Increased Aβ production prompts the onset of glucose intolerance and insulin resistance

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Submitted 23 September 2011; accepted in final form 7 March 2012

Jiménez-Palomares M, Ramos-Rodríguez JJ, López-Acosta JF, Pacheco-Herrero M, Lechuga-Sancho AM, Perdomo G, García-Alloza M, Cózar-Castellano I. Increased Aβ production prompts the onset of glucose intolerance and insulin resistance. Am J Physiol Endocrinol Metab 302: E1373–E1380, 2012. First published March 13, 2012; doi:10.1152/ajpendo.00500.2011.—Type 2 diabetes (T2D) mellitus and Alzheimer’s disease (AD) are two prevalent diseases with comparable pathophysiological features and genetic predisposition. Patients with AD are more susceptible to develop T2D. However, the molecular mechanism linking AD and T2D remains elusive. In this study, we have generated a new mouse model to test the hypothesis that AD would prompt the onset of T2D in mice. To test our hypothesis, we crossed Alzheimer APPswe/PS1dE9 (APP/PS1) transgenic mice with mice partially deficient in leptin signaling (db/+). Body weight, plasma glucose, and insulin levels were monitored. Phenotypic characterization of glucose metabolism was performed using glucose and insulin tolerance tests. β-Cell mass, islet volume, and islet number were analyzed by histomorphometry. APP/PS1 coexpression in mice with intact leptin receptor signaling did not show any metabolic perturbations in glucose metabolism or insulin sensitivity. In contrast, APP/PS1 coexpression in db/+ mice resulted in nonfasting hyperglycemia, hyperinsulinemia, and hypercholesterolemia without changes in body weight. Conversely, fasting blood glucose and cholesterol levels remained unchanged. Coinciding with altered glucose metabolism, APP/PS1 coexpression in db/+ mice resulted in glucose intolerance, insulin resistance, and impaired insulin signaling. In addition, histomorphometric analysis of pancreata revealed augmented β-cell mass. Taken together, these findings provide experimental evidence to support the notion that aberrant Aβ production might be a mechanistic link underlying the pathology of insulin resistance and T2D in AD.

Type 2 diabetes: Alzheimer’s disease; β-amyloid peptide; APPswe/PS1dE9 mouse; db/db mouse; β-cell mass

Alzheimer’s disease (AD) and type 2 diabetes (T2D) are two prevalent diseases in developed countries with comparable pathological features and genetic predisposition (3, 4, 7). Several clinical and epidemiological studies have shown a relationship between AD and T2D. Patients with T2D exhibit an increased risk for developing dementia and AD (1, 11, 12, 14, 15, 19). On the other hand, patients suffering AD are more vulnerable to develop T2D (10). Patients with AD show a remarkable deposition of β-amyloid peptide (Aβ) in brain, whereas patients with T2D present islet amyloid polypeptide deposition in pancreatic β-cells (6). On the other hand, patients with T2D are glucose intolerant and insulin resistant, revealing decreased insulin signaling in peripheral tissues, whereas patients with AD show signs of impaired insulin signaling in the brain (16). Taken together, these observations have spurred the hypothesis that these pathological alterations may underline the mechanistic link between T2D and AD.

To elucidate the underlying molecular mechanism linking T2D and AD, Takeda et al. (18) developed two mouse models of AD and diabetes. In the first model, they crossed an animal model for AD (APP23-transgenic mice) with leptin deficient ob/ob mice as a model for T2D and obesity. In the second model, they crossed APP23 mice with Nagoya-Shibata-Yasuda (NSY) mice, a model of T2D with mild obesity. They demonstrated that diabetic predisposition exacerbated cognitive dysfunction, which was associated with cerebrovascular inflammation and cerebral amyloid angiopathy in both mouse models. In addition, brain insulin signaling was impaired, which was associated with neuropathological changes (18). However, this study does not demonstrate completely whether AD could accelerate the development of the diabetic phenotype.

