Age-related differences in the pancreatic β-cell response to hyperglycemia after eccentric exercise

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Krishnan, Raj K., Jazmir M. Hernandez, David L. Williamson, Donal J. O'Gorman, William J. Evans, and John P. Kirwan. Age-related differences in the pancreatic β-cell response to hyperglycemia after eccentric exercise. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E463–E470, 1998.— Eccentric exercise (ECC) causes muscle damage, insulin resistance, and increased pancreatic β-cell secretion in young individuals. However, the effects of age on the pancreatic β-cell response to glucose after ECC are unknown. Hyperglycemic clamps (180 min, 10.0 mM) were performed on eight young (age 22 ± 1 yr) and eight older (age 66 ± 2 yr) healthy sedentary males without exercise (CONT) and 48 h after ECC. ECC increased (P < 0.02) muscle soreness ratings and plasma creatine kinase concentrations in both groups. Insulin and C-peptide secretions were similar between young and older subjects during CONT clamps. ECC increased (P < 0.05) first-phase (0–10 min) C-peptide area under the curve in young (4.2 ± 0.4 vs. 3.7 ± 0.6 nM·min; ECC vs. CONT, respectively) but not in older subjects (3.2 ± 0.7 vs. 3.5 ± 0.7 nM·min; ECC vs. CONT), with significant group differences (P < 0.02). Indeed, ECC repressed (P < 0.05) first-phase peak C-peptide concentrations in older subjects (0.93 ± 0.16 vs. 1.12 ± 0.11 nM; ECC vs. CONT). Moreover, first-phase C-peptide-to-insulin molar ratios suggest age-related differences (P < 0.05) in insulin/C-peptide clearance after ECC. Furthermore, the observed C-peptide response after ECC was related to abdominal adiposity [r = −0.62, P < 0.02, and r = −0.66, P < 0.006, for first and second (10–180 min) phases, respectively]. In conclusion, older individuals did not exhibit the compensatory increase in β-cell secretion observed among young individuals after ECC. Thus, with increasing age, the pancreatic β-cell may be less responsive to the physiological stress associated with ECC.

hyperglycemic clamp; C-peptide; insulin; exercise-induced muscle damage; abdominal adiposity

HUMAN AGING IS ASSOCIATED with the development of glucose intolerance (24), insulin resistance (8, 23), and abnormal pancreatic β-cell secretion (5, 11, 14, 32). A decline in physical activity and changes in body composition with advancing age may contribute to the deterioration of glucose metabolism (25). It has been suggested that a combination of β-cell dysfunction and insulin resistance in older individuals may lead to the eventual onset of impaired glucose tolerance (IGT) (33) and type 2 diabetes (41). However, the relative contributions of pancreatic β-cell secretion and insulin action to the disturbances in glucose metabolism with aging are not clear. In contrast, some individuals maintain normal glucose tolerance and β-cell secretion as they age. It is unknown whether this subset of the older population sustains a normal pancreatic β-cell response to glucose under conditions of physiological stress.

Recently, acute and chronic exercise has been used as a physiological stressor to examine pancreatic β-cell responsivity and insulin action among the older population. Chronic exercise training studies have shown reduced β-cell secretion and enhanced insulin action in older individuals (23), comparable to what has been shown previously in young individuals (19). In contrast, an acute bout of exercise with a predominance of eccentric (muscle fiber lengthening) rather than concentric (muscle fiber shortening) contractions (2) has been shown to induce transient insulin resistance (3, 22) and increase the pancreatic β-cell response to glucose (20, 21) in young individuals. Eccentric exercise results in myofibrillar damage (12), muscle soreness (17), and elevated plasma myocellular protein levels (31). The metabolic consequences of exercise-induced muscle damage have not been determined among the older population, particularly with regard to the response of the pancreatic β-cell.

The purpose of this investigation was to determine whether the physiological stress associated with eccentric exercise alters the pancreatic β-cell response to hyperglycemia in healthy sedentary older individuals. The effects of age on pancreatic β-cell function were determined by comparing the β-cell response to hyperglycemia after eccentric exercise for the older individuals with the response among a group of healthy sedentary young individuals.

