changes in hepatic glucose production versus altered peripheral sensitivity to insulin can be evaluated.

During the euglycemic insulin clamp study, tissue sensitivity to insulin in the old subjects was reduced by 29% compared with subjects in their twenties. After the administration of insulin, hepatic glucose production was reduced by 96% in the old age group. Since I have previously shown that there is no net uptake of glucose by the liver during hyperinsulinemia as long as the glucose concentration is not above basal levels,[43] the primary site of insulin resistance must reside in peripheral tissues. It should be noted, however, that, in contrast to intravenous glucose administration, after the ingestion of oral glucose, the liver uptake of glucose accounts for about 60% of the glucose load. The present results do not exclude the possibility that a defective insulin-mediated hepatic glucose uptake after oral glucose might also contribute to the glucose intolerance of aging. Since it is known that adipose tissue disposes of less than 3%–5% of an administered glucose load,[44,45] the present results are most consistent with a defect in muscle uptake of glucose. This conclusion is in agreement with studies in vitro demonstrating an impaired insulin effect on diaphragm muscle from old versus young rats[46,47] and the recent demonstration of abnormalities in insulin binding as well as defects in glucose transport and intracellular metabolism from cultured fibroblasts.[48] It is also possible that the decrease in lean body mass (primarily muscle) known to occur with aging[21,49] contributes to the impairment in glucose disposal, since there would be less tissue available to metabolize the glucose.

The M/I ratio during the hyperglycemic clamp study also provides an independent measure of tissue sensitivity to insulin. This study differs from the euglycemic insulin clamp

study in that tissue sensitivity is examined at hyperglycemic levels and the insulin released is endogenously secreted. Nonetheless, we have shown that, when the M/I ratio is determined in the same subjects with both the euglycemic and hyperglycemic clamp techniques, a high degree of correlation is observed in both normal ($r = 0.816$; $P < 0.01$)[50] and in pathologic ($r = 0.874$; $P < 0.01$)[51] states. In the old subjects, the M/I ratio decreased 26% during the +125 mg/dl hyperglycemic clamp and 35% during the +40 mg/dl clamp. These values agree well with the 29% decrease documented with the euglycemic clamp. Thus, whether tissue sensitivity to insulin in old subjects is examined at hyperglycemic or basal levels, a significant impairment in insulin action is observed.

Previous studies documented an age-related increase in percent adiposity.[52] Since insulin action is known to be impaired in obesity[53] and insulin secretion has been shown to be augmented by obesity,[54] it is possible that the insulin resistance and normal insulin secretory response could be explained by an age-related increase in adipose tissue mass. However, no correlation could be found between the obesity index and either the M/I during the euglycemic and hyperglycemic clamp studies or the plasma insulin response to hyperglycemia. Since all subjects were close to ideal body weight (within 13%), the failure to observe such a correlation is not surprising. What role a relative increase in obesity may play in the observed insulin resistance cannot be determined by the present study.

In summary, the present results document an age-related decline in glucose tolerance. Under the present experimental conditions employing intravenous glucose and/or insulin, impaired tissue sensitivity to insulin is the primary factor responsible for the decrease in glucose tolerance observed with advancing age. This impairment in insulin action can be demonstrated under both hyperglycemic and euglycemic conditions. The beta cell response to glucose is not significantly impaired with age. Although a slight impairment in the early insulin response can be demonstrated in old subjects with small elevations in the plasma glucose concentration, this cannot account for the decrease in glucose metabolism observed in the present studies.

ACKNOWLEDGMENT

I wish to thank Dr. Rosa Hendler for performing the insulin determinations, Yih Fen Wu for expert technical assistance, and Joan Vieira for excellent secretarial help. This work was supported by National Institutes of Health grant AG-00764.

REFERENCES

[1] Spence, J. W.: Some observations on sugar tolerance, with special reference to variations found at different ages. Q. J. Med. *14*:314–26, 1920–21.

[2] Andres, R.: Aging and diabetes. Med. Clin. N. A. *55*:835–45, 1971.

[3] Davidson, M. D.: The effect of aging on carbohydrate metabolism. A review of the English literature and a practical approach to the diagnosis of diabetes mellitus in the elderly. Metabolism *28*:688–705, 1979.

[4] Hales, C. N., Greenwood, F. C., and Mitchell, F. L.: Blood-glucose, plasma-insulin and growth hormone concentrations of individuals with minor abnormalities of glucose tolerance. Diabetologia *4*:73–82, 1968.

[5] Welborn, T. A., Stenhouse, N. S., and Johnstone, C. C.: Factors determining serum insulin response in a population sample. Diabetologia *5*:263–66, 1969.

[6] Bjorntorp, P., Berchtold, P., and Tibblin, G.: Insulin secretion in relation to adipose tissue in men. Diabetes *20*:65–70, 1971.

[7] O'Sullivan, J. B., Mahan, C. M., Freedlender, A. E., and Williams, R. F.: Effect of age on carbohydrate metabolism. J. Clin. Endocrinol. Metab. *33*:619–23, 1971.

