World Congress on Insulin Resistance, Diabetes, and Cardiovascular Disease

Part 4

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INSULIN RESISTANCE AND CARDIOVASCULAR DISEASE —
Stephen Daniels (Denver, CO) discussed the influence of obesity and insulin resistance on the heart and vasculature during childhood. In a classic epidemiologic study comparing inactive bus drivers with physically active bus conductors, the former had greater waist circumference and higher risk of both total and fatal myocardial infarction (1). Daniels noted the substantial increase in severe obesity in school-age children over the past few decades and suggested that there is evidence of a relationship between childhood obesity and adult obesity (2) and that childhood obesity is associated with elevation in cardiovascular risk factors, implying that childhood obesity contributes to adult cardiovascular disease (CVD). A dramatic example is the increasing prevalence of childhood diabetes. Type 2 diabetes is certainly a cardiovascular risk factor in adults, with lag in adults of 10–15 years from diagnosis of diabetes to CVD, typically preceded by a 5- to 10-year lag from onset of hyperglycemia to diagnosis of diabetes. A similar time course for individuals developing type 2 diabetes in adolescence would begin to cause cardiovascular morbidity in their fourth decade of life. On a population level, both mean blood pressure and the prevalence of hypertension have increased, again with circumstantial evidence of a relationship with obesity. Both adiposity and blood pressure determine left ventricular mass in childhood (3,4), with all these factors correlating with autopsy findings of early atherosclerosis in children (5), with evidence of calcification of the coronary arteries (6), and in an epidemiologic study of 276,835 Danish school children, with demonstration of a significant relationship between childhood BMI and CVD in adulthood (7). Potential mechanisms of the association of CVD with obesity include insulin resistance, adipokines, and as suggested by Gerald Reaven at the beginning of the Congress (see part 1 of this series), hyperinsulinemia per se. Insulin resistance is associated with abnormalities of lipids and blood pressure, of left ventricular mass and carotid intima-media thickness, and in the Framingham Offspring Study, with impaired endothelial function (8). The prevention and treatment of obesity will, Daniels said, lead to reduction in insulin resistance and to eventual improvement in CVD, but to accomplish this one must focus on obesity in young individuals, which he termed "the challenge for pediatricians now."

Mark Kearney (Leeds, U.K.) discussed the role of insulin resistance in the balance between vascular tissue damage and repair. The pattern of presentation of heart disease is changing, he noted, with younger insulin-resistant patients not showing expected responses to intervention. Vascular disease in type 2 diabetes affects all arterial beds, with insulin resistance present throughout the continuum of CVD, from the earliest stages through left ventricular dysfunction to the syndrome of heart failure, with diabetes particularly detrimental in changing this phenotype. Temporal trends from 1995 to 2003 show similar and high prevalence among both diabetic and nondiabetic patients of use of statins, aspirin, and β-blockers, but whereas among nondiabetic patients postmyocardial infarction mortality decreased nearly one-third to ~25% from 1995 to 2003, among diabetic patients mortality was ~40% in both years (9). Primary percutaneous intervention is, Kearney stated, the current treatment of choice. In a study of some 2,600 patients at his institution, however, 1-year mortality was ~5% in the nondiabetic but 17% in the diabetic patients. Diabetic patients with ischemic cardiomyopathy similarly showed doubling of mortality at 1 and 2 years.

Cardiovascular insulin resistance is in certain ways a progressive disorder, accompanied by endothelial cell damage and death, with the atherosclerotic process developing as a pathologic response to injury. Insulin resistance leads to imbalance between endothelial cell damage and repair, favoring atherosclerosis. Nitric oxide (NO) is involved in vasodilation, vascular smooth muscle cell growth and migration, and decreasing platelet adherence, acting to reduce atherosclerosis; in insulin resistance, these reparative processes are attenuated. Endothelial cell repair involves mobilization of precursor cells from bone marrow with subsequent homing to sites of injury. Insulin resistance blunts progenitor cell mobilization, with ~50% reduction in circulating endothelial progenitor cell levels. Flow-mediated vasodilation is decreased, whereas endothelial microparticles, indicators of endothelial cell death, are increased. In an animal model of insulin resistance in which glucose tolerance was preserved at the expense of hyperinsulinemia, aortic rings showed normal responsiveness to acetylcholine but reduction in the vasodilatory response to insulin and to L-arginine, an NO precursor. Circulating endothelial progenitor cell levels were decreased, and their mobilization in response to vascular endothelial growth factor was blunted, with delay in reendothelialization following wire injury of the femoral artery. Transfusion of spleen-derived mononuclear cells or bone marrow–derived cells from normal animals

restored this process, while such cells from animals with reduced insulin receptor expression were less effective in restoring endothelial repair.