METHODS

Subjects. Eight young (age 21–28 yr) and eight older (age 59–75 yr) male volunteers provided informed consent in accordance with The Pennsylvania State University guidelines for the protection of human subjects. All of the subjects were healthy and were not diagnosed for any acute/chronic disease or using any medications. In addition, all of the subjects were sedentary, with a similar activity level between groups, as assessed by a physical activity questionnaire. None of the subjects was involved in any regular exercise regimen for ≥6 mo before the time of testing. All participants had a normal plasma glucose response to a 75-g oral glucose tolerance test (30) and did not have a family history of diabetes mellitus.

Height without shoes was measured to the nearest 0.1 cm. Body weight was measured to the nearest 0.1 kg. Body circumferences were measured to the nearest 0.1 cm for the waist (at the level of the umbilicus) and hip (at the point of widest circumference around the buttocks). Waist-to-hip ratio

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using the Siri equation (36). Residual lung electronic force cube transducers with voltage outputs, as described previously by Akers and Buskirk (1). Underwater weight was determined using density was determined by hydrostatic weighing after an overnight fast. For water displacement, the subject postexercised for 3 days preceding each trial. During the clamp procedure, a urine sample was obtained for the determination of glucose concentration. 

Analytic methods. Plasma insulin and C-peptide concentrations were determined in duplicate by double-antibody RIA (29) with the use of commercial kits (for insulin: Linco Research, St. Charles, MO; for C-peptide: Diagnostic Products, Los Angeles, CA). To reduce interassay variability, all samples for each subject were run in the same assay. Plasma CK concentrations were measured in duplicate using a quantitative colorimetric procedure (Sigma procedure no. 520; Sigma Diagnostics, St. Louis, MO).

Statistics. The MIXED procedure for the Statistical Analysis System (SAS Institute, Cary, NC) was used for ANOVA by the rank transformation (nonparametric) approach to identify statistical differences in the data. Group differences in the descriptive data were determined using a one-way ANOVA. Primary dependent variables were analyzed by a two-way repeated-measures ANOVA, with the main effects being group (young and older) and trial (CONT and ECC). Model-adjusted P values from a comparison of the least squared means were used to determine differences between ECC and CONT within groups. Group-by-trial interaction was used to demonstrate group differences in the measured responses when ECC was compared with CONT within groups. In addition, Spearman product-moment correlations were used to determine the relationship between C-peptide response and body composition. All values are expressed as means ± SE. An alpha level of 0.05 was used to determine statistical significance.

RESULTS

Subjects. Physical characteristics are summarized in Table 1. Body weight, body mass index, and fat-free mass (FFM) were similar among subjects. However, percent body fat, fat mass, and WHR were higher (P < 0.04) in the older subjects.

Exercise. All subjects performed 10 sets of 10 repetitions of leg extension (right and left legs, separately) and chest press, respectively. Measurements of muscle soreness in the upper body and lower body were obtained at 24 and 36 h after exercise, as described previously by Edwards et al. (10). Ratings of perceived soreness were obtained while a constant 40 N (4.1 kg) of pressure was applied to test sites using a spring-loaded pressure applicator with a 2-cm-diameter probe end. The scale for determination of perceived soreness ranged from 0 ("absence of soreness") up to 9 ("unbearable soreness") arbitrary units. Plasma creatine kinase (CK) concentrations were measured 48 h after both CONT and ECC on the morning of the clamp procedure.