[8] Nolan, S., Stephan, T., Chae, S., Vidalon, C., Gegick, C., Khurana, R. C., and Danowski, T. S.: Age-related insulin patterns in normal glucose tolerance. J. Am. Geriatr. Soc. *21*:106–11, 1973.

[9] Smith, M. J., and Hall, M. R. P.: Carbohydrate tolerance in the very aged. Diabetologia *9*:387–90, 1973.

[10] Sanberg, H., Yoshimine, N., Maeda, S., Symons, D., and Zavodnick, J.: Effects of an oral glucose load on serum immunoreactive insulin, free fatty acid, growth hormone and blood sugar levels in young and elderly subjects. J. Am. Geriatr. Soc. *21*:433–39, 1973.

[11] Sinha, M. K., Mondal, A. N., and Rastogi, G. K.: Influence of age on glucose tolerance in normal subjects. Acta Diabetol. Lat. *11*:78–83, 1974.

[12] Duckworth, W. C., and Kitabchi, A. E.: The effect of age on plasma proinsulin-like material after oral glucose. J. Lab. Clin. Med. *88*:359–67, 1976.

[13] Fedele, D., Valerio, A., and Molinari, M.: Glucose tolerance, insulin, and glucagon secretion in aging. Diabetologia *13*:392, 1977.

[14] Schreuder, H. B.: Influence of age on insulin secretion and lipid mobilization after glucose stimulation. Isr. J. Med. Sci. *8*:832–34, 1972.

[15] Boyns, D. R., Crossley, J. N., Abrams, M. E., Jarrett, R. J., and Keen, H.: Oral glucose tolerance and related factors in a normal population sample. 1. Blood sugar, plasma insulin, glyceride and cholesterol measurements and the effects of age and sex. Br. Med. J. *1*:595–98, 1969.

[16] Ryan, W. C., Schwartz, T. B., and Nibbe, A. F.: Serum immunoreactive insulin levels during glucose tolerance and intensive islet stimulation. Diabetes *20*:404–09, 1971.

[17] Welborn, T. A., Rubenstein, A. H., Haslam, R., and Fraser, R.: Normal insulin response to glucose. Lancet *1*:280–83, 1966.

[18] Chlouverakis, C., Jarrett, R. J., and Keen, H.: Glucose tolerance, age and circulating insulin. Lancet *1*:806–09, 1967.

[19] Johansen, K.: A new principle for the comparison of insulin secretory responses. I. The effect of age on insulin secretion. Acta Endocrinol. *74*:511–23, 1973.

[20] Palmer, J. P., and Ensinck, J. W.: Acute-phase insulin secretion and glucose tolerance in young and aged normal men and diabetic patients. J. Clin. Endocrinol. Metab. *41*:498–503, 1975.

[21] Dudl, R. J., and Ensinck, J. W.: Insulin and glucagon relationships during aging in man. Metabolism *26*:33–41, 1977.

[22] Metz, R., Surmaczynska, B., Berger, S., and Sobel, G.: Glucose tolerance, plasma insulin, and free fatty acids in elderly subjects. Ann. Intern. Med. *64*:1042–48, 1966.

[23] Zeytinoglu, I.Y., Gherondache, C. N., and Pincus, G.: The process of aging: serum glucose and immunoreactive insulin levels during the oral glucose tolerance test. J. Am. Geriatr. Soc. *17*:1–14, 1969.

[24] Woldow, A., Shapiro, B., Cohen, J. J., and Kollman, G.: Relationship of lipids to glucose tolerance and insulin response in the aged. J. Am. Geriatr. Soc. *20*:515–20, 1972.

[25] Crockford, P. M., Harbeck, R. J., and Williams, R. H.: Influence of age on intravenous glucose tolerance and serum immunoreactive insulin. Lancet *1*:465–67, 1966.

[26] Barbagallo-Sangiorgi, G., Laudicina, E., Bompiani, G. D., and Durante, F.: The pancreatic beta-cell response to intravenous administration of glucose in elderly subjects. J. Am. Geriatr. Soc. *18*:529–38, 1970.

[27] Himsworth, H. P., and Kerr, R. B.: Age and insulin sensitivity. Clin. Sci. *4*:153–57, 1939–42.

[28] Silverstone, R. A., Brandfonbrener, M., Shock, N. W., and Yiengst, M. J.: Age differences in the intravenous glucose tolerance tests and the response to insulin. J. Clin. Invest. *36*:504–14, 1957.

[29] Franckson, J. R. M., Malaisse, W., Arnould, E., Rasio, E., Ooms, H. A., Balasse, E., Conard, V., and Bastenie, P. A.: Glucose kinetics in obesity. Diabetologia *2*:96–103, 1966.

[30] Calloway, N. O., and Kujak, R.: Age and the kinetics of response to sugars and insulin. J. Am. Geriatr. Soc. *19*:122–30, 1971.

[31] Hochstaedt, B. B., Schneebaum, M., and Shadel, M.: Adrenocortical responsivity in old age. Gerontol. Clin. *3*:239–46, 1961.