To further clarify the relationship between AD and T2D, we investigated the underlying mechanisms linking AD and T2D with an alternative approach. We hypothesized that genetic predisposition for developing AD would prompt the onset of T2D. To test this hypothesis, we crossed APPswe/PS1dE9 (APP/PS1) transgenic mice, a well-established animal model for AD, with heterozygous leptin receptor-deficient mice (db/+) as a mouse model for T2D and obesity. In this model, they crossed APP23 mice with Nagoya-Shibata-Yasuda (NSY) mice, a model of T2D with mild obesity. These models were purchased from Harlan Laboratories (Boxmeer, The Netherlands). We used the APPswe/PS1dE9 line 85 as a mouse model of AD. These mice coexpress a chimeric mouse/human APP695 harboring the Swedish K670M/N671L mutations (Mo/
HuAPPsw) and human PS1 with the exon-9 deletion mutation (PS1dE9) (9). The two transgenes cointegrate and segregate as a single locus. APPsw/PS1dE9 mice were purchased from The Jackson Laboratory (Bar Harbor, ME). All mice were fed standard rodent chow diet and water ad libitum in ventilation-controlled cages under a 12:12-h light-dark cycle.

The experimental cohorts used in this study were males and females of the F2 generation. The F1 generation was composed of heterozygous db/db;APPsw/PS1dE9 from crosses of db/db and APPsw/PS1dE9 in the parental generation. Twelve independent cohorts were used for the metabolic studies and collection of tissues.

Mice were bred at the animal facility of the University of Cadiz, Cadiz, Spain.

Mouse genotyping. Wild-type (WT), db/db and db/+ mice were generated from crosses between heterozygous db/+ mice. The introgression of an RsaI site by the Lepr (db) mutation in the leptin receptor gene was detected by PCR. Briefly, genomic DNA from mouse tail was isolated using GenElute Mammalian Genomic DNA Miniprep Kit (Sigma, St. Louis, MO) according to the manufacturer’s instructions, followed by a PCR reaction to amplify a 135-bp fragment spanning the Lepr (db) mutation (primers: Lepr forward, 5′-AGAGCCG-GACACTCTTTGAAGTCTC-3′; Lepr reverse, 5′-CATTCAACCATGATTTAAGGGTGTGTG-3′). Afterward, a total of 20 μL of PCR product was digested by RsaI (Invitrogen Europe) and resolved in 10% polyacrylamide gels. Mice carrying the homozygous Lepr (db) mutation produced fragments of 108 and 27 bp, heterozygous mice produced fragments of 135, 108, and 27 bp, and WT mice produced a fragment of 135 bp.

APP/PS1 mice were generated from crosses between WT and hemizygote transgenic mice. Mice genotyping were performed as described previously (8) with some modifications. Briefly, genomic DNA from mouse tail was isolated as described above, followed by a PCR reaction to amplify a 760-bp fragment in WT mice, whereas transgenic mice produced fragments of 760 and 240 bp (primers: 1,501, 5′-AAAGGCCCAAAGCCTGGAGGTTGGAACA-3′; 1,502, 5′-TGCTGATACCCCTCCCCAGCCTAGACCA-3′; and 1,503, 5′-CTGACCACCTCTGACGGTTTGGT-3′).

**Determination of Aβ levels in brain and plasma.** Immunohistochemistry for Aβ was performed on 30 μm of paraformaldehyde-fixed brain sections. Sections were washed in TBS and pretreated with 1% normal goat serum overnight at 4°C. After washing in TBS, sections were incubated with anti-mouse Alexa Enol phospho pyruvate carboxykinase (PEPCK) forward (5′-CTCA-GGTCATATAACCGTGCTGG-3′), PEPCK reverse (5′-GCTTTC-CTCAAGTCTCTCT-3′); glucose-6-phosphatase (G-6-Pase) forward (5′-GGAGAAGGAATGACACCT-3′), G-6-Pase reverse (5′-GTCAGTCGTCCTCAAGGGAC-3′), 18S ribosomal RNA (18S) forward (5′-GGGAGACCCGGAGATCCCAAGG-3′), 18S reverse (5′-GCCCCTAACATGGATCTGGT-3′). Data are presented as the fold change in PEPCK, and G-6-Pase gene expression was normalized to the levels of the housekeeping gene 18S.

**Statistical analysis.** Statistical analyses of data were performed by Student’s t-test. Data were expressed as means ± SD. P values <0.05 were considered significant.

**RESULTS**

**Effect of APP/PS1 transgenic expression on glucose homeostasis.** A neuropathological feature of AD is increased Aβ production and secretion in neurons. Transgenic APP/PS1 mice overexpress Aβ, which is detected in circulation (~300 pg/mL). To evaluate the impact of increased Aβ production on glucose...
metabolism, we characterized transgenic APP/PS1 mice at 5–7 wk of age.

Transgenic APP/PS1 mice displayed normal body weight (Fig. 1A), blood glucose (Fig. 1B), and plasma insulin levels (Fig. 1C) compared with control littermates. Likewise, body weight, nonfasting blood glucose, and nonfasting plasma insulin at 10 and 32 wk of age were not different between APP/PS1 mice and their controls (Fig. 1, D–F). Finally, transgenic APP/PS1 mice exhibited similar glucose (Fig. 2, A and B) and insulin tolerance (Fig. 2, C and D) than control littermates at 7 wk of age.

Taken together, these results suggest that increased Aβ production per se does not alter glucose homeostasis or insulin sensitivity.

Effect of APP/PS1 transgenic expression on glucose homeostasis in db/db mice. Because we did not detect any metabolic phenotype on glucose homeostasis or insulin sensitivity in APP/PS1 mice, we investigated whether coexpressing APP/PS1 in a genetic background prone to develop obesity and T2D would alter glucose homeostasis. To this end, we used the db/db mouse model of obesity and T2D. The db/db mouse develops obesity, glucose intolerance, insulin resistance, and diabetes at 6–7 wk of age. However, the heterozygous db/+ mouse does not develop any metabolic phenotype. Thus, we characterized the glucose homeostasis in mice coexpressing APP/PS1 in a genetic background prone to developing T2D and obesity (db/+;APPswe/PS1dE9) compared with control mice (db/+;WT). Interestingly, although db/+;APP/PS1 mice did not show brain Aβ plaques at 5–7 wk of age (Fig. 3A), they did show increased expression of Aβ in plasma compared with db/+;WT (Fig. 3B).

As shown in Fig. 4A, coexpression of APP/PS1 genes in db/+ male and female mice at 5–7 wk of age did not alter body weight (Fig. 4A). Likewise, fasting blood glucose levels remained unchanged between control and db/+;APP/PS1 mice (Fig. 4B). In contrast, nonfasting blood glucose levels were elevated significantly in db/+;APP/PS1 compared with control mice (Fig. 4B). Interestingly, nonfasting hyperglycemia paralleled with nonfasting and fasting hyperinsulinemia in db/+;APP/PS1 mice (Fig. 4C). Finally, db/+;APP/PS1 mice showed elevated nonfasting plasma cholesterol levels compared with control mice, whereas fasting cholesterol levels remained unchanged (Fig. 4D). Taken together, these results indicate that Aβ overproduction alters glucose homeostasis in mice with a genetic predisposition to develop T2D.

Effect of APP/PS1 transgenic expression on glucose tolerance and insulin sensitivity in db/+ mice. To further investigate the effect of Aβ overproduction on glucose homeostasis, we evaluated the impact of APP/PS1 gene expression on glucose tolerance and insulin sensitivity in db/+ mice. To this end, we used the db/db mouse model of obesity and T2D. The db/db mouse develops obesity, glucose intolerance, insulin resistance, and diabetes at 6–7 wk of age. However, the heterozygous db/+ mouse does not develop any metabolic phenotype. Thus, we characterized the glucose homeostasis in mice coexpressing APP/PS1 in a genetic background prone to developing T2D and obesity (db/+;APPswe/PS1dE9) compared with control mice (db/+;WT). Interestingly, although db/+;APP/PS1 mice did not show brain Aβ plaques at 5–7 wk of age (Fig. 3A), they did show increased expression of Aβ in plasma compared with db/+;WT (Fig. 3B).

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end, we performed intraperitoneal (IP) GTT and IPITT in db/H11001;APPswe/PS1dE9 and control mice (db/H11001;WT). As shown in Fig. 5, A and B, db/H11001;APP/PS1 mice exhibited impaired glucose tolerance compared with control mice. In addition, we measured glucose-stimulated insulin release during the glucose tolerance test. As expected, db/H11001;APP/PS1 mice exhibited higher plasma insulin levels than control mice immediately before (time 0) glucose injection (Fig. 5C). However, after 15 min (time 15) of glucose injection, plasma insulin levels were similar between groups (Fig. 5C). Interestingly, db/H11001;APP/PS1 mice showed decreased insulin sensitivity compared with control mice (Fig. 5, D and E). Thus, our results indicate that Aβ overproduction is associated with glucose intolerance and insulin resistance in db/H11001 mice.

In physiological conditions during the postprandial state, insulin inhibits hepatic gluconeogenesis, and consequently hepatic glucose output is abolished. In pathophysiological conditions of hepatic insulin resistance, insulin is unable to suppress hepatic gluconeogenesis; thus hepatic glucose output goes awry, contributing to elevate postprandial blood glucose levels. Hence, hepatic insulin resistance is a major contributor to hyperglycemia and T2D. To further investigate the insulin resistance observed in db/H11001;APP/PS1 mice, we tested peripheral insulin signaling (Akt phosphorylation) in skeletal muscle, gastrocnemius (Fig. 6, A and B) and soleus (Fig. 6, C and D), and liver (Fig. 6, E and F). Interestingly, whereas db/H11001;WT mice exhibited activation of the insulin-stimulated Akt pathway, db/H11001;APP/PS1 mice did not show activation of insulin signaling (Fig. 6). In the same sense, we also studied the mRNA levels of two enzymes responsible for hepatic gluconeogenesis (PEPCK and G-6-Pase; Fig. 6G). PEPCK and G-6-Pase mRNA levels were downregulated by insulin in the liver of db/H11001;WT mice, although it was statistically significant only for G-6-Pase. In contrast, insulin was unable to down-regulate the expression levels of PEPCK and G-6-Pase in the liver of db/H11001;APP/PS1 mice. Taken together, these results support the notion that hepatic insulin resistance is a contributing factor to elevate postprandial blood glucose levels in db/H11001;APP/PS1 mice.
Transgenic APP/PS1 coexpression increases β-cell mass in db/+ mice. Under conditions of insulin resistance, the pancreatic β-cells compensate by increasing insulin secretion in an effort to sustain normoglycemia. Two different mechanisms are involved in β-cell compensation: enhancing cellular secretory capacity and/or increasing β-cell mass. As we showed above, glucose-stimulated insulin secretion was not altered in db/+; APP/PS1 mice (Fig. 5C); however, insulin secretion in basal conditions is increased in db/+; APP/PS1 mice with respect to their controls. To elucidate the cause of increased insulin secretion, we performed a histomorphometric analysis of β-cell mass in db/+; APP/PS1 and control mice (db/+; WT) to determine the impact of transgenic coexpression of APP/PS1 transgenes on β-cell mass. Pancreas weight in the two groups was not significantly different (data not shown). As shown in Fig. 7, β-cell mass and β-cell area were elevated significantly in db/+; APP/PS1 compared with db/+; WT mice (Fig. 7, A–C). In contrast, pancreatic islet number remained unchanged between db/+; APP/PS1 and db/+; WT mice (Fig. 7D). These results suggest that β-cell mass expansion is at least one mechanism by which db/+; APPswe/PS1dE9 mice compensate for insulin resistance.

Fig. 7. APPswe/PS1dE9 coexpression in db/+ mice is associated with glucose intolerance and insulin resistance. The effect of APPswe/PS1dE9 coexpression on glucose tolerance and insulin sensitivity was investigated in db/+; APPswe/PS1dE9 and control mice (db/+; WT) at 5–7 wk of age. A: body weight in females and males (n = 19–30/genotype). B: blood glucose in nonfasting and fasting conditions (n = 19–30/genotype). C: plasma insulin in nonfasting and fasting conditions (n = 19–30/genotype). D: plasma cholesterol levels in nonfasting and fasting conditions (n = 18–25/genotype). P < 0.05 vs. control group (db/+; WT).

Fig. 5. APPswe/PS1dE9 coexpression in db/+ mice is associated with altered glucose metabolism. The effect of APPswe/PS1dE9 coexpression on body weight and glucose metabolism was investigated in db/+; APPswe/PS1dE9 and control mice (db/+; WT) at 5–7 wk of age in nonfasting and fasting state. A: body weight in females and males (n = 19–30/genotype). B: blood glucose in nonfasting and fasting conditions (n = 19–30/genotype). C: plasma insulin in nonfasting and fasting conditions (n = 19–30/genotype). D: plasma cholesterol levels in nonfasting and fasting conditions (n = 18–25/genotype). P < 0.05 vs. control group (db/+; WT).

DISCUSSION

Epidemiological, clinical, and basic studies have shown a relationship between AD and T2D. Despite advances in our knowledge, definitive molecular mechanisms involved in the pathophysiology observed in both diseases remain unrevealed. In this study, we hypothesized that AD would prompt the onset of T2D. To test this hypothesis, we have developed a new mouse model crossing the APPswe/PS1dE9 mouse, a well-established AD mouse model, into the db/+ background.
Fig. 6. APPswe/PS1dE9 (APP/PS1) coexpression in db/+ mice impairs insulin signaling in skeletal muscle and liver. The effect of APPswe/PS1dE9 on insulin signaling was investigated in db/+ mice 5–7 wk of age. A: representative Western blot of phosphorylated (p)-Akt (Ser473) in gastrocnemius muscle in response to insulin overload. B: quantification of 4 different Western blots. C: representative Western blot of p-Akt (Ser473) in soleus muscle in response to insulin overload. D: quantification of 4 different Western blots. E: representative Western blot of p-Akt (Ser473) in liver in response to insulin overload. F: quantification of 4 different Western blots. G: quantitative PCR of hepatic phosphoeno/pyruvate (PEPCK) and glucose-6-phosphatase (G-6-Pase) in response to insulin overload. *P < 0.05 vs. control group (db/+;WT).

Aβ OVEREXPRESSION AND INSULIN RESISTANCE

AJP-Endocrinol Metab • doi:10.1152/ajpendo.00500.2011 • www.ajpendo.org
Other mouse models have been developed to investigate the pathophysiological interaction between T2D and AD. Takeda et al. (18) crossed the APP23 transgenic mice, a well-established AD mouse model, with leptin-deficient mice (ob/ob) or polygenic NSY mice as a model of diabetes mellitus. They demonstrated that the onset of diabetes exacerbated Alzheimer-like cognitive dysfunction in APP+/-ob/ob mice in addition to cerebrovascular inflammation and severe amyloid angiopathy. On the other hand, APP+/-ob/ob mice showed an accelerated diabetic phenotype compared with ob/ob mice. Likewise, NSY mice overexpressing APP23 exhibited severe glucose intolerance. Thus, Takeda et al. (18) suggest that Alzheimer amyloid pathology could aggravate diabetes.

Of note, these mouse models of AD and T2D have some limitations. First, leptin signaling is completely abolished because leptin production has been eliminated. Leptin signaling plays an important role in regulating synaptic function and energy homeostasis, and thus some of the phenotypes in APP+/-ob/ob mice might result from the lack of leptin signaling. Second, the ob/ob mice are obese, glucose intolerant, and insulin resistant at an early stage of development. Insulin signaling plays an important role regulating neuronal and synaptic functions (2, 20) in addition to regulating glucose homeostasis. Again, some of the metabolic phenotypes in those mice might result from impaired insulin signaling rather than APP23 overexpression. In contrast, our mouse model exhibits only partial leptin signaling deficiency in the absence of perturbed insulin signaling. Furthermore, db/+ mice do not exhibit obesity, glucose intolerance, or insulin avoidance, interfering interference to investigate the impact of aberrant Aβ production on glucose homeostasis.

Takeda et al. (18) used APP23 mice to reproduce Aβ deposition observed in AD patients. APP23 mice bear the Swedish mutation APP751, and the first deposits appear at 6 mo of age. However, severe Aβ deposition is observed only at later stages (~18 mo of age) (17). More recent models, including double- and triple-transgenic mice, have been developed to induce Aβ deposition at earlier ages, leading to a more severe version of the illness. In this sense, APPswe/PS1dE mice harboring the Swedish (K594M/N595L) mutation and exon-9-deleted PS1 (9) show Aβ deposition as early as 4 mo of age. By 6 mo of age these animals present robust senile plaque deposition in cortex and hippocampus (5), significantly shortening the time needed to reproduce AD-related pathology.

Studies in humans and mice indicate that T2D can predispose to dementia and AD. However, whether AD may affect the pathology of T2D remains incompletely understood (1, 10–12, 14, 15, 19). In this study, we showed that APPswe/PS1dE coexpression in the brain prompted the onset of glucose intolerance and insulin resistance accompanied by augmented pancreatic β-cell mass. Thus, in addition to the inability of insulin to repress the expression of hepatic PEPCK and G-6-Pase, it is plausible to hypothesize that aberrant plasma glucagon and/or glucocorticoid levels may also be contributing factors to explain the upregulation of PEPCK and G-6-Pase genes. Further work is warranted to investigate whether plasma Aβ might regulate the levels of glucagon and/or glucocorticoids.

It has been shown that insulin signaling is disrupted by soluble Aβ oligomers in cultures of hippocampal neurons (21). Thus, it is tempting to hypothesize that Aβ-mediated insulin...
resistance in brain is one potential mechanism underlying the pathological alterations observed in patients with AD and T2D. This hypothesis is strengthened by the findings of Obici et al. (13), which demonstrated that disruption of hypothalamic insulin signaling impaired the ability of circulating insulin to inhibit glucose production, suggesting that hypothalamic insulin resistance can contribute to hyperglycemia in T2D. Interestingly, in our mouse model, Aβ overproduction in the brain (APPswe/PS1dE9 gene coexpression under the control of a prion promoter) results in elevated plasma Aβ levels. Therefore, peripheral Aβ might impair insulin signaling and contribute to postprandial glucose excursions and T2D. This notion is supported by two observations. First, there were no amyloid plaques at 7 wk of age, and second, we have demonstrated that high plasma Aβ levels were associated with insulin resistance in peripheral tissues such as skeletal muscle and liver. Nonetheless, we cannot exclude the hypothesis that Aβ mediates hypothalamic insulin resistance in our mouse model. Further studies are warranted to test this hypothesis.

In conclusion, we have generated a new mouse model to investigate the impact of Aβ on the early onset of T2D. We demonstrated that AD prompts the early onset of impaired insulin signaling and glucose intolerance. In addition, our findings support the notion that Aβ is a mechanistic link underlying AD and T2D and suggest that Aβ is a therapeutic target in the prevention and treatment of insulin resistance in AD patients.

REFERENCES