All subjects performed 10 sets of 10 repetitions of leg extension (right and left legs, separately) or the arms and lowered the weight at full extension of either of the legs (right and left legs, separately) or the arms and lowered the weight in a steady fashion through the full range of motion, with ~3 s for each repetition. When the time of contraction fell below ~3 s, the resistance was reduced by 2.3 and 4.5 kg for the leg extension and chest press, respectively. Measurements of muscle soreness in the upper body and lower body were determined after the clamp procedure (15–180 min) to determine plasma insulin and C-peptide concentrations during the first (0–10 min) and second (10–180 min) phases of β-cell secretion. At the conclusion of the clamp, a urine sample was obtained for the determination of glucose concentration.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n = 8)</th>
<th>Older (n = 6)</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>22 ± 1</td>
<td>66 ± 2</td>
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<tr>
<td>Height, cm</td>
<td>181.0 ± 1.0</td>
<td>172.1 ± 2.1*</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>76.1 ± 5.5</td>
<td>75.7 ± 4.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4 ± 1.9</td>
<td>25.5 ± 1.2</td>
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<tr>
<td>FFM, kg</td>
<td>63.9 ± 3.0</td>
<td>58.5 ± 2.9</td>
</tr>
<tr>
<td>C-peptide</td>
<td>12.2 ± 3.0</td>
<td>17.2 ± 1.7*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.83 ± 0.02</td>
<td>0.91 ± 0.01*</td>
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</table>

Values are means ± SE. BMI, body mass index; FFM, fat-free mass; WHR, waist-to-hip ratio. *Significantly different from young group, P < 0.05.
(P < 0.01), respectively. Older subjects lifted 24.1 ± 2.6, 23.9 ± 2.4, and 35.8 ± 4.5 kg for the right leg, left leg, and chest exercises, respectively, with reduced resistances (%/10 sets) of −4.6 (P < 0.01), −1.3 (NS), and −13.4 (P < 0.01), respectively. Muscle soreness ratings for the upper body and lower body were elevated (P < 0.005) at 24 and 36 h after exercise compared with preexercise in all subjects, with no age group differences. Peak soreness at 36 h was exhibited in the triceps (7.1 subjects, with no age group differences. Peak soreness and 36 h after exercise compared with preexercise in all pectorals (6.3 upper body and lower body were elevated (P = 0.005) at 24 and 36 h after exercise compared with preexercise in all subjects, with no age group differences. Peak soreness at 36 h was exhibited in the triceps (7.1 ± 0.8 and 5.6 ± 0.8 units for young and older subjects, respectively), pectorals (6.3 ± 0.7 and 5.5 ± 0.6 units for young and older subjects), and quadriceps (4.3 ± 0.9 and 3.9 ± 0.6 units for young and older subjects). Plasma CK concentrations were elevated (P < 0.02) on the morning of the ECC clamp compared with CONT trial in both young (1,179 ± 480 vs. 58 ± 17 IU/l; ECC vs. CONT, respectively) and older subjects (629 ± 418 vs. 49 ± 15 IU/l; ECC vs. CONT), with no age group differences.

Basal glucose, insulin, and C-peptide. Fasting glucose, insulin, and C-peptide concentrations were similar on the morning of the clamp in both the young (5.1 ± 0.1 vs. 5.1 ± 0.1 mM, 52 ± 3 vs. 52 ± 2 pM, and 0.38 ± 0.07 vs. 0.34 ± 0.08 nM for glucose, insulin, and C-peptide, respectively; ECC vs. CONT) and older subjects (5.3 ± 0.1 vs. 5.3 ± 0.1 mM, 56 ± 4 vs. 57 ± 4 pM, and 0.39 ± 0.08 vs. 0.42 ± 0.10 nM for glucose, insulin, and C-peptide, respectively; ECC vs. CONT).

