Compelling evidence indicates that excess consumption of sugar-sweetened beverages plays an important role in the epidemic of obesity, a major risk factor for type 2 diabetes mellitus. Type 2 diabetes mellitus has been associated with a higher incidence of Alzheimer disease (AD). High fat diets promote AD-like pathology in mice. It is not known whether consumption of excess sugar as in calorically sweetened beverages with an otherwise normal diet affects the development of AD. In the present study, we provided 10% sucrose-sweetened water to a transgenic mouse model of AD with a normal rodent diet. Compared with the control mice with no sucrose added in the water, the sucrose group gained more body weight and developed glucose intolerance, hyperinsulinemia, and hypercholesterolemia. These metabolic changes were associated with the exacerbation of memory impairment and a 2–3-fold increase in insoluble amyloid-β protein levels and deposition in the brain. We further showed that the levels of expression and secretase-cleaved products of amyloid-β precursor protein were not affected by sucrose intake. The steady-state levels of insulin-degrading enzyme did not change significantly, whereas there was a 2.5-fold increase in brain apoE levels. Therefore, we concluded that the up-regulation of apoE accelerated the aggregation of Aβ, resulting in the exacerbation of cerebral amyloidosis in sucrose-treated mice. These data underscore the potential role of dietary sugar in the pathogenesis of AD and suggest that controlling the consumption of sugar-sweetened beverages may be an effective way to curtail the risk of developing AD.

Added sugars, mainly sucrose and high fructose corn syrup, are major components of a modern human diet. Compelling evidence indicates that excess consumption of sweet foods, particularly sugar-sweetened beverages, plays an important role in the epidemic of obesity around the world (1). In the United States, the percentage of children who are overweight has doubled, and the percentage of teenagers who are overweight has tripled (2, 3). Overweight children are at an increased risk to become obese adults (4). Even moderate obesity can contribute to chronic metabolic abnormalities leading to type 2 diabetes mellitus (5) characterized by glucose intolerance and hyperinsulinemia.

Alzheimer disease (AD) is a progressive neurodegenerative disease characterized clinically by progressive cognitive impairment. Pathological hallmarks of the AD brain include intracellular neurofibrillary tangles and deposits of aggregated amyloid-β protein (Aβ) in neuritic plaques and cerebral vessels. The pathogenic mechanisms that lead to the development of AD, however, are not fully understood. One of the main hypotheses is that β-amyloidosis (production and deposition of Aβ) plays a crucial role in the pathogenesis of AD (6). Aβ (39–43 amino acids) is derived from a large transmembrane glycoprotein, amyloid-β precursor protein (APP), via proteolytic processing by secretases (6). This hypothesis is supported by discoveries of causative mutations in the gene encoding APP and in genes of presenilin (PS)-1 and -2 in early onset familial AD (7).

Recently, numerous epidemiological studies suggest that type 2 diabetes mellitus is associated with an increased risk of AD (reviewed in Ref. 8), independent of the risk for vascular dementia (9, 10). The mechanisms by which type 2 diabetes mellitus may impact AD, however, are not well understood. Several lines of evidence indicate that insulin itself and metabolic abnormalities pertinent to diabetes may affect the generation and degradation of Aβ (11). Higher fat intake and excess body weight increase the risk of AD (12). We and others have shown that in transgenic mouse models of AD, high fat diets promote the development of AD-type neuropathology (13–16) and cognitive impairment (16). Insulin resistance may be one of the underlying mechanisms for the effects of high fat diets on AD (17). Whether excess consumption of simple sugars as in calorically sweetened beverages with an otherwise normal diet affects the development of AD has not been investigated experimentally. In the present study, we provided sucrose-sweetened water to APP/PS1 double transgenic mice (18, 19), an established model of AD, fed a regular low fat diet and assessed the effect of added sucrose in water on AD-like behavior and neuropathology. Our results showed that intake of sucrose-sweet-
enized water induced insulin resistance and exacerbated AD-like memory impairment and cerebral amyloidosis.