[32] Martin, F. I. R., Pearson, M. J., and Stocks, A. E.: Glucose tolerance and insulin sensitivity. Lancet *1*:1285–86, 1968.

[33] Kalk, W. J., Vinik, A. I., Pimstone, B. L., and Jackson, W. P. U.: Growth hormone response to insulin hypoglycemia in the elderly. J. Gerontol. *28*:431–33, 1973.

[34] McGuire, E. A. H., Helderman, J. H., Tobin, J. D., Andres, R., and Berman, M.: Effects of arterial versus venous sampling. An analysis of glucose kinetics in man. J. Appl. Physiol. *41*:565–73, 1976.

[35] Sherwin, R. S., Kramer, K. J., Tobin, J. D., Insel, P. A., Liljenquist, J. E., Berman, M., and Andres, R.: A model of the kinetics of insulin in man. J. Clin. Invest. *53*:1481–92, 1974.

[36] Sherwin, R. S., Hendler, R., DeFronzo, R. A., Wahren, J. A., and Felig, P.: Glucose homeostasis during prolonged suppression of glucagon and insulin secretion by somatostatin. Proc. Natl. Acad. Sci. USA *74*:348–52, 1977.

[37] Steel, R.: Influence of glucose loading and of injected insulin on hepatic glucose output. Ann. N.Y. Acad. Sci. *82*:420–30, 1959.

[38] Cowan, J. S., and Hetenyi, C.: Glucoregulatory responses in normal and diabetic dogs recorded by a new tracer method. Metab. Clin. Exp. *20*:360–72, 1971.

[39] Radziuk, J., Norwich, K. H., and Vranic, M.: Measurement and vali-

dation of nonsteady state turnover rates with application to the insulin and glucose systems. Fed. Proc. *33*:1855–64, 1974.

[40] Snedecor, G. W., and Cochran, W. G.: Statistical Methods, 6th edit. Ames, Iowa State University Press, 1967.

[41] Wise, J. K., Hendler, R., and Felig, P.: Influence of glucocorticoids on glucagon secretion and plasma amino acid concentrations in man. J. Clin. Invest. *52*:2774–82, 1973.

[42] Grodsky, G. M., Batts, A. A., Bennett, L. L., Vcella, C., McWilliams, N. B., and Smith, D. F.: Effects of carbohydrates on secretion of insulin from isolated rat pancreas. Am. J. Physiol. *205*:638–44, 1963.

[43] DeFronzo, R. A., Ferrannini, E., Hendler, R., Wahren, J., and Felig, P.: Influence of hyperinsulinemia, hyperglycemia and the route of glucose administration on splanchnic glucose exchange. Proc. Natl. Acad. Sci. USA *75*:5173–77, 1978.

[44] Bjorntorp, P., Berchtold, P., and Larson, B.: The glucose uptake of human adipose tissue in obesity. Eur. J. Clin. Invest. *1*:480–83, 1971.

[45] Bjorntorp, P., Krotkjewski, M., Larson, B., and Somlo-Szues, Z.: Effects of feeding states on lipid radioactivity in liver, muscle, and adipose tissue after injection of labeled glucose in the rat. Acta Physiol. Scand. *80*:29–38, 1970.

[46] Davidson, M. B.: In vitro carbohydrate metabolism in the rat after chronic exposure to hypoxia. J. Appl. Physiol. *25*:105–07, 1968.

[47] Gommers, A., Dehez-Delhaye, M., and Jeajean, M.: The effect of age on the in vitro response to insulin in the rat. I. Glucose metabolism on the diaphragm. Gerontology *23*:131–41, 1977.

[48] Goldstein, S., and Harley, C. B.: Studies of age-associated diseases in vitro. Fed. Proc. In press, 1978.

[49] Malina, R. M.: Quantification of fat, muscle and bone in man. Clin. Orthop. *65*:9–18, 1969.

[50] DeFronzo, R. A., Tobin, J. D., and Andres, R.: The glucose clamp technique. A method for the quantification of beta cell sensitivity to glucose and of tissue sensitivity to insulin. Am. J. Physiol. *237*:E214–E223, 1979.

[51] DeFronzo, R. A., Tobin, J. D., Rowe, J. W., and Andres, R.: Glucose intolerance in uremia. Quantification of pancreatic beta cell sensitivity to glucose and tissue sensitivity to insulin. J. Clin. Invest. *62*:425–35, 1978.

[52] Kekwick, A.: Adiposity. *In* Handbook of Physiology, Section 5. Adipose Tissue. Renold, A. E., and Cahill, G. F., editors. Washington, D.C., American Physiologic Society, 1965, pp. 617–24.

[53] DeFronzo, R. A., Soman, V., Sherwin, R., Hendler, R., and Felig, P.: Insulin binding to monocytes and insulin action in human obesity, starvation, and refeeding. J. Clin. Invest. *62*:204–13, 1978.

[54] Bagdade, J. D., Bierman, E. L., and Porte, D., Jr.: The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. J. Clin. Invest. *46*:1549–57, 1967.