Insulin and C-peptide. Insulin and C-peptide responses to glucose were determined for the first (0–10 min) and second (10–180 min) phases of β-cell secretion by the calculated area under the curve (AUC) with the use of a trapezoidal model. No differences were observed for either insulin or C-peptide AUC when older subjects were compared with young subjects during CONT clamps for either the first or second phase. However, the first-phase C-peptide AUC (Table 2) was increased (P < 0.05) after ECC compared with CONT in the young subjects but not among older subjects. Moreover, the first-phase C-peptide AUC response when ECC was compared with CONT within age groups was different (P < 0.02) between age groups. Indeed, peak C-peptide concentrations for the first phase were lower (P < 0.05) when ECC was compared with CONT among the older subjects (0.93 ± 0.16 vs. 1.12 ± 0.11 nM; ECC vs. CONT). Insulin AUC response for the first and second phases and the C-peptide AUC response for the second phase, when ECC was compared with CONT, were similar in both groups, with no age group differences (Table 2). Second-phase peak C-peptide concentrations (for 150–180 min) were different (P < 0.05) between young (1.65 ± 0.16 vs. 1.41 ± 0.19 nM; ECC vs. CONT) and older (1.53 ± 0.23 vs. 1.68 ± 0.23 nM; ECC vs. CONT) groups. C-peptide-to-insulin (CPI) molar ratios were calculated from AUC values for insulin and C-peptide (34). The response of CPI ratios (Table 2) was similar between groups for CONT clamps (CPICONT) and within age groups when ECC was compared with CONT (CPIECC – CPICONT) for the first and second phases. However, the response of CPI ratios (CPIECC – CPICONT) was different (P < 0.05) between young and older subjects for the first but not the second phase.

Spearman correlation coefficients revealed an inverse relationship between the C-peptide response to ECC (C-peptide AUCECC – C-peptide AUCCONT) and WHR for the first (r = −0.62, P < 0.02; Fig. 1) and second phases (r = −0.66, P < 0.006) of β-cell secretion. However, there was no correlation between C-peptide response and percent body fat or fat mass. Furthermore, there was no correlation between either the insulin or C-peptide response during CONT clamps and body composition of the subjects.

Glucose. Mean plasma glucose concentrations during the first 15 min (0–15 min) of the ECC and CONT clamps were 8.9 ± 0.2 and 8.8 ± 0.2 mM, respectively, for the young and 8.5 ± 0.2 and 8.5 ± 0.1 mM for the older subjects. Mean plasma glucose concentrations were maintained at 10.0 ± 0.1 mM during the last 165 min (15–180 min) of all clamps. Coefficients of variation (15–180 min) for the ECC and CONT clamps were 4.6 ± 0.5 and 4.6 ± 0.5%, respectively, for the young and 4.5 ± 0.5 and 5.0 ± 0.5% for the older subjects.

Glucose disposal rates (M values, calculated from the glucose infusion rates) for 15–180 min were not different.

<table>
<thead>
<tr>
<th>Table 2. C-peptide AUC, insulin AUC, and C-peptide-to-insulin molar ratios for the first and second phases of pancreatic β-cell secretion during hyperglycemic clamps</th>
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<tbody>
<tr>
<td><strong>First Phase</strong></td>
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<tr>
<td><strong>CONT</strong></td>
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<tr>
<td><strong>C-peptide AUC, nM·min</strong></td>
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<td>Young</td>
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<td>Older</td>
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<td><strong>Insulin AUC, pM·min</strong></td>
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<td>Young</td>
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<td>Older</td>
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<tr>
<td><strong>C-peptide-to-insulin molar ratio</strong></td>
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<tr>
<td>Young</td>
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<tr>
<td>Older</td>
</tr>
</tbody>
</table>

Values are means ± SE. First phase, 0–10 min; second phase, 10–180 min; CONT, control; ECC, eccentric exercise; AUC, area under the curve; ΔECC-CONT, calculated difference between means for ECC – CONT. *ECC significantly different from CONT, P < 0.05. †Significantly different response from young, P < 0.05.
between ECC and CONT clamps in either young (7.1 ± 0.6 vs. 7.8 ± 0.6 mg·kg FFM⁻¹·min⁻¹; ECC vs. CONT) or older subjects (4.5 ± 0.3 vs. 4.8 ± 0.5 mg·kg FFM⁻¹·min⁻¹; ECC vs. CONT). However, regardless of trial (ECC or CONT), the M values were lower (P ≤ 0.002) for the older subjects compared with the young subjects. M-to-I ratios were calculated as M (150–180 min) divided by the average insulin (I) concentration (150–180 min). The M-to-I ratios were unchanged when ECC was compared with CONT in both the young (4.9 ± 0.7 vs. 5.4 ± 0.7 mg·kg FFM⁻¹·min⁻¹; ECC vs. CONT) and older subjects (3.0 ± 0.3 vs. 3.4 ± 0.5 mg·kg FFM⁻¹·min⁻¹; ECC vs. CONT). However, the M-to-I ratios for the older group were lower (P < 0.03) than for the young group, regardless of trial (ECC or CONT).