**EXPERIMENTAL PROCEDURES**

**Animals and Diets**—APP/PS1 double transgenic mice used in this study were obtained from Jackson Laboratory (Bar Harbor, ME) (strain name B6C3-Tg(APPsw,PSEN1dE9)85Dbo/J; stock number 004462). These mice express a chimeric mouse/human amyloid-β precursor protein containing the K595N/M596L. Swedish mutations and a mutant human presenilin 1 carrying the exon 9-deleted variant under the control of mouse prion promoter elements, directing transgene expression predominantly to central nervous system neurons (18, 19). The two transgenes co-segregate in these mice. APP/PS1 mice were maintained as double hemizygotes by crossing with wild-type mice on a B6C3F1/J background strain (Jackson Laboratories stock number 100010) and were genotyped by PCR analysis of genomic DNA from tail biopsies. APP/PS1 mice develop AD-like memory deficits and amyloid plaques in the brain by 6 months of age. In this study, 2-month-old male APP/PS1 mice were provided with either a solution of 10% sucrose or water (control) ad libitum. These mice were kept on a normal rodent diet (Harlan Teklad mouse diet 7012: 19% protein, 5% fat, and 60% complex carbohydrate). Main ingredients of this diet are ground corn, soybean meal, ground oats, wheat middlings, soybean oil, alfalfa meal, and corn gluten meal with supplements of minerals, amino acids, and vitamins. Sucrose and food intake of mice were determined by monitoring the volumes of water/sucrose solution and amounts of food consumed. After 25 weeks of the experiment, the mice were subjected to a battery of behavioral tests followed by assessments of metabolic changes and AD-related neuropathology as discussed below. All animal procedures used for this study were prospectively reviewed and approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham.

**Assessment of Behavioral Functions**—Three AD-related behavioral functions (spatial learning and memory, exploration of environmental stimuli, and anxiety) were assessed. The testing schedule included exploration of the T-maze (days 1–10), the open field (days 1–3), the elevated plus-maze test for anxiety levels (days 4 and 5), and spatial learning in the Morris water maze (days 6–11). All equipment and software were purchased from SD Instruments (San Diego, CA). All testing procedures have been described in detail previously (20, 21).

Briefly, spatial learning and memory were evaluated in the Morris water maze consisting of a round basin filled with water with abundant extra-maze visual cues. The acquisition of the spatial task consisted of placing the mice next to and facing the N side. The time spent in the previously correct (target) quadrant was measured in a single 60-s trial. Two hours later, the visible platform version of the test was performed with the escape platform lifted 1 cm above water level and shifted to the SE quadrant. A pole was inserted on top of the escape platform as a viewing aid.

**Assessment of Metabolic Changes**—An intraperitoneal glucose tolerance test was conducted as previously described (17) with some modifications. Briefly, fasted mice were given a single dose of intraperitoneal injection of glucose (2 g/kg body weight), and blood samples were obtained from the tail vein periodically over a 2-h period. Blood glucose content was determined by using the Accu-Chek Advantage System (Roche Applied Science), following the manufacturer’s instructions. Fasting plasma insulin levels were determined by using the enzyme-linked immunosorbent assay (ELISA) kit (LINCO Research, St. Charles, MO). Fasting plasma total and high density lipoprotein cholesterol levels were determined colorimetrically with commercial reagents (Infinity™ cholesterol reagent; Thermo Electron Corp., Melbourne, Australia). Fasting plasma triglyceride levels were determined with the triglyceride determination kit (Sigma).

**Brain Tissue Preparation**—Mice were anesthetized with sodium pentobarbital, and blood was collected via cardiac puncture with heparin as an anticoagulant. Following transcardial perfusion with ice-cold 0.1 M phosphate-buffered saline (pH 7.4), brains were cut sagittally into left and right hemispheres. The right hemisphere was fixed in phosphate-buffered formalin for histological analysis. After removing the olfactory lobe and cerebellum, the left hemisphere was snap frozen in liquid nitrogen and stored at −80 °C for biochemical analysis.