Nikolaos Frangogiannis (Bronx, NY) discussed the phases of healing after myocardial infarction: an initial inflammatory response followed after 2–7 days by a proliferative process with suppression of inflammation. Subsequent phases of maturation lead to scar formation. Defects in any step of the healing process lead to abnormal cardiac remodeling, involving functional and hypertrophic cardiac tissue.

The reparative process involves the complement cascade, reactive oxygen species, toll-like receptor-mediated pathways, and nuclear factor-κB activation. Leukocytes and proinflammatory cytokines are beneficial in removing necrotic tissues, though in so doing potentially damage viable cellular elements. Defective interleukin-1 signaling decreases inflammation following myocardial infarction but does not reduce infarct size, actually enhancing adverse remodeling by increasing matrix metalloprotein expression (10,11). In a rodent myocardial infarction model, high levels of chemokines such as monocyte chemoattractant protein-1 were seen. Animals not expressing monocyte chemoattractant protein-1 showed delay in formation of granulation tissue and in phagocytosis of necrotic cardiomyocytes again without change in infarct size but with reduction in the degree of ventricular dilation, suggesting that this anti-inflammatory approach might prevent adverse remodeling. "In the heart," Frangogiannis said, "defective resolution of inflammation would be expected to be catastrophic," suggesting that it might be optimal to mimic endogenous "stop signals" that suppress inflammation and protect from adverse remodeling. Particular mononuclear cell subsets exhibit inhibitory properties, whereas other monocyte populations promote repair. In rodents not expressing the chemokine receptor (CCR5), matrix metalloprotein expression and cellular remodeling apparently increased because of impaired recruitment of the suppressive Tregs leukocytes. Additional pathways for resolution of inflammation may be mediated through clearance of apoptotic cells. Frangogiannis speculated that transforming growth factor-β acts as a "master switch" mediating the transition from inflammation to fibrosis, activating Smad-dependent and -independent pathways (12). Rodents not expressing Smad3 show reduced dilative remodeling after myocardial infarction, and in vitro, fibroblasts require smad3 for myfibroblast transdifferentiation (13). The fibrotic response also needs to be regulated because excessive fibrosis would be expected to cause defective repair and cardiac dysfunction. Frangogiannis reviewed, as an example, a study of mice not expressing interferon-γ–inducible protein 10, showing excessive fibrosis following myocardial infarction (14). Other critical steps in myocardial infarction healing include fibroblast apoptosis and angiogenesis and vascular maturation, for which controlling factors have not been established.

PREDIABETES, CVD, AND APPROPRIATE DIAGNOSTIC CRITERIA

—Sir George Alberti (London, U.K.) discussed the new diagnostic criteria for diabetes and the state variously referred to as prediabetes and "at risk for diabetes" (either impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]) and questioned whether the new criteria "make sense." He concluded that the importance of these concepts is in their relationship to complications, and in particular to likelihood of CVD.

The 2010 American Diabetes Association (ADA) practice guidelines suggest that the first diagnostic test for diabetes be A1C ≥6.5% and that increased risk of diabetes be considered A1C 5.7–6.4%. Alberti suggested that diabetes should be considered the condition characterized by both hyperglycemia and increased risk of microvascular complications. In 1997, an ADA Expert Committee and World Health Organization (WHO) consultation took into account then new data and endeavored to identify a glucose threshold for presence of complications (15). Rather than endorse the approach previously taken of defining cutoff glucose levels of bimodal glucose distributions in populations with high risk of diabetes, the committee suggested using as a "takeoff point" the glycemic threshold above which there is increased risk of retinopathy. In Pima Indian, Egyptian, and National Health and Nutrition Evaluation Survey III datasets, risk increased at fasting glucose levels of 123, 129, and 120 mg/dL and at 2-h postload glucose levels of 200, 207, and 195 mg/dL, respectively. As a compromise, cutoff criteria were set at fasting and 2-h postload glucose levels of 126 and 200 mg/dL, respectively, with the proviso that among asymptomatic individuals the glucose test be repeated for confirmation, although repeat testing has not typically been done in population studies. There are a number of problems with this analysis: the lack of glycemic threshold for macroangiopathy; the variability of oral glucose tolerance in a given individual, particularly in those more sensitive with regard to 2-h glucose; and the need for dietary preparation, with low carbohydrate consumption the night before a test leading to worse glucose tolerance. In 1999 and 2006, WHO committees recommended that A1C not be used for diagnosis, but in 2008 and 2009 an international expert committee convened by the ADA and a WHO expert committee did suggest that A1C criteria would be useful.