**DISCUSSION**

The principal finding in this investigation was an age-related difference in the pancreatic β-cell response to hyperglycemia after the physiological stress induced by ECC. After ECC, healthy sedentary young subjects showed an ~16% increase in the first-phase C-peptide AUC above control, indicating an increase in the pancreatic β-cell response to glucose that is consistent with previous findings by Kirwan et al. (21) and King et al. (20). In contrast, healthy sedentary older subjects did not show an increase in the first-phase C-peptide response to hyperglycemia. Indeed, first-phase peak C-peptide concentrations in the older subjects suggest that the increase in β-cell response to hyperglycemia was ~11% lower after ECC compared with control. The percent changes in insulin and C-peptide response to hyperglycemia indicate that young and older subjects show opposite trends in β-cell secretion after ECC for both the first and second phases (Fig. 2). Our data suggest a pancreatic β-cell dysfunction in healthy older individuals that prevents the "normal" increase in β-cell secretion after a physiological stress such as ECC.

The older subjects tested in this study had fasting glucose/insulin/C-peptide levels similar to those of young subjects. Moreover, the older subjects exhibited a normal pancreatic β-cell response to a similar glycemic stimulus as young subjects during control clamps. These data are in contrast to previous suggestions of abnormal basal (14, 32), first- (32), and second-phase (5, 11) β-cell secretion with aging. However, subject composition and the control of activity/diet may account for the discrepancy in findings. In the present investigation, the older group had a normal oral glucose tolerance test, and subjects were free from medica-
tion and acute/chronic disease. In addition, our older subjects were physically inactive for ≥6 mo before testing and had activity levels similar to those of sedentary young subjects. Physical activity was controlled before testing through residence at the GCRC, and a standard diet was provided to maintain adequate carbohydrate storage. Given the imposed restrictions, our data suggest that, with advancing age, normal glucose tolerance and β-cell response to hyperglycemia may be inadequate clinical predictors of normal β-cell secretory capacity under the combined conditions of hyperglycemia and the physiological stress associated with ECC. Hence, although adjustments in β-cell secretion with increasing age help to maintain glucose tolerance, older individuals may be predisposed to an eventual loss in reserve capacity of the pancreas with further advances in age.

All subjects experienced significant whole body muscle soreness and apparent muscle damage after ECC, with no age-related differences in the response to exercise. Elevated muscle soreness ratings, muscular stiffness, and inflammation 24–48 h after exercise suggest that all subjects exhibited delayed onset muscle soreness, a symptom of exercise-induced muscle damage (17). It has been shown that augmented plasma CK levels after intense lengthening contractions are associated with myofibrillar disruption and increased membrane permeability (31). Thus, in the present study, elevated plasma CK concentrations in both groups provide additional support for the presence of exercise-induced muscle damage. Elevations in plasma CK levels have been reported previously in young subjects with ECC-induced increases in β-cell secretion (20, 21).

Dynamic forced lengthening contractions have been shown to induce transient whole body insulin resistance and decreased glucose uptake in young individuals (20, 21). In the current study, glucose disposal rates (M and M-to-I ratios) were not altered by ECC, which is consistent with other data from hyperglycemic clamps (20, 21). Assessments of insulin action using hyperglycemic clamp-derived glucose disposal rates are inaccurate because of variability in the metabolism of infused glucose, incomplete suppression of hepatic glucose production by portal insulin, and the possible contributions of non-insulin-mediated glucose disposal. Indeed, studies using euglycemic hyperinsulinemic clamps (3, 22) quantitatively demonstrate reductions in whole body glucose disposal rates and thus insulin resistance in young subjects after unaccustomed ECC. Hence, the increase in pancreatic β-cell secretion in young subjects after ECC in the present study and other studies (20, 21) may be the normal β-cell compensation in response to a physiological stress at the muscle that mimics a state of insulin resistance. Moreover, similar increases in β-cell response have been observed after nicotinic acid-induced insulin resistance in young subjects (18).

In contrast, when healthy older subjects are presented with a combination of hyperglycemia and ECC, they demonstrate an inability of the pancreas to alter β-cell responsivity. ECC was used as a physiological stress in an attempt to study stress-mediated alterations in β-cell secretion with human aging. Other physiological stresses with increasing age include insulin resistance, type 2 diabetes, and obesity. The current findings are perplexing in light of previous data showing that the β-cell of older subjects adapts to the stress associated with aerobic exercise in a manner comparable to young subjects (23). In this study, healthy older subjects show a β-cell response to ECC-induced stress similar to that observed in other conditions of physiological stress. Moreover, it is not apparent why the observed decrements in β-cell secretion are pronounced during the first phase, rather than the second phase. β-Cell decompensation occurs during the transition toward type 2 diabetes, in which the first phase is either reduced (33, 41) or may show a paradoxical fall below basal (26). A specific first-phase β-cell dysfunction has been previously noted with aging (8) and may predict the onset of type 2 diabetes in prediabetic IGT patients (37). Likewise, trends toward blunted second-phase secretion are seen with IGT (5) and type 2 diabetes (41). In the present investigation, the decline in β-cell responsivity in older subjects after ECC-induced stress may suggest a mechanism that temporarily parallels the metabolic state associated with insulin resistance. Furthermore, the vulnerability of the first phase to physiological stressors such as type 2 diabetes and exercise-induced muscle damage may suggest a metabolic disorder of this initial secretory response common to both conditions.

The observed group differences in C-peptide response after ECC, in conjunction with a similar insulin response, beg the question of age-related differences in insulin/C-peptide clearance from circulation. The pancreas secretes equimolar amounts of insulin and C-peptide into the portal circulation (6). The liver extracts a significant portion of the insulin but not the C-peptide during the clamp procedure (34). The relative molar quantities of insulin and C-peptide in peripheral circulation (CPI ratios) have been used as an index of hepatic insulin clearance (34). In the present study, CPI ratios suggest that both groups had similar insulin clearance during CONT clamps. However, older subjects exhibited a significantly different first-phase CPI ratio response (CPI_ECC – CPI_CONT) compared with the young. Although not significant, the change in CPI ratios (CPI_ECC vs. CPI_CONT) in young (+16 and +15%; first and second phases, respectively) and older subjects (−14 and −5%; first and second phases, respectively) suggests opposite group trends. Whereas the young increased, the older subjects may have decreased hepatic insulin clearance after ECC, particularly during the first phase. Abnormalities in hepatic insulin extraction have been seen in other conditions of physiological stress, such as obesity (35) and type 2 diabetes (38). In addition, it has been suggested that renal clearance of C-peptide is altered after exercise (19). Although a previous study showed no significant changes in renal C-peptide clearance after ECC (21), the reported ~38% decrease in the mean urinary C-peptide concentrations suggests some role for renal clearance. In the present study, the contributions of
hepatic and renal clearance mechanisms may explain why similar circulating insulin levels were maintained in both groups, despite differences in C-peptide. Our findings suggest that aging is associated with abnormal clearance of insulin and/or C-peptide after exercise-induced muscle damage, perhaps via hepatic and/or renal mechanisms.

Body composition may account for some of the differences in β-cell response to hyperglycemia after ECC between groups. Although body mass index was similar, the older group had more body fat compared with the young group. Furthermore, the WHR data indicate that older subjects had greater upper body fat distribution. However, it is important to note that the older subjects were not obese on the basis of either total or regional adiposity. Pancreatic β-cell secretion before exercise was not related to body composition. However, the C-peptide response to ECC (C-peptide AUCC Ecc – C-peptide AUCC CONT) was inversely related to WHR but not percent body fat. These data indicate that, with advancing age, the reduced ability to increase β-cell secretion after ECC may be related to an increase in abdominal adiposity but not total adiposity. There is growing evidence linking the accumulation of abdominal fat to disturbances in glucose metabolism and insulin action (23, 25). Albeit the relationship between body fat distribution and β-cell secretory response has received little attention, Walton et al. (40) have suggested that central adiposity is associated with abnormal insulin and C-peptide secretion. Although the effects of abdominal adiposity on pancreatic β-cell function after ECC were not a primary question, our observations contribute to previous findings regarding central obesity, insulin resistance, and abnormal β-cell secretion.

The mechanisms responsible for the age-associated decline in β-cell responsivity after ECC are not apparent. An unidentified factor(s) related to exercise-induced muscle damage, or resultant insulin resistance (3, 22), may act on the pancreas to increase β-cell secretion in young individuals. Thus it is possible that older individuals possess an acute pathophysiological maladaptation under which 1) the β-cell may be less sensitive to a potential physiological signal(s), 2) this signal(s) may also act on the liver/kidney to affect insulin/C-peptide clearance, and 3) the accumulation of abdominal fat may potentially affect this signaling mechanism(s). Exercise-induced muscle injury has been shown to initiate an immune response (acute-phase response), mediated by cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α (7). Recent reports indicate that TNF-α may be associated with insulin resistance (16) and altered β-cell secretion (28). Thus increases in TNF-α or other cytokines after ECC could contribute to the observed changes in β-cell responsivity. King et al. (20) proposed that ECC-mediated increases in IL-1β may stimulate β-cell secretion, as reported previously in an animal model (13). Although free fatty acids have also been reported to induce insulin resistance and stimulate β-cell secretion (4), free fatty acid levels remain unchanged 48 h after ECC (22). Neural or hormonal changes may be potential stimuli. However, Kirwan et al. (22) showed no change in plasma glucagon, cortisol, epinephrine, and norepinephrine levels 48 h after ECC. Therefore, numerous mechanisms may be responsible for signaling between the muscle, pancreas, liver, or kidney after a physiological stress such as exercise. With advancing age, an abnormality in these potential pathways may be responsible for the observed differences, with some contribution arising from increased abdominal adiposity.

In summary, this is the first study to examine the effects of ECC on the pancreatic β-cell response to hyperglycemia in older individuals. In healthy sedentary young individuals, an increase in β-cell sensitivity to glucose serves as a normal adaptation to either ECC per se or a phenomenon related to transient insulin resistance (3, 22). Although healthy sedentary older individuals may maintain apparently normal glucose tolerance and β-cell secretion, they exhibit a decline in β-cell function that is revealed when presented with the combined conditions of hyperglycemia and the physiological stress of exercise-induced muscle damage. The observed age-related maladaptations specific to C-peptide may have metabolic significance in light of emerging findings suggesting that C-peptide may assist in skeletal muscle glucose uptake in healthy young individuals but may be defective in both type 2 diabetics and nondiabetic healthy older individuals (39). In addition, abnormal insulin and/or C-peptide clearance may also play a role, potentially through hepatic and/or renal mechanisms. Thus a secretion/clearance paradigm that is involved in other metabolic states, such as aging, obesity, type 2 diabetes, and exercise, may also apply to the ECC/muscle damage model. However, the relative contributions of β-cell secretion and subsequent clearance to the metabolic abnormalities observed in this study are not clear. Furthermore, our data linking the β-cell decompensation to abdominal adiposity provide a critical experimental base to examine relationships between regional adiposity and β-cell function with advancing age. We conclude that human aging is associated with a decline in the pancreatic β-cell responsivity after the physiological stress associated with ECC.

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