**Brain Aβ ELISA, Cholesterol, and Immunoblot Analysis**—To measure carbonate soluble and insoluble (guanidine soluble) fractions of Aβ, frozen brain samples were Dounce-homogenized first in carbonate buffer (100 mM Na2CO3, 50 mM NaCl, pH 11.5) containing protease inhibitors (10 µg/ml aprotinin and 1 mM 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride). An aliquot of homogenate was centrifuged at 18,300 × g for 20 min at 4 °C. The supernatant (soluble fraction) was transferred to another tube and stored at −80 °C until analyzed. The pellet was then subjected to further homogenization in the guanidine solution (5 M guanidine HCl in 50 mM Tris-HCl, pH 8.0). The homogenate was rocked for 3–4 h at room temperature. Following centrifugation at 18,300 × g for 20 min at 4 °C, the supernatant (insoluble fraction) was transferred to another tube and stored at −80 °C until analyzed. The levels of Aβ40 and Aβ42 in the soluble and insoluble fractions were determined with Aβ40- and Aβ42-specific ELISA kits (BioSource International) using the manufacturer’s protocol. The cholesterol content in the brain homogenate was determined with the Infinity™ cholesterol reagent (Thermo Electron). For immunoblot analysis, another aliquot of carbonate homogenate was subjected to further homogenization with the SDS sample buffer (Invitrogen) and processed as we described in detail previously (20, 21). Primary antibodies used for immunoblot analysis included 6E10 (a monoclonal antibody raised against amino acids next to and facing the N side. The time spent in the previously correct (target) quadrant was measured in a single 60-s trial. Two hours later, the visible platform version of the test was performed with the escape platform lifted 1 cm above water level and shifted to the SE quadrant. A pole was inserted on top of the escape platform as a viewing aid.

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Intake of Sucrose-sweetened Water Induces Insulin Resistance in APP/PS1 Mice—A, mice with free access to sucrose (10%)-sweetened water (sucrose) gained significantly more body weight than mice drinking water with no added sucrose (control) after 5 weeks. B, intraperitoneal glucose tolerance response. Blood glucose content was monitored over time following an intraperitoneal injection of glucose (2 g/kg body weight) to fasted mice. The sucrose group showed impaired glucose tolerance compared with the control group. C, fasting plasma insulin levels. The sucrose group showed hyperinsulinemia. D, fasting plasma lipid levels. The sucrose group showed an increase in total cholesterol (TC) levels but had no change in the levels of high density lipoprotein cholesterol (HDL-C) and TG.

Characteristics of APP/PS1 Mice—The APP/PS1 mice used in this study co-overexpress a chimeric mouse/human APP containing the K595N/M596L Swedish mutations and a mutant human PS1 with the exon 9 deletion under the control of mouse prion promoter elements (18, 19). The two transgenes co-segregate in these mice. APP/PS1 mice were maintained as double hemizygotes. They develop AD-like memory deficits and amyloid plaques in the brain by 6 months of age. In this study, 2-month-old male APP/PS1 mice were fed a normal rodent diet and provided with either a solution of 10% sucrose or water (control) ad libitum. After 25 weeks of treatment at an age of ~8 months, the mice were subjected to a battery of behavioral tests followed by assessments of metabolic changes and AD-related neuropathology.

Intake of Sucrose-sweetened Water Led to Increased Body Weight, Glucose Intolerance, Hyperinsulinemia, and Hypercholesterolemia in APP/PS1 Mice—Food and water intake of the mice were monitored during the experiment. When given the sucrose-sweetened water, the mice drank significantly more. Although the sucrose group decreased their food intake, total daily caloric intake was 15% higher (p < 0.001) in the sucrose group (20.5 ± 0.4 kcal/mouse, 43% of which was supplied by sucrose) than in the water control group (17.8 ± 0.4 kcal/mouse). Consistently, weekly body weight monitoring showed that the mice with free access to sucrose-sweetened water started to gain significantly more body weight than the mice without the sucrose supplement at 5 weeks, and this trend was observed for the rest of the experiment (Fig. 1A). At the end of the experiment, the body weight of the sucrose group was 17% higher than that of the control group (47.1 ± 2.0 versus 40.3 ± 1.9 g, p < 0.05).