Alberti questioned whether A1C is truly useful, noting that although it is stable, time averaged, reproducible, and that fasting is not required, "A1C is not all it is cracked out to be," as it is affected by a variety of conditions (16), such as age, ethnicity, hematologic abnormalities, dyslipidemia, and renal disease. Alberti noted as an example the 0.4% lower A1C of Caucasians than of African Americans with IGT/IFG in the Diabetes Prevention Program (17). A1C requires standardization, is somewhat expensive, is not available worldwide, few data are available, and the cut point is uncertain. In contrast, Alberti observed, diabetes is a disease of glucose, which is time honored and for which there are extensive data, with international comparisons available and a fairly accurate assay. He acknowledged that accuracy is not equal in all laboratories, with poor quality assurance and that there are preanalytical problems, such as the 15% reduction in blood glucose during the initial 2 h after sampling with improper handling. Furthermore, an oral glucose tolerance test is ideally required, and this is more complex than a single sample.

The ADA group recommended use of A1C, whereas the WHO committee suggested that glucose testing is preferred, although Alberti observed that A1C use with appropriate standardization was included in the WHO recommendations. He acknowledged the imperfections of glucose measurement, particularly with use of fasting glucose alone, and concluded that although he was "uncertain," A1C could be useful with appropriate precautions in its interpretations, particularly because A1C is being used all around the world for this purpose. "Prediabetes," he stated, "is a horrible term which should never have been invented," but he suggested that the notion is relevant in ascertaining future macroangiopathy risk (18). He observed that there is rather poor correlation of A1C, IGT, and

IFG and expressed concern that the use of A1C rather than glucose criteria would reclassify huge numbers of individuals and decrease the reported prevalence both of diabetes and of prediabetes (19,20).

INSULIN RESISTANCE AND SLEEP

—David Ehrmann (Chicago, IL) discussed metabolic dysfunction in polycystic ovary syndrome (PCOS), "a metabolic disorder with reproductive consequences," defined by the combination of oligo/anovulation and hyperandrogenemia with hirsutism, acne, and alopecia. Patients with PCOS have numerous metabolic and cardiovascular derangements related to insulin resistance, obesity, β-cell dysfunction, abnormal glucose tolerance, dyslipidemia, hypercoagulability, hypertension, endothelial dysfunction, and obstructive sleep apnea (OSA). There is high prevalence (35–45%) of glycemic abnormality in young adults with PCOS, similar to that among Pima Indians, the single population with the highest known diabetes prevalence. The U.S. population prevalence of PCOS is 5–8%, amounting to some 5–10 million individuals, of whom 10% have type 2 diabetes and 35% IGT/IFG; many of those remaining have normal glucose tolerance but marked hyperinsulinemia (21) both with and without obesity (22).

"Obesity of course plays a significant role," Ehrmann said, "but in PCOS there is another factor.... It's not just the obesity." He pointed out that testosterone influences both neural control of breathing and upper-airway mechanics and hence is a risk factor for sleep apnea so that the hyperandrogenism of PCOS may predispose to this as well. OSA is characterized by recurrent episodes of partial or complete upper-airway obstruction during sleep, leading to intermittent hypoxia, sleep fragmentation, sleep loss, and shallow sleep with reduction in slow-wave activity. It affects 24% of men and 9% of women. Because women have longer duration of slow-wave activity during sleep, they may to some extent be protected against sleep fragmentation and sleep apnea. Among obese men and women, approximately one-half and one-third, respectively, have OSA. Other risk factors are older age; craniofacial anatomic factors including retrognathia, enlarged soft palate and tonsils, macroglossia, and neck circumference >40 cm; family history; and ethnic minority status. Over the past decade, evidence has emerged of increased prevalence of OSA in obese women with PCOS (23,24). Comparing women with PCOS versus those without PCOS, Ehrmann presented evidence that 44 vs. 6%, respectively, had an apnea-hypopnea index (AHI) >15/h. In another study comparing 52 women having PCOS with 21 control subjects, 56 vs. 19%, respectively, had OSA. Adjusting for confounders including age, BMI, and ethnicity, PCOS was associated with a sevenfold increase in likelihood of OSA (25). In this study, testosterone levels did not vary between women with and without OSA or with severity of OSA. Sleep debt, such as that seen with OSA, is in turn associated with endocrine dysfunction, insulin resistance, and reduced insulin response and glucose tolerance (26). Sleep disruption during slow-wave sleep for just 3 days reduces glucose tolerance and insulin sensitivity (27).

