Genetic background determines the extent of islet amyloid formation in human islet amyloid polypeptide transgenic mice

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In humans, the development of type 2 diabetes is a complex process comprising both genetic and environmental elements that result in β-cell dysfunction and insulin resistance. The evidence for a genetic component comes from the increased risk of developing type 2 diabetes among different ethnic groups, such as the Pima Indians in Arizona (25), relatives of individuals with type 2 diabetes (4, 35), and, rarely, families with one of several monogenic mutations that are inherited in an autosomal dominant manner and are known as maturity onset diabetes of the young (11). Furthermore, familial aggregation of both insulin sensitivity (15, 30) and insulin responses (10, 15) has been described, in keeping with at least partial genetic determination of these important components of glucose metabolism.

Similarly in mice, genetic background strain is recognized as an important contributor to the development of metabolic abnormalities. The increasing use of genetically modified mice to study the role of various proteins or metabolic pathways in the pathogenesis of type 2 diabetes has highlighted the importance of genetic background strain in determining phenotypes. This has been demonstrated in several studies showing marked differences in phenotypes resulting from dietary or genetic interventions, when expressed on different background strains (7, 13, 14, 21, 27, 28, 36).

It is not known what contribution genetic background strain makes to islet amyloid formation in hIAPP transgenic mice, although evidence exists that it may play a role. Early studies using hIAPP transgenic mice with various genetic backgrounds failed to demonstrate islet amyloid formation (9, 12, 17, 45). Subsequently, it was found that environmental or genetic manipulations were required for amyloid to form. Interbreeding of hIAPP transgenic mice with mice carrying genetic mutations (Aβ+/a or db/db) associated with β-cell dysfunction together with severe obesity and insulin resistance that leads to diabetes (16, 37) was required to observe amyloid deposits resembling those seen in human type 2 diabetes. These mice were originally produced and maintained on FVB (12, 22) or C57BL/6J genetic backgrounds (17, 45). In contrast, our colony of hIAPP transgenic mice was produced on a C57BL/6J × DBA/2J (F1) background (9), and islet amyloid developed in a nonamyloidogenic. Thus transgenic mice expressing the amyloidogenic human IAPP (hIAPP) in their islet β-cells have been developed by a number of groups as models of islet amyloid formation (9, 12, 17, 45).

In the present study, we investigated the role of genetic background on hIAPP transgenic mice to determine whether amyloid deposition would occur in a nonamyloidogenic strain. For this purpose, we studied male hIAPP mice on each genetic background strain (BL6, C57BL/6J, and DBA/2J) male mice expressing DBA/2J genes (F1 and DBA2) strain (BL6, C57BL/6J, and DBA/2J) with mice expressing DBA/2J genes (F1 and DBA2) strain (BL6, C57BL/6J, and DBA/2J) with mice expressing DBA/2J genes (F1 and DBA2) strain (BL6, C57BL/6J, and DBA/2J). The majority of mice in each group developed islet amyloid deposits (14 ± 3%, BL6; 5.7 ± 2.3%, DBA2; p < 0.001) mice but not BL6 mice (14 ± 3%, BL6; 5.7 ± 2.3%, DBA2; p < 0.001) mice but not BL6 mice (14 ± 3%, BL6; 5.7 ± 2.3%, DBA2; p < 0.001) mice but not BL6 mice (14 ± 3%, BL6; 5.7 ± 2.3%, DBA2; p < 0.001) mice. Islet amyloid deposition was quantified by 10.220.33.2 on June 26, 2017 from http://ajpendo.physiology.org/.

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http://www.ajpendo.org
these mice when they were fed a diet containing moderate amounts of fat (9%/wt/wt; see Ref. 40). Based on the apparent importance of genetic background in the development of islet amyloid, in the present study, we sought to determine the relative contribution of each parental strain, C57BL/6J (BL6) and DBA/2J (DBA2), to islet amyloid formation in hIAPP transgenic mice in our dietary fat feeding model.