To assess glucose tolerance in these mice, an intraperitoneal glucose tolerance test was conducted in which blood glucose content was monitored using a histomorphometry system. Multiple images were captured and analyzed from serial sections of each mouse brain. A total area of 50 mm² giving the highest total Aβ immunoreactivity was chosen to calculate the amyloid load expressed as a percentage of total area covered by Aβ immunoreactivity.

Statistical Analysis—Data were expressed as means ± S.E. Comparison of different genotype groups was performed by two-tailed Student’s t test (for normally distributed data), Mann-Whitney rank sum test (for nonnormally distributed data), and repeated measures analysis of variance. SigmaStat software (SPSS Science, Chicago, IL) was used for all statistical analyses. p < 0.05 was considered statistically significant.
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A performance of the mice during the acquisition phase of the Morris water maze test. Non-Tg mice learned normally to locate the submerged platform, and untreated control APP/PS1 mice showed learning deficits but retained some learning ability over the 5-day testing, whereas the sucrose-treated APP/PS1 mice failed to learn the task. B, times crossed over the location of previously hidden platform in the target quadrant. Although untreated control APP/PS1 mice crossed over the previous platform location less often than non-Tg mice, the sucrose-treated APP/PS1 mice showed no memory of the platform location. Data represent means ± S.E., n = 7–8 per group. *, p < 0.05; **, p < 0.01.

Effect on levels of high density lipoprotein (HDL) cholesterol and triglyceride (Fig. 1D). These data demonstrate that intake of sucrose-sweetened water led to increased body weight and induced insulin resistance in APP/PS1 mice fed a normal diet.

Exacerbation of Spatial Learning and Memory Deficits in APP/PS1 Mice Taking Sucrose-sweetened Water—To assess whether sucrose intake affects behavioral functions in APP/PS1 mice, a battery of behavioral tests was conducted. The Morris water maze test was performed to assess the spatial learning and memory of the mice. To serve as a normal control, a group of age-matched nontransgenic mice (non-Tg, littermates of APP/PS1 mice) were included in the test. As shown in Fig. 2A, non-Tg mice learned to locate the submerged platform (analysis of variance, p < 0.001). Compared with non-Tg mice, untreated APP/PS1 control mice showed learning deficits but retained some learning ability over the 5-day testing (analysis of variance, p < 0.01). The sucrose-treated APP/PS1 mice, however, failed to learn the task at the end of 5-day training (Fig. 2A). The concurrent longer path length traveled by the sucrose group indicates a spatial learning deficit as opposed to a decreased swimming speed (data not shown). Indeed, there was no difference in swimming speed between groups (16–18 cm/s).

In a 60-s probe trial 24 h after the acquisition, although non-Tg mice spent 46.1 ± 5.0% of their time in a previously platform-containing quadrant, the time spent by APP/PS1 mice (untreated and sucrose-treated) was not longer than the random 25% level (31.6 ± 4.8 and 18.2 ± 3.0%, respectively). Although the untreated APP/PS1 mice crossed over the previous platform location less often than non-Tg mice, the sucrose-treated APP/PS1 mice showed no memory of the platform location (Fig. 2B). In the visible platform version of the Morris water maze, all groups performed similarly, indicating that there were no changes of visual acuities and swimming abilities associated with sucrose consumption.

In addition, sucrose intake had no significant effects on motor activity in an open field, on exploration in a T-maze, or on anxiety in an elevated plus-maze (Table 1). These data further indicate that impairment of learning and memory by sucrose intake was not caused by other noncognitive behavioral changes.

Aggravation of Cerebral β-Amyloidosis in APP/PS1 Mice Taking Sucrose-sweetened Water—To determine the effect of sucrose-sweetened water intake on cerebral APP/β metabolism in APP/PS1 mice, Aβ contents in the carbonate soluble and insoluble (guanidine-soluble) fractions in the cerebrum were quantified by ELISA. Although no difference in soluble Aβ40 and Aβ42 was found between the two groups (Fig. 3A), insoluble Aβ42 contents were increased significantly (about 2-fold) in the cerebrum of mice taking sucrose-sweetened water (Fig. 3B). Immunoblot analyses also showed that total Aβ level was increased by 3.6-fold in the sucrose group (Fig. 4, A and B). Consistent with these findings, immunohistochemical and morphometric analyses showed that there was a 2.9-fold increase in Aβ deposition in the brain of mice in the sucrose group (Fig. 4, C–E).

TABLE 1
Exploratory activities and anxiety levels of APP/PS1 mice

| Tests                          | Control (n = 8) | Sucrose (n = 7) | p    |
|-------------------------------|----------------|----------------|------|
| Spontaneous alternation (T-maze) |                |                |      |
| Rate (%)                      | 70.0 ± 5.0     | 69.0 ± 7.0     | 0.87 |
| Latency (s)                   | 17.8 ± 2.2     | 13.5 ± 1.9     | 0.17 |
| Motor activity (open field)   |                |                |      |
| Path length (cm)              |                |                |      |
| Day 1                         | 2108.9 ± 200.0 | 1616.2 ± 110.7 | 0.06 |
| Day 2                         | 1851.0 ± 213.6 | 1604.9 ± 213.8 | 0.43 |
| Day 3                         | 1377.0 ± 231.7 | 1339.3 ± 256.1 | 0.92 |
| Percentage of time in the central zone |                |                |      |
| Day 1                         | 6.4 ± 1.0      | 4.6 ± 1.2      | 0.27 |
| Day 2                         | 4.4 ± 1.2      | 3.2 ± 0.8      | 0.42 |
| Day 3                         | 6.0 ± 2.3      | 3.2 ± 1.5      | 0.35 |
| Anxiety (elevated plus-maze)  |                |                |      |
| Entries to open arms          |                |                |      |
| Day 1                         | 12.8 ± 2.8     | 11.0 ± 2.1     | 0.63 |
| Day 2                         | 5.1 ± 1.9      | 7.7 ± 2.3      | 0.40 |
| Percentage of time in open arms |            |                |      |
| Day 1                         | 41.1 ± 9.8     | 47.8 ± 9.3     | 0.63 |
| Day 2                         | 12.1 ± 4.3     | 24.5 ± 8.8     | 0.54 |
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FIGURE 3. Quantification of cerebral Aβ levels by ELISA. A, Aβ40 and Aβ42 levels in the carbonate-soluble fraction of cerebral homogenate. No significant differences were found in the level of soluble Aβ between the two groups. B, Aβ40 and Aβ42 levels in the carbonate-insoluble (guanidine-soluble) fraction of cerebral homogenate. The insoluble Aβ42 level was significantly increased in the sucrose group. Data represent means ± S.E., n = 7–8 per group. **, p < 0.01. wt, weight.

FIGURE 4. Aggravation of cerebral amyloidosis in APP/PS1 mice taking sucrose-sweetened water. A, immunoblot analysis of total Aβ levels in the cerebral homogenate. B, densitometric analysis of immunoblots (normalized by the amount of tubulin) with the levels in control group set as 100%. Data represent means ± S.E., n = 7–8 per group. *, p < 0.05; **, p < 0.01. MW, molecular weight.

Sucrose Intake Had No Effect on Levels of the APP Transgene Expression and C-terminal Fragments (CTF) of APP Produced by α- and β-Secretase Cleavages—To investigate whether the increase of Aβ levels in the brain of mice in the sucrose group was caused by an increase in the generation of Aβ from APP, we determined the levels of full-length APP and CTF of APP produced by α- and β-secretase cleavages by immunoblot analyses. The results showed that there were no differences in the amount of full-length APP, α-CTF, and β-CTF (Fig. 5), indicating that the expression of the APP transgene and the processing of APP by α- and β-secretases were not affected by excess intake of sucrose-sweetened water in APP/PS1 mice.

Effect of Sucrose Intake on the Steady-state Levels of IDE, ApoE, and Cholesterol in the Brain of APP/PS1 Mice—With no significant changes observed in the production of Aβ from APP, we next examined the factors that are involved in Aβ degradation and aggregation. IDE, originally recognized for its ability to degrade insulin, has been identified as one of the enzymes to degrade Aβ (22). We hypothesized that the increase of Aβ in the brain of mice in the sucrose group might be caused by a decrease of cerebral IDE, which has been associated with insulin resistance and AD pathology (17, 23). The level of IDE in the brain was determined by immunoblot analyses. The results showed that the level of IDE in the sucrose group was decreased by about 30% compared with that of the control group (Fig. 6). However, this decrease did not reach statistical significance (p = 0.10).

We next determined the level of apoE in the brain. ApoE plays a critical role in the development of AD-like amyloid pathology in mouse models of AD (24). Mouse endogenous apoE is strongly amyloidogenic and promotes aggregation and fibril formation of Aβ (25). Our results demonstrated that the level of apoE was elevated about 2.5-fold in the brain of mice in the sucrose group compared with that in the control group (Fig.
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In this study, we showed that long term consumption of sucrose-sweetened water led to increased body weight, glucose intolerance, insulin resistance, and hypercholesterolemia in APP/PS1 mice fed a normal low fat rodent diet. These metabolic changes were associated with exacerbation of spatial learning and memory impairment and cerebral Aβ deposition in this mouse model of AD.

One of the mechanisms by which consumption of sugar-sweetened beverages causes body weight gain is thought to be the increase of total caloric intake (26). This appears to be the case in the present study. The reduction in food intake was not enough to compensate for the caloric gain from sucrose-sweetened water. The sucrose group had an average of 15% increase in total caloric intake, which accounts for the 17% increase in body weight.

In the mice drinking sucrose-sweetened water, 43% of total caloric intake was provided by sucrose. Based on a 2000-calorie diet for humans, this level of consumption approximates 5 cans of 12-oz sugar-sweetened beverages (usually ~11% sugar) a day. Although this may appear to be on the upper limit of beverage consumption in humans, it is assumed that there is no additional sugar intake from solid foods. In addition, it may not be appropriate to extrapolate the data from mice to humans directly because the basal metabolic rate of mice is about 7 times higher than that of humans (27). Therefore, in humans, it is possible that a lower level of sucrose consumption could result in similar effects as we observed in mice. Although it is not possible to distinguish between the effects caused by increased sucrose intake and increased caloric intake from the present study, previous human studies have shown that isocaloric exchange of dietary starch with sucrose (25–30% of total calories) produces undesirable changes in glucose and insulin metabolism (28, 29). Fructose contained in sucrose may be responsible for the metabolic and pathologic changes.

Sucrose is a disaccharide that is cleaved to a 50:50 molar mixture of glucose and fructose in the intestine. After absorption, glucose and fructose enter the portal circulation and are transported to the liver or pass into the general circulation. Fructose is more lipogenic than glucose, because it bypasses a major rate-controlling step in glycolysis and is converted to fatty acids in the liver at a greater rate (30, 31). In addition, circulating glucose increases insulin release and subsequent leptin secretion, whereas fructose does not stimulate insulin and leptin secretion (1). Because leptin inhibits food intake, the lower leptin concentrations induced by fructose may enhance food intake. This would result in an increase in body weight.

Because of the preferential entry of fructose into lipogenesis, an increased intake of sucrose has been shown to induce hyperlipidemia, in particular an increase of triglyceride (TG) levels in humans (32) and rodents (33). Interestingly, in this study, intake of sucrose-sweetened water did not significantly affect fasting plasma triglyceride levels in APP/PS1 mice (there was actually a trend for a decreased level of TG in the sucrose group). However, we did not measure the postprandial TG levels, which could be increased in the sucrose group. Interestingly, plasma non-HDL cholesterol levels (equal to total cholesterol − HDL cholesterol) were elevated significantly in these mice. Consistent with our findings, an increase of plasma non-HDL cholesterol levels has been observed in humans (34, 35) and rodents (33, 36) with an increased intake of sucrose.