Continuous positive airway pressure (CPAP) treatment of OSA has been studied to determine whether it improves PCOS or its metabolic abnormalities. In a study of 19 individuals, 10 were poorly compliant with CPAP, but of the 9 using it for at least 4 h nightly AHI decreased and slow-wave sleep increased, with a trend to reduction in blood pressure and improvement in the parasympathetic-to-sympathetic activity ratio, reduction in 24-h norepinephrine levels, and improvement in insulin sensitivity (28).

Eve Van Cauter (Chicago, IL) further discussed sleep loss and OSA and their links with obesity, insulin resistance, and diabetes. She reviewed evidence that "the U.S. leads the way in this phenomenon of sleep curtailment" (29), a major change in lifestyle, commenting that in 1960 the average American slept 8.5 h/night but now the average is 6.7 h on work days and 7.8 h on weekends, a reduction in sleep duration by of 1.5 hours over the past 5 decades. Interestingly, insufficient sleep is greatest in the southeast U.S., with geographic distribution similar to those of diabetes and of obesity. Sleep duration is inversely associated with obesity. Van Cauter noted that 48 of 56 epidemiologic studies have shown this association and discussed mechanisms derived from animal models. In a study comparing 4 h with 10 h sleep for 2 days, ghrelin levels increased, whereas leptin decreased, in association with an increased sense of hunger and particular craving for carbohydrates after short sleep sessions (30). Another study compared individuals sleeping on average 8.5 h/night subjected to 4.5 h/night sleep restriction and allowed ad lib feeding. There was a 432-calorie increase in food intake, with particular increase in carbohydrate and fat; weight gain would be anticipated "if this behavior were to continue," leading Van Cauter to wonder whether much of the increase in prevalence of obesity in the U.S. is related to sleep curtailment. In a meta-analysis of studies of over 100,000 individuals, there was a 28% increase in diabetes risk with short sleep, controlling for age, sex, BMI, and other confounders (31). A second meta-analysis of nearly 200,000 individuals comparing sleep duration <5 and 5–6 with 7–8 h/night found 1.46-fold and 1.1-fold increases, respectively, in likelihood of diabetes.

Van Cauter reviewed physiologic studies of effects of sleep restriction showing that it rapidly leads to decreased insulin sensitivity and impaired β-cell compensation, decreasing the disposition index (26,32). Potential mediators of this effect include reduction in brain glucose utilization, loss of diurnal cortisol cycling with higher levels later in the day, higher ghrelin and growth hormone levels during waking, increase in the sympathetic-to-parasympathetic tone ratio, and inflammation, with evidence that sleep restriction increases C-reactive peptide. Decreased insulin sensitivity in OSA is, Van Cauter stated, proportional to AHI, with consequent glucose intolerance. Prospective studies link OSA with increased diabetes risk (33–35). Furthermore, sleep testing of diabetic patients shows that the majority have OSA, with the severity of the sleep apnea predicting the patient's A1C level (36).

INSULIN RESISTANCE AND THE BRAIN

—Randy Seeley (Cincinnati, OH) discussed central effects of glucagon-like peptide (GLP)-1. In addition to its peripheral production in the L cells of the distal gut in response to the presence of nutrient in the proximal intestine, acting on the β-cell as well as other tissues, there is a central GLP-1 system, with production in the nucleus tractus solitarius (NTS), having receptors in the brainstem, hypothalamus, and amygdala, involved in control of food intake. Peripheral GLP-1 is generally thought of as a hormone, increasing glucose-induced β-cell insulin secretion (37) and lowering glucose levels in diabetes (38). Perhaps, Seeley speculated, GLP-1 does not act systemically as a hormone. It is rapidly degraded in plasma by dipeptidyl peptidase 4, with a circulating half-life of no more than 1–2 min and with significant hepatic clearance

so that ≤15% of