Human aging is associated with parallel reductions in insulin and amylin release

CYNTHIA J. DECHENES, C. BRUCE VERCHERE, SOFIANOS ANDRIKOPOULOS, AND STEVEN E. KAHN
Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington, Seattle 98195; and Veterans Affairs Puget Sound Health Care System, Seattle, Washington 98108

Dechenes, Cynthia J., C. Bruce Verchere, Sofianos Andrikopoulos, and Steven E. Kahn. Human aging is associated with parallel reductions in insulin and amylin release. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E785–E791, 1998.—Aging is associated with an increased risk of type 2 diabetes. To determine whether the insulin resistance of aging is associated with an increase in amylin release or whether amylin release parallels the reduction in insulin release, we studied 10 older (72 ± 2 yr) and 9 young (25 ± 1 yr) subjects. Insulin sensitivity was quantified as the insulin sensitivity index (S_{I}) and B cell function as the acute insulin and amylin responses to iv glucose (AIRg and AARg, respectively) and iv arginine (AIRmax and AARmax). To account for the effect of S_{I} to modulate B cell function, we calculated S_{I} × B cell function. Older subjects were insulin resistant (S_{I} 4.6 ± 0.8 vs. 8.6 ± 1.4 × 10^{-5} min^{-1}pM, P < 0.05). Acute responses to glucose [AIRg (older vs. young): 420 ± 106 vs. 537 ± 87 pm; AARg: 6.5 ± 1.7 vs. 9.0 ± 1.5 pm] and arginine [AIRmax: 1.096 ± 203 vs. 1.572 ± 307 pm; AARmax: 14.0 ± 3.5 vs. 16.5 ± 2.4 pm] did not differ despite the difference in S_{I}. When adjusted for S_{I}, insulin responses were reduced in older subjects (S_{I} × AIRg: 1.54 ± 0.29 vs. 4.10 ± 0.63 × 10^{-2} min^{-1}pM, P = 0.001; S_{I} × AIRmax: 4.03 ± 0.52 vs. 12.7 ± 2.9 × 10^{-2} min^{-1}pM, P < 0.01), as was amylin release (S_{I} × AARg: 2.46 ± 0.59 vs. 6.85 ± 0.95 × 10^{-4} min^{-1}pM, P < 0.001; S_{I} × AARmax: 4.71 ± 0.52 vs. 13.5 ± 2.2 × 10^{-4} min^{-1}pM, P < 0.001). Amylin and insulin release was proportionate, with a molar ratio of 1.5% in older and 1.4% in young subjects. Thus aging is associated with parallel impairments in the adaptation of insulin and amylin release to insulin resistance. It is unlikely that an alteration in amylin release contributes to the increased risk of type 2 diabetes.

islet amyloid polypeptide; glucose; B cell; insulin sensitivity; body adiposity

AGING is associated with an increased risk of glucose intolerance without fasting hyperglycemia (10). This alteration in glucose metabolism has been documented to be the result of insulin resistance and a failure of the B cell to appropriately increase its insulin response to this decline in insulin sensitivity (6, 11, 22). Similar, although more severe, alterations in insulin sensitivity and insulin secretion have been observed in subjects with type 2 diabetes mellitus (23). Type 2 diabetes is also characterized by the presence of islet amyloid deposits (34) that replace islet area, thereby probably contributing to the decline in insulin secretion (7, 31, 39, 44). It has been recognized for some 40 years that the prevalence of islet amyloid increases with age (2); however, it is unclear whether amyloid deposits are related to the increased prevalence of diabetes that occurs with aging or whether it is simply a function of the aging process per se.

Islet amyloid deposits are comprised primarily of a 37-amino acid peptide called amylin or islet amyloid polypeptide (9, 43). This peptide is a normal secretory product of the islet B cell that is cosecreted with insulin in response to glucose and non-glucose secretagogues both in vivo and in vitro (5, 8, 19). The magnitude of release of these B cell peptides is dependent on the nature of the secretagogue presented and on factors such as insulin resistance that modulate the response of the B cell (24, 41). Thus, for example, in obesity it has been demonstrated that human subjects secrete increased quantities of both insulin and amylin (28) as a result of the increased secretory demand placed on the B cell in response to obesity-associated insulin resistance (24). However, although insulin release and amylin release commonly occur in parallel, it has also been demonstrated that the release of these two peptides can be dissociated under a number of conditions, including rodent models of type 2 diabetes (14, 27, 32).

We have hypothesized that changes in amylin processing and/or secretion may be responsible for the increased propensity of this peptide to form islet amyloid (36). Because aging is associated with insulin resistance, reduced insulin release, and glucose intolerance, we sought to determine whether amylin release is also altered in aging. Specifically, we wished to examine whether the insulin resistance of aging is associated with a compensatory increase in amylin release such as occurs in obesity-associated insulin resistance or whether insulin release and amylin release decrease in parallel in older individuals.

SUBJECTS AND METHODS

Subjects. The subjects consisted of 10 older (7 males/3 females) and 9 young (7 males/2 females) subjects who were each studied on two occasions, with the exception of one young subject who did not have an oral glucose tolerance test (OGTT). No subject was taking medications known to affect glucose metabolism. Each subject gave informed written consent to participate in the study, which was reviewed and approved by the Human Subjects Review Committee at the University of Washington.

Study methods. Body adiposity was determined as body mass index (BMI), calculated as weight (kg)/height^2 (m).
All studies were performed after a 10-h overnight fast. On one study day, subjects underwent a 75-g OGTT. After two basal blood samples were obtained, the glucose load was administered and samples were drawn at 30, 60, 90, and 120 min for glucose, insulin, and amylin measurements. The results of this test were used to determine glucose tolerance and insulin and amylin release in response to oral nutrient ingestion.

On another study day, a tobutamide-modified frequently sampled intravenous glucose tolerance test (FSIGT) was performed to quantify insulin sensitivity and first-phase insulin and amylin release. After basal sampling, glucose (11.4 g/m²) was administered intravenously over 60 s, and 20 min later tobutamide (125 mg/m²) was given intravenously over 30 s. Blood samples were obtained 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, and 240 min after glucose administration. The addition of the tobutamide injection and prolonged sampling were performed to improve parameter identifiability (37) when the glucose and insulin data were analyzed using the minimal model of glucose kinetics developed by Bergman et al. (3). Glucose and insulin were measured on all samples, whereas amylin levels were determined on samples drawn up to 10 min after glucose injection.

After the withdrawal of the 240-min sample for the FSIGT, the plasma glucose level was raised to 25 mM with a variable-rate glucose infusion by use of a previously described algorithm (42). After clamping at this glucose level and 30 min after commencement of the variable-rate glucose infusion, a 5-g bolus dose of arginine was administered intravenously over 30 s. Blood samples for insulin and amylin measurement were drawn −5, −1, 2, 3, 4, 5, 7, and 10 min relative to the arginine injection.

Assays. All blood samples were drawn into tubes containing EDTA and kept on ice before being separated; after separation, plasma was stored at −70°C before being assayed. Plasma glucose was measured by an automated glucose oxidase method. Plasma immunoreactive insulin (IRI) was measured by a radioimmunoassay that has inter- and intra-assay coefficients of variation of 12 and 8%, respectively. Plasma amylin-like immunoreactivity (ALI) was quantified using a two-site enzyme-linked immunoassay system developed by Amylin Pharmaceuticals by use of antibodies F002 and F025 (35). This assay measures both glycosylated and nonglycosylated forms of the peptide (35, 38). It has inter- and intra-assay coefficients of variation of <15 and <10%, respectively, with a minimum detectable concentration of 1.6 pM. Each sample was measured in duplicate for IRI and in triplicate for ALI.

Calculations and statistical analysis. The incremental glucose (ΔG), IRI (ΔIRI), and ALI (ΔALI) responses were calculated as the difference between the values 30 min after oral glucose ingestion and those before glucose intake. The trapezoidal rule was used to calculate the incremental area under the curve (AUC) for glucose, IRI, and ALI for the duration of the OGTT. Insulin sensitivity was quantified as the insulin sensitivity index (SI) by use of the minimal model of glucose kinetics (3). First-phase insulin (AIRg) and amylin (AARg) responses were calculated as the mean incremental response above basal from samples drawn during the first 10 min after intravenous glucose administration. The maximal potentiation of insulin (AIRmax) and amylin (AARmax) release was determined as the mean incremental arginine-stimulated insulin and amylin responses at the damped glucose level of 25 mM. This incremental response was determined from samples drawn at 2, 3, 4, 5, 7, and 10 min after arginine injection, with the average of the samples obtained at −5 and −1 min before arginine administration being the prestimulus values.

Statistical analysis was performed using Statview SE + Graphics (Abacus Concepts, Berkeley, CA). Data are presented as means ± SE. Comparisons within a group were performed by Student’s paired t-test, whereas those between groups were done with an unpaired Student’s t-test except when variables were nonnormally distributed, when the Mann-Whitney U-test was performed. Correlations were performed by linear regression. A P value of <0.05 was considered significant.

RESULTS

Demographics. The demographic and fasting metabolic data for the 10 older and 9 young subjects are listed in Table 1. The older subjects were more obese, as assessed by BMI, and had higher fasting glucose levels, whereas the fasting IRI and ALI levels did not differ between the two groups. The mean values for glucose, IRI, and ALI were not different on either of the two study days.

Glucose, IRI, and ALI levels during the OGTT. As expected, the older subjects had higher plasma glucose concentrations during the OGTT (Fig. 1). On the basis of World Health Organization criteria, neither group had impaired glucose tolerance, although four of the older subjects had a level that exceeded 7.8 mM at 120 min. The ΔG response during the first 30 min of the test was not significantly different in the two groups (2.0 ± 0.3 vs. 2.6 ± 0.3 mM, P = 0.16). Glucose levels peaked at 90 min in the older subjects and at 30 min in the young subjects. In keeping with the reduced glucose tolerance in older individuals, the AUC for glucose tended to be greater in the older subjects, but this change was not significant (246.5 ± 38.2 vs. 193.3 ± 34.8 mM at 120 min).

IRI and ALI responses to oral glucose are also illustrated in Fig. 1. As expected, levels of IRI and ALI increased in response to glucose ingestion in both the older and young subjects. In the older subjects, the levels of IRI tended to be lower in the initial phase of the OGTT, but by the end of the test, the levels were

Table 1. Demographic and fasting plasma glucose, immunoreactive insulin, and amylin-like immunoreactivity in older and young subjects

<table>
<thead>
<tr>
<th></th>
<th>Older (n = 10)</th>
<th>Young (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>71.5 ± 1.7</td>
<td>25.1 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.2 ± 1.0</td>
<td>25.9 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OGTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose, mM</td>
<td>5.3 ± 0.2</td>
<td>4.5 ± 0.1*</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Fasting plasma IRI, mM</td>
<td>68.4 ± 5.6</td>
<td>50.5 ± 7.0*</td>
<td>0.06</td>
</tr>
<tr>
<td>Fasting plasma ALI, mM</td>
<td>4.4 ± 0.7</td>
<td>3.2 ± 0.4*</td>
<td>NS</td>
</tr>
<tr>
<td>FSIGT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose, mM</td>
<td>5.3 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Fasting plasma IRI, mM</td>
<td>72.0 ± 8.0</td>
<td>57.2 ± 4.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Fasting plasma ALI, mM</td>
<td>4.7 ± 0.8</td>
<td>4.0 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE of measurements determined on the day of an oral glucose tolerance test (OGTT) and a frequently sampled intravenous glucose tolerance test (FSIGT). IRI, immunoreactive insulin; ALI, amylin-like immunoreactivity. *OGTT measures were made in only 8 young subjects.
greater than in the young subjects. IRI reached a peak of 501 ± 85 pM at 120 min in the older subjects and 442 ± 117 pM at 30 min in the young subjects, whereas ALI reached a peak of 14.3 ± 2.4 pM at 120 min in the older subjects and 9.9 ± 1.6 pM at 120 min in the young subjects. The AUC for IRI was similar in both older and young subjects (37.0 ± 8.3 vs. 33.8 ± 10.1 nM at 120 min), as was that for ALI (719 ± 189 vs. 598 ± 103 pM at 120 min).

Over the first 30 min of the OGTT, the ΔIRI was similar in the two subject groups (277 ± 83 vs. 391 ± 118 pM, not significant [NS]), as was the ΔALI (3.8 ± 1.1 vs. 3.9 ± 0.9 pM, NS). Using these values and that of ΔG for the same time period, we determined the ΔRI/ΔG and ΔALI/ΔG as estimates of B cell function to account for the differences in basal glucose and incremental responses in older and young subjects. Both the ΔRI/ΔG and ΔALI/ΔG were similar in the older and young subjects, being 154 ± 41 and 2.2 ± 0.5 pM/mM, respectively, in the older subjects compared with 147 ± 34 and 2.4 ± 0.3 pM/mM in the young subjects.

S₁ and B cell function from intravenous testing. Insulin sensitivity quantified from the FSIGT indicated that the group of older subjects were, as expected, insulin resistant. S₁ was 4.6 ± 0.8 × 10⁻⁵ min⁻¹/pM in older subjects and 8.6 ± 1.4 × 10⁻⁵ min⁻¹/pM in the young subjects (P < 0.05).

The AIRg and AARg responses to intravenous glucose administration did not differ in absolute terms between the older and young subjects (AIRg: 420 ± 106 vs. 537 ± 87 pM, NS; AARg: 6.5 ± 1.7 vs. 9.0 ± 1.5 pM, NS). Because insulin sensitivity is a regulator of the B cell response and the older subjects were insulin resistant, it would be expected that these responses should be increased in the older individuals. Because the relationship between S₁ and B cell function is determined by a closed feedback loop and the elements are related in a hyperbolic manner (4, 24), we examined the appropriateness of B cell function by calculating the product of S₁ and B cell function (S₁ × B cell function). As illustrated in Fig. 2, A and B, when the appropriateness of B cell function is examined in this manner, it is apparent that the B cell response is reduced in older subjects in keeping with their reduced glucose tolerance. In older subjects, S₁ × AIRg was 37% that in the young being 1.54 ± 0.29 × 10⁻² min⁻¹ compared with 4.10 ± 0.63 × 10⁻² min⁻¹ (P < 0.005). In the case of S₁ × AARg, this function was also significantly reduced in the older individuals, being 2.46 ± 0.59 × 10⁻⁴ min⁻¹, which is 36% that in the young (6.85 ± 0.95 × 10⁻⁴ min⁻¹; P < 0.001).

At the completion of the sampling phase of the FSIGT and before commencement of the variable-rate glucose infusion, the glucose, IRI, and ALI levels had returned to baseline, being 4.6 ± 0.1 mM, 63.4 ± 7.6 pM, and 3.9 ± 0.8 pM, respectively, in the older subjects and 4.5 ± 0.1 mM, 49.6 ± 3.9 pM, and 3.0 ± 0.4 pM in the young subjects. The clamped glucose level achieved after 30 min of a variable-rate glucose infusion was 33.8 ± 1.7 mM in the older subjects, which was similar to the 35.6 ± 1.2 mM value in the young subjects. At this elevated glucose concentration and before arginine administration, IRI levels were 501 ± 105 pM in the older subjects and 738 ± 107 pM in the young subjects, and the ALI levels were 11.6 ± 2.0 pM in the older and 16.9 ± 2.7 pM in the young subjects. After arginine administration, the IRI and ALI levels increased in all subjects. In the older subjects, both of these responses were similar to those in the young (AIRmax: 1.096 ± 203 vs. 1.572 ± 307 pM; AARmax: 14.0 ± 3.5 vs. 16.5 ± 2.4 pM). However, when these responses were evaluated relative to the prevailing insulin sensitivity (Fig. 2, C and D), it was apparent that they were relatively...
deficient in the older subjects, being 31% those in the young for $S_I$, 35% for $S_{AIR_{max}}$, and 20% for $S_{AAR_{max}}$. These differences are significant ($P < 0.01$) and consistent with the known hyperbolic relationship between insulin sensitivity and B cell function.

Relationship between ALI and IRI. In the fasting state, the molar ratio between ALI and IRI ($ALI/IRI$) was similar in the two groups of subjects (6.7 ± 1.0 vs. 6.9 ± 1.0%, NS). When release of the peptides was stimulated by either oral or intravenous stimulus presentation, the ratio declined in both older and young subjects, compatible with the fact that amylin clearance is slower than that of insulin (28), and for the same reason the basal ratio will tend to be higher. After oral glucose, the $D_{ALI}/D_{IRI}$ (at 30 min) was similar in the two groups, being 1.6 ± 0.3% in the older subjects and 1.2 ± 0.2% in the young subjects. Age did not impact the proportion of ALI and IRI released, with these two measures being highly correlated ($r = 0.64$, $P < 0.005$) and the absolute values for each overlapping in older and young subjects (Fig. 3A). When the two subjects with the highest values for $D_{ALI}$ and $D_{IRI}$ were excluded from the analysis, the findings remained the same. This study is the first to examine amylin and insulin release in response to a number of secretagogues presented intravenously or orally in the same subjects and to relate these responses to differences in insulin sensitivity. Although the absolute amounts of insulin and amylin released and the molar proportion of the peptides are similar in older and young subjects, the fact that the two groups differ in terms of their insulin sensitivity indicates that the appropriateness of the

DISCUSSION

The results of the present study confirm previous findings that aging is associated with insulin resistance and that the B cell’s response to this reduction in insulin sensitivity is inadequate, so that insulin output is not appropriately increased in association with reduced glucose clearance (6, 10, 11, 22). Because the present cohort of older subjects typify the effect of aging in terms of glucose metabolism and obesity, they represent an appropriate group to examine the effect of aging on amylin secretion. Using this group, we have documented that the changes in insulin secretion that occur with healthy aging are paralleled by changes in amylin release. Because four of the older subjects had impaired glucose tolerance, we also analyzed the data without them. Such an analysis did not alter the significance of the findings (data not shown).

This study is the first to examine amylin and insulin release in response to a number of secretagogues presented intravenously or orally in the same subjects and to relate these responses to differences in insulin sensitivity. Although the absolute amounts of insulin and amylin released and the molar proportion of the peptides are similar in older and young subjects, the fact that the two groups differ in terms of their insulin sensitivity indicates that the appropriateness of the
responses differs between the two groups. It is well accepted that insulin sensitivity is a determinant of islet B cell function such that insulin resistance, as occurs spontaneously in young subjects with obesity or experimentally during nicotinic acid or glucocorticoid treatment, is associated with increased insulin release (1, 18, 33). Bergman et al. (4) hypothesized that the relationship between insulin sensitivity and B cell function is governed by a feedback loop that would best be represented by a hyperbolic function. We were able to demonstrate in a group of healthy human subjects under the age of 45 yr who had varying degrees of obesity and normal glucose metabolism that this is the case, so that the product of insulin sensitivity and insulin secretion remains constant (24). When this product is reduced, glucose intolerance occurs (17). Such is the case with aging (21, 22, 25), which is also commonly associated with the development of obesity and particularly central adiposity (40). In keeping with the impact of aging on body adiposity, the present cohort of older subjects were more obese. However, in response to this obesity and its probable attendant insulin resistance, the older subjects did not demonstrate the predicted increase in insulin release compared with the young subjects.

Because amylin and insulin are packaged in the same secretory granules (30) and are cosecreted from the B cell in response to glucose and nonglucose secretagogues (5, 8, 15, 19), it would be expected that the effect of insulin resistance would be to modulate amylin output along with insulin. Thus it would appear that amylin release is reduced for the degree of B cell demand imposed by the insulin resistance of aging. The fact that the molar ratio of amylin to insulin does not differ in older and young subjects suggests that the insulin resistance of aging or aging per se does not grossly alter the process by which amylin and insulin are stored and released, because any such change would have been predicted to result in an alteration in the molar proportions of the peptides released. Finally, although a hyperbolic relationship has not been demonstrated between insulin sensitivity and amylin secretion, amylin release has been shown to increase with increasing body size and insulin resistance (13, 26, 28). It is therefore reasonable to assume a similar relationship between insulin sensitivity and B cell function for amylin release as has been shown for insulin release. With this assumption, and with similar molar proportions of amylin to insulin in older and young subjects, we conclude that amylin release is impaired in older subjects, as supported by our findings that the products of insulin sensitivity and amylin were significantly different in the older and young subjects.

We have found that the molar proportion of amylin to insulin released (1–2%) is low no matter what secretagogue is administered or the mode of presentation and is similar to what we have previously found in vitro (19, 20). Because there is a substantial first-pass extraction of insulin by the liver, which would not appear to be the case for amylin (28), the molar proportion within the human B cell secretory granule is likely to be even less and may approach the 0.6% we have found in extracted rat islet cells (19). However, the difference in the ratio we have documented after intravenous glucose vs. arginine administration in this group of 19 subjects of varying ages suggests the possibility that this amylin-
to-insulin ratio may differ depending on the secretagogue presented, or that different pools of secretory granules contain different proportions of the two peptides. This finding would seem to be worthy of future study.

The finding of reduced amylin release in aging is compatible with other data that have examined the release of this peptide in humans with reduced B cell function. In the only other such study of older humans, Edwards et al. (12) performed OGTTs in young, middle-aged, and older groups and concluded that amylin release is lower in middle-aged subjects than in the other two groups. These conclusions were based on calculations of the AUC for amylin and did not account for the fact that the glucose area differed among the three groups, increasing with age. Because glucose is an important islet B cell stimulant, these differences in glucose concentrations would be expected to impact amylin (and insulin) secretion. Examination of the data of Edwards et al. and accounting for this difference in glucose area together support the idea that amylin release is reduced with aging. Finally, Edwards et al. did not account for the fact that amylin release in their subjects may have been impacted by differences in insulin sensitivity. The fact that it was likely to be reduced in their older subjects would further support the conclusions from the present study.

We recently reported another study of a large cohort of Japanese Americans with varying degrees of glucose tolerance and found that the incremental amylin response 30 min after oral glucose ingestion decreased as glucose tolerance declined (26). The decline in amylin release in these subjects with varying glucose tolerance was paralleled by changes in insulin release, as observed in the present study of older and young subjects. Other investigators have examined amylin release and also found that the release of this peptide can differ in pathophysiologic states. Thus Enoki et al. (13) found increased basal amylin levels and amylin responses to oral glucose in obese subjects and delayed but augmented amylin responses to oral glucose in subjects with impaired glucose tolerance. In a study examining the effect of experimental insulin resistance on the proportions of amylin and insulin released, dexamethasone-induced insulin resistance resulted in increases in amylin and insulin levels after oral glucose ingestion (29), but it is unclear whether the islet’s response was appropriate for the degree of change in insulin sensitivity.

The findings of the present study can be used to extrapolate the role of altered amylin release in the pathophysiology of the changes in insulin sensitivity and insulin secretion that are seen in older individuals and in subjects with type 2 diabetes mellitus. It has been hypothesized that amylin may impair both insulin action and secretion (16). Such effects have been observed in vitro and in situ, although high concentrations are generally required (8). The present data suggest that the insulin resistance of aging is unlikely to be related to an increase in circulating amylin levels. If amylin were to be implicated, it would be expected that the plasma concentrations would be elevated. In fact, as discussed earlier, amylin levels do not differ between older and young subjects whereas the older subjects are insulin resistant, suggesting that, if anything, amylin release is inappropriately low. When the potential impact of amylin to reduce insulin (and its own) release is considered, it would be expected that such an effect would be mediated by either a direct effect to inhibit peptide output in a negative feedback manner or the formation of islet amyloid that destroys islet endocrine cells. We have no evidence to support either of these possibilities, as the mechanism for reduced islet peptide release and the changes we observed may simply be part of the aging process and totally unrelated to amylin.

In conclusion, we have examined amylin and insulin release in older and young subjects and have found that the release of these two peptides occurs in parallel. Thus older subjects do not increase their insulin and amylin output as expected in response to the diminished insulin sensitivity that characterizes aging. This parallel reduction in amylin release also suggests that amylin is unlikely to be responsible for the insulin resistance observed in aging or type 2 diabetes.

We are grateful to Brenda Montgomery for care of the subjects and to Maggie Abrahamson, Vicki Haagland, and Ruth Hollingsworth for technical assistance. We thank Dr. Daniel Porte, Jr., for useful comments during the preparation of this manuscript. The amylin kits used in this study were a gift of Amylin Pharmaceuticals.

This work was supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, National Institute of Diabetes and Digestive and Kidney Diseases Grants DK-17047, DK-31170, and DK-50703; the Medical Research Council of Canada; the American Diabetes Association; and the Juvenile Diabetes Foundation. C. J. Dechenes performed this work as a medical student supported by the American Federation for Aging Research.

Present addresses: C. B. Verchere, BC Research Institute for Children’s and Women’s Health, 950 W. 28th Ave., Vancouver, BC, Canada V5Z 4H4; S. Andrikopoulos, Dept. of Medicine, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.

Address for reprint requests: S. E. Kahn, VA Puget Sound Health Care System (151), 1660 S. Columbian Way, Seattle WA 98108.

Received 20 May 1998; accepted in final form 5 August 1998.

REFERENCES