Many studies have shown that high fat and/or high sucrose diets induces insulin resistance in rodents (17, 33, 37, 38). The mechanisms by which high fat and/or high sucrose diets cause insulin resistance are not fully understood. It has been shown that high fat and high sucrose diets may affect the metabolism of insulin and glucose differentially (37). In this study, the mice were fed a regular low fat rodent diet. The addition of sucrose in their drinking water induced glucose intolerance and hyperinsulinemia, demonstrating that chronic consumption of sugar-sweetened beverages could lead to insulin resistance syndrome independent of dietary fat intake.

Supporting the notion that type 2 diabetes mellitus is associated with cognitive impairment (11), this study showed that sucrose-induced insulin resistance exacerbated learning and memory deficits in APP/PS1 mice. In agreement with our findings, a high fat diet-induced insulin resistance was also associated with poor learning and memory performance in a different mouse model of AD (17). The mechanisms by which insulin affects memory may involve the regulation of insulin signaling pathways in the brain (39). Although an acute increase of peripheral insulin concentration increases the insulin concentration in the brain, chronic peripheral hyperinsulinemia down-regulates blood-brain barrier insulin receptors and...
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reduces insulin transport into the brain (40). It has been shown that insulin receptor-mediated signal transduction is decreased in the brains of mice with a high fat diet-induced insulin resistance (17). In contrast, increasing peripheral insulin sensitivity by rosiglitazone treatment improves spatial learning and memory abilities in a mouse model of AD (41).

Accompanying the exacerbation of cognitive impairment, the amyloid deposition was increased in the brain of APP/PS1 mice taking sucrose-sweetened water. Increased cerebral Aβ deposition may be caused by either increased production, decreased clearance, or increased aggregation of Aβ. Our results showed that the expression level of the APP transgene did not change. The levels of α- and β-CTF of APP, determined by secretase activities, also were not altered. In addition, the levels of Aβ40 and Aβ42 in the soluble fraction of the brain homogenate did not differ between the two groups of mice. These results suggest that the production of Aβ from APP was not affected significantly by excess sucrose consumption.

Prior studies have shown that high fat diet-induced insulin resistance is associated with a decrease of cerebral IDE (17), a metalloprotease that degrades insulin and Aβ. In this study, there was a trend for a reduced level of IDE in the sucrose group. However, the modest decrease of IDE could not account for a 2.9-fold increase in Aβ deposition in these mice. Consistent with this, there was no change in soluble Aβ levels, indicating that there were no significant effects from IDE, since IDE degrades soluble monomeric Aβ primarily (23).

A significant increase of Aβ deposition suggests that aggregation of Aβ could be increased in the mice taking sucrose-sweetened water. In this line of APP/PS1 mice, the levels of Aβ42 are higher than the levels of Aβ40 in both pre- and postdeposit mice because of the presence of PS1-dE9 transgene that specifically elevates the production of Aβ42 (19). Our results showed that the level of insoluble Aβ42 increased significantly in the brains of sucrose-treated APP/PS1 mice. Aβ42 is more amyloidogenic than Aβ40, leading to more Aβ deposition (19). In addition, there was a significant increase in the level of apoE in the brains of these mice. Mouse apoE has been shown to promote aggregation and fibril formation of Aβ (25). How apoE in the brain is up-regulated in these mice is not clear. Previous studies have shown that a sucrose diet increases hepatic apoE synthesis (42). It appears that brain apoE expression is also up-regulated by sucrose intake as we observed in this study. A 2.5-fold increase of apoE agreed well with a 2.9-fold increase of Aβ deposition in the brain. Therefore, these results suggest that the exacerbation of cerebral amyloidosis in sucrose-treated APP/PS1 mice resulted mainly from increased aggregation of Aβ induced by the up-regulation of apoE.

In conclusion, we have shown that long-term consumption of sucrose-sweetened water (or consequent increase of caloric intake) causes more weight gain, induces insulin resistance, and exacerbates AD-like cognitive impairment and cerebral amyloid deposition independent of dietary fat intake in a mouse model of AD. Our findings are of tremendous importance given that the consumption of sugar-sweetened beverages has increased dramatically in the past decades and will most likely remain high in modern societies. Controlling the consumption of sugar-sweetened beverages may be an effective way to curtail the risk of developing AD.

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