**MATERIALS AND METHODS**

**Transgenic mice.** Hemizygous transgenic mice with islet β-cell expression of hIAPP were generated as previously described (9). Transgenic mice were backcrossed to a C57BL/6J (BL6; n = 13) or DBA/2J (DBA2; n = 11) background for at least eight generations. C57BL/6J × DBA/2J hIAPP transgenic mice (F1; n = 17) were the control group from a study looking at the effects of rosiglitazone and metformin on islet amyloid deposition (20), which was performed concurrently with the present study. F1 hIAPP transgenic mice were generated by intercrossing C57BL/6J female mice carrying the hIAPP transgene with DBA/2J wild-type male mice. Only male mice were used in this study, since in previous studies we observed islet amyloid in 81% of male hIAPP transgenic mice compared with only 11% of female transgenic littermates (40). Transgenic status was determined by PCR using oligonucleotide primers directed against the hIAPP transgene (2). Nontransgenic male littermates of DBA/2J (n = 6) and C57BL/6J (n = 13) hIAPP transgenic mice were also studied. Mice were followed for one year on a diet containing 9% (wt/wt) fat (Mouse diet 2021; Purina Mills, St. Louis, MO) and were allowed ad libitum access to food unless otherwise stated. The study was approved by the Institutional Animal Care and Use Committee at the Veterans Affairs Puget Sound Health Care System.

**Metabolic measurements.** Body weight was measured at baseline and at 6 and 12 mo. At 12 mo, a subset of mice (hIAPP transgenic mice: BL6: n = 8, F1; n = 11, DBA2: n = 11; nontransgenic mice: DBA2: n = 5, BL6: n = 8) underwent an overnight fast followed by an intravenous glucose tolerance test (IVGTT) in which dextrose (1 g/kg iv) was administered in the jugular vein under pentobarbital sodium anesthesia. Blood samples were drawn before and 2, 5, 10, 20, 30, and 45 min after glucose injection and were used to assess intravenous glucose tolerance and glucose-stimulated immunoreactive insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release. At death, a portion of the pancreas was snap-frozen for homogenization in isopropanol/trifluoroacetic acid and insulin (IRI) release.

**Assays.** Plasma glucose was determined using a glucose oxidase method. Plasma levels and pancreatic content of IRI were measured by manually outlining the islet visualized on the thioflavin S channel, where the outline of the islet is clearly visible, whereas amyloid area and insulin-positive area were computed as the areas corresponding to fluorescence above a preset threshold, as we have done previously (19, 41).

**Calculations and data analysis.** Islet area, thioflavin S-positive (amyloid) area, and insulin-positive (β-cell) area data for each mouse were used to calculate islet amyloid prevalence (percentage of islets containing amyloid), islet amyloid severity (Σ amyloid area/Σ islet area × 100%), mean islet area, mean β-cell area per islet, and the proportion of islet area comprised of β-cells (Σ insulin positive area/Σ islet area × 100%).

The acute insulin response to iv glucose (AIRg) was calculated as the mean incremental IRI response above baseline from 2 to 10 min after glucose administration. Intravenous glucose tolerance was expressed as Kg, the slope of the regression line describing the relationship of natural log of the glucose concentration to time, from 10 to 45 min after glucose administration, expressed as percent change per minute. Area under the insulin curve was calculated for incremental IRI above baseline from 0 to 45 min using the trapezoidal method. Data are expressed as means ± SE. Changes in glucose and insulin over time during the IVGTT were analyzed using a general linear model (SPSS, Chicago, IL) with time after glucose administration and genetic background or transgenic status as independent variables. Comparisons of continuous data between the three hIAPP transgenic groups were performed using the Kruskal-Wallis nonparametric test. Three group comparisons of categorical variables were made using Chi-squared tests. Two group comparisons were made with the Mann Whitney U nonparametric test. Correlation analyses were performed using simple linear regression. P ≤ 0.05 was considered significant.

**RESULTS**

**Body weight.** Body weight was similar at baseline and increased in all three groups of hIAPP transgenic mice over the course of the 12-mo study (Table 1). No differences in body weight over time were observed among the three groups at 6 mo. However, F1 hIAPP transgenic mice had significantly higher body weight compared with BL6 and DBA2 mice at the end of the study (P < 0.01, F1 vs. BL6 and DBA2). Glucose tolerance and insulin release. To determine the effect of genetic background on glucose disposal and insulin release, mice underwent an IVGTT after an overnight fast at the end of the study. Fasting plasma glucose was not different among groups (7.8 ± 1.0, 8.7 ± 0.7, 8.1 ± 0.9 mmol/l for BL6, F1, and DBA2, respectively; Fig. 1A). The glucose excursion in F1 hIAPP transgenic mice was higher than in the other two groups (33.6 ± 2.1, 42.4 ± 1.5, 32.8 ± 2.4 mmol/l; P < 0.005 for plasma glucose level 2 min after iv glucose; Fig. 1A), but the rate of glucose disposal, expressed as the glucose disappearance constant Kg, was not different between F1 and DBA2 hIAPP transgenic mice (2.5 ± 0.3 vs. 3.3 ± 0.6%/min). In contrast, glucose disposal was delayed in BL6 transgenic

**Table 1. Body weight at baseline and after 6 and 12 mo on a 9% (wt/wt) fat diet in BL6, F1, and DBA2 hIAPP transgenic mice**

<table>
<thead>
<tr>
<th>Body wt, g</th>
<th>BL6</th>
<th>F1</th>
<th>DBA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>26.4 ± 1.7</td>
<td>25.4 ± 1.2</td>
<td>25.8 ± 1.3</td>
</tr>
<tr>
<td>6 mo</td>
<td>40.6 ± 2.7</td>
<td>47.5 ± 2.3</td>
<td>41.2 ± 1.6</td>
</tr>
<tr>
<td>12 mo</td>
<td>44.2 ± 2.1*</td>
<td>55.8 ± 2.5</td>
<td>44.6 ± 1.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. BL6, C57BL/6J mice; F1, C57BL/6J × DBA/2J mice; DBA2, DBA/2J mice; hIAPP, human islet amyloid polypeptide. *P < 0.01 vs. F1 hIAPP transgenic mice.
mice (1.0 ± 0.1%/min, P < 0.005 vs. F1 and DBA2 hIAPP transgenic mice).

Fasting plasma insulin levels before the IVGTT were higher in F1 and DBA2 compared with BL6 hIAPP transgenic mice (92 ± 23, 1,339 ± 736, 858 ± 188 pmol/l, P < 0.005 for BL6 vs. F1 and DBA2; Fig. 1B). Insulin release during the IVGTT was similar between F1 and DBA2 hIAPP transgenic mice but was markedly higher in both groups than in BL6 hIAPP transgenic mice when examined as change in plasma insulin levels over time (P < 0.05 among groups; Fig. 1B) or as AIRg (BL6: 306 ± 117, F1: 2,189 ± 857, DBA2: 1,455 ± 355 pmol/l, P < 0.01 for BL6 vs. F1 and BL6 vs. DBA2).

Islet amyloid formation. To determine the contribution of genetic background to islet amyloid deposition, pancreatic sections were examined for the presence of amyloid by thioflavin S staining. The majority of hIAPP transgenic mice developed amyloid, with the proportion being similar among groups (91, 76, 100% for BL6, F1, and DBA2, respectively). The prevalence of islet amyloid (%islets containing amyloid; Fig. 2A) was lower in BL6 compared with both F1 and DBA2 hIAPP transgenic mice and was similar between the latter two groups (14 ± 3, 44 ± 8, 49 ± 9; P < 0.05 for BL6 vs. F1 and P < 0.01 for BL6 vs. DBA2). Similarly, the severity of islet amyloid (%islet area occupied by amyloid; Fig. 2B) was comparable between F1 and DBA2 hIAPP transgenic mice but was significantly lower in the BL6 mice (0.03 ± 0.01, 9.2 ± 2.9, 5.7 ± 2.3, P = 0.01 for BL6 vs. F1 and P < 0.001 for BL6 vs. DBA2).

Islet morphology. Mean islet area was similar between F1 and DBA2 hIAPP transgenic mice, but was significantly lower in BL6 hIAPP transgenic mice (14,166 ± 1,876, 43,736 ± 5,255, 43,580 ± 7,060 μm² for BL6, F1, and DBA2, respectively, P < 0.001 for BL6 vs. F1 and P < 0.001 for BL6 vs. DBA2). Similarly the mean β-cell area per islet was lower in BL6 hIAPP transgenic mice than the other two groups (8,851 ± 1,162, 23,593 ± 2,262, 21,318 ± 3,586 μm², P<0.001 for BL6 vs. F1 and P<0.001 for BL6 vs. DBA2). To assess the effect of islet amyloid to alter β-cell area among strains, β-cell area was expressed as a proportion of islet area. This measure was significantly higher in BL6 hIAPP transgenic mice (69.3 ± 2.4, 58.0 ± 3.1, 58.1 ± 2.7% for BL6, F1, and DBA2, P < 0.05). The increased islet amyloid severity in F1 and DBA2 hIAPP transgenic mice was strongly negatively correlated with the proportion of β-cell area per islet ($r^2$=0.75, P < 0.001 for F1 and $r^2$=0.87, P < 0.001 for DBA2.)
Although islet area was similar between DBA2 nontransgenic (35.34 ± 7.531 µm²) and DBA2 hIAPP transgenic mice (43.580 ± 5.333 µm²; Fig. 3A), the proportion of islet area occupied by β-cells was significantly lower in the DBA2 hIAPP transgenic mouse (65.1 ± 2.7 vs. 58.1 ± 2.7% for DBA nontransgenic and DBA hIAPP transgenic mice, respectively, \( P < 0.05 \); Fig. 3B). Furthermore, the reduction in β-cell area was strongly negatively correlated with islet amyloid severity in the DBA2 hIAPP transgenic mice (\( r^2=0.87, P < 0.001 \)). Iset area was similar between BL6 nontransgenic (12.949 ± 2.368 µm²) and BL6 hIAPP transgenic mice (15.124 ± 2.165 µm²; Fig. 3A). In contrast to the finding with DBA2 mice, the proportion of islet area occupied by β-cells was similar between BL6 nontransgenic and BL6 hIAPP transgenic mice (70.4 ± 1.2 vs. 69.3 ± 1.2%; Fig. 3B). This measure did not correlate with islet amyloid severity in the BL6 hIAPP transgenic mice (\( r^2=0.07 \)), consistent with minimal amyloid deposition in this group.

Body weight at the end of the study was identical between DBA2 nontransgenic (44.9 ± 1.3 g) and DBA2 hIAPP transgenic mice (44.6 ± 1.5 g), whereas it was slightly but not significantly higher in BL6 nontransgenic mice (43.7 ± 2.4 g) compared with BL6 hIAPP transgenic mice (39.0 ± 2.0 g). Glucose levels during an IVGTT were similar between DBA2 hIAPP transgenic and nontransgenic mice (Fig. 3C). Consequently, glucose tolerance was similar between the two groups of DBA2 mice (3.23 ± 0.67%/min for DBA2 nontransgenic and 3.29 ± 0.57%/min for DBA2 hIAPP transgenic mice). Surprisingly, fasting plasma glucose and glucose levels throughout the IVGTT were significantly higher in BL6 nontransgenic mice than in BL6 hIAPP transgenic mice (Fig. 3C;
P = 0.002). However, glucose tolerance was identical between BL6 nontransgenic (1.01 ± 0.09%/min) and BL6 hIAPP transgenic (1.02 ± 0.14%/min) mice. Fasting plasma insulin was higher in DBA2 hIAPP transgenic mice (348 ± 76 vs. 856 ± 188, P = 0.05), but insulin release during the IVGTT was reduced (Fig. 3D), resulting in a nonsignificant decrease in A1Rg in DBA2 hIAPP transgenic mice (5,504 ± 2,748 vs. 1,455 ± 355 pmol/l) and a significant decrease in insulin release when expressed as the incremental area under the insulin curve (79,400 ± 20,443 vs. 15,780 ± 9,769 pmol/l, 45 min for DBA2 nontransgenic and DBA2 hIAPP transgenic mice, respectively, P < 0.05). In contrast, no significant differences existed in plasma insulin levels between nontransgenic and hIAPP transgenic BL6 mice at any time during the IVGTT (Fig. 3D).

DISCUSSION

We have shown that, in hIAPP transgenic mice, genetic background is an important determinant of the magnitude of islet amyloid formation, with mice expressing DBA/2J genes (F1 and DBA/2J hIAPP transgenic mice) showing increased susceptibility.

The propensity of hIAPP transgenic mice with DBA/2J genes to develop more severe amyloid deposits seems to be a dominantly inherited trait, with both the prevalence and severity of islet amyloid in F1 hIAPP transgenic mice being similar to that in DBA/2J hIAPP transgenic mice. The mechanism underlying the increased amyloid deposition in the hIAPP transgenic mice on the F1 and DBA/2J compared with the C57BL/6J background may be related to increased susceptibility to the effects of dietary fat-related factors on the islet or increased insulin (and thus hIAPP) secretion in the former two groups. β-Cell output appears to be an important determinant of islet amyloid formation, since induction of obesity and insulin resistance in hIAPP transgenic mice by increased dietary fat feeding (18) or crossbreeding with A/32a or ob/ob transgenic mice (16, 37) resulted in increased secretory demand and increased islet amyloid deposition, whereas decreased β-cell secretion in hIAPP transgenic mice carrying a heterozygote knockout mutation in β-cell glucokinase was associated with a marked reduction in islet amyloid deposition (2).

Hypersecretion of insulin appears to be a primary feature of islets from DBA/2J mice, with increased insulin release in response to glucose being present in DBA/2J mice, compared with age-matched C57BL/6J mice, as young as 1 day (27). This increased secretion persisted through at least 10 wk of age and did not appear to occur as an adaptive response to insulin resistance, since insulin sensitivity was similar between strains and glucose-stimulated insulin secretion remained higher in isolated islets from DBA/2J compared with C57BL/6J mice (27). Similarly, a recent study showed DBA/2J mice to hypersecret insulin in response to intraperitoneal glucose at 6 mo of age relative to age-matched C57BL/6J mice in the face of greater insulin sensitivity in the DBA/2J mice, whereas no difference in insulin release was detected between strains at 2 mo of age (13). In the present study, an innate hypersecretion of insulin (and IAPP) in the DBA/2J hIAPP transgenic mice was likely responsible for the more severe islet amyloid deposition.

In contrast, several studies have shown that decreased glucose-stimulated insulin release is a feature of C57BL/6 mice fed laboratory chow (13, 27) or a high-fat diet (36). Isolated islets from C57BL/6 mice show reduced insulin secretion compared with islets from other strains (27, 39), suggesting that reduced insulin release, rather than changes in insulin sensitivity, likely explains the well-known propensity for glucose intolerance in C57BL/6J mice (1, 13, 27, 36, 38, 39). Genetic loci that are associated with impaired islet glucose metabolism and decreased glucose-stimulated insulin secretion have recently been identified in C57BL/6 mice (39). This provides a genetic mechanism whereby insulin release may be decreased in C57BL/6 mice. Consistent with these data, in the present study, both C57BL/6J hIAPP transgenic and nontransgenic mice displayed markedly lower insulin secretion compared with the other groups, and developed glucose intolerance. Thus decreased insulin (and thereby IAPP) output seems to be a feature of both hIAPP transgenic and nontransgenic mice on a C57BL/6J genetic background, and this may have contributed to the low extent of islet amyloid formation seen in our C57BL/6J hIAPP transgenic mice. However, islet amyloid appears not to have played a role in this reduced glucose tolerance. Interestingly, in the present study, the F1 hIAPP transgenic mice attained a body weight greater than either DBA/2J or C57BL/6J hIAPP transgenic mice. However, although the absolute values for insulin release and amyloid severity were highest in the F1 mice, these were not statistically significantly different from the DBA/2J hIAPP transgenic mice.

Strain-related differences in islet mass likely contributed to the differences in insulin output seen among the mice. Mean islet size was significantly smaller in both groups of C57BL/6J mice than in DBA/2J mice, in agreement with the recent findings of Bock et al. (3), whereas islet density did not differ between the two strains (data not shown). Because islet size is highly correlated with islet mass (r² = 0.80, P < 0.0001, n = 54; unpublished observation), it is likely that reduced islet size, but not islet number, contributed to decreased islet mass and thus reduced insulin secretory capacity in both hIAPP transgenic and nontransgenic C57BL/6J mice.

Although we have shown that genetic background is important in determining the extent of islet amyloid deposition, it is not sufficient by itself to induce islet amyloid. In the original description of our colony of hIAPP transgenic mice, we failed to observe islet amyloid deposition despite the fact the mice were on a C57BL/6J × DBA/2J F1 background (9). The additional intervention of increased dietary fat was required for deposition of light microscopy visible islet amyloid to occur (40). Similarly, others have successfully demonstrated extensive islet amyloid deposition in hIAPP transgenic mice on a C57BL/6J background, albeit in the presence of marked obesity and insulin resistance resulting from additional genetic mutations (16, 37). Thus, although genetic background is important, additional intervention(s) resulting in β-cell dysfunction and/or increased secretory demand appear to be a prerequisite for islet amyloid formation. We believe that this likely reflects the situation in human type 2 diabetes, where both insulin resistance and β-cell dysfunction are key features. During the early stages of diabetes development, β-cell dysfunction is present and IAPP output parallels insulin release (23, 26). The presence of chronic insulin resistance results in increased insulin
and IAPP levels compared with lean subjects, resulting in an islet milieu similar to that in the present study. These conditions likely promote islet amyloid deposition, leading to β-cell loss and further β-cell dysfunction. Once amyloid formation is initiated, despite the fact that insulin and IAPP release may be decreased in impaired glucose tolerance and type 2 diabetes (23), IAPP may continue to be laid down as amyloid, leading to an expansion of these classical deposits that characterize the disease.

A possible explanation for the difference in islet amyloid formation among the three different hIAPP transgenic mouse strains is a difference in copy number of the hIAPP transgene between the DBA/2J and C57BL/6J hIAPP transgenic lines. This is extremely unlikely as the hIAPP transgenic mice used in the backcrosses were derived from the same original founding line. Furthermore, the F1 mice used in the present study were generated by breeding C57BL/6J hIAPP transgenic mice with DBA/2J wild-type mice. Thus the F1 and C57BL/6J hIAPP transgenic mice in the present study were bred from the same transgenic parents (with identical expression of the hIAPP transgene), with wild-type DBA/2J parents conveying the genes required for increased susceptibility of developing severe amyloid deposits to their F1 offspring.

We have demonstrated that the genetic background is an important determinant of the extent of islet amyloid deposition, perhaps resulting from genetically determined insulin (and IAPP) secretory output. Detrimental effects of hIAPP production and islet amyloid on islet morphology or secretory function were assessed by comparing DBA/2J and C57BL/6J hIAPP transgenic mice with nontransgenic mice of the same strain. DBA/2J hIAPP transgenic mice displayed amyloid-associated β-cell loss and impaired glucose-stimulated insulin secretion, in keeping with our previous observations with increased dietary fat feeding in F1 hIAPP transgenic mice (18). The strong relationship between increased islet amyloid severity and decreased β-cell area was present both in those F1 hIAPP transgenic mice (18, 41) and the DBA/2J hIAPP transgenic mice. In contrast, the minimal islet amyloid deposition in the C57BL/6J hIAPP transgenic mice was not associated with changes in β-cell area or function compared with nontransgenic C57BL/6J mice. Thus our data suggest that the effect of islet amyloid to result in β-cell loss is similar between F1 and DBA/2J hIAPP transgenic mice, and, although C57BL/6J hIAPP transgenic mice were not completely protected against developing islet amyloid, the milder extent of amyloid deposition was sufficient to protect against the deleterious effects of islet amyloid.

Our finding that increased islet amyloid deposition in DBA/2J hIAPP transgenic mice was strongly correlated with β-cell loss and was associated with a reduction in β-cell function manifest as impaired insulin release during the IVGTT suggests that this strain provides a good model for studying the mechanisms underlying islet amyloid deposition. In the presence of the susceptible DBA/2J genetic background, this deleterious effect of islet amyloid can be shown in hIAPP transgenic mice with only a mild intervention, such as one year on a diet containing 9% fat. Furthermore, the innate increased insulin output and increased susceptibility to develop severe islet amyloid deposits suggest that hIAPP transgenic mice on a DBA/2J background are at increased risk of long-term islet failure. This is consistent with data showing that DBA/2J islets are vulnerable to β-cell dysfunction and decreased viability when cultured in chronically elevated glucose (33) and to β-cell degeneration in vivo (29). In the present study, DBA/2J hIAPP transgenic mice showed increased fasting insulin, indicative of insulin resistance, and decreased insulin secretion, but these abnormalities were not sufficient to induce glucose intolerance. It is possible that DBA/2J mice are resistant to developing diet-induced glucose intolerance and may have increased insulin-independent glucose disposal, which is known to be a predominant form of glucose disposal in mice (32). We hypothesize that a more stringent intervention such as increased dietary fat or crossbreeding with a genetic model of obesity and insulin resistance would result in an inability of the DBA/2J islets to compensate for that increased secretory demand, leading to glucose intolerance and eventually diabetes.

In summary, we have shown that the genetic background upon which the hIAPP transgene is expressed is an important determinant of the extent of islet amyloid deposition. Thus hIAPP transgenic mice carrying some or all of the DBA/2J genes provide a useful model to further study the impact of islet amyloid to reduce β-cell mass and function as it pertains to the pathogenesis of human type 2 diabetes. Identification of the genes responsible for the susceptibility of DBA/2J hIAPP transgenic mice to develop islet amyloid could be important in determining the mechanism(s) underlying islet amyloid formation and its role in the pathogenesis of type 2 diabetes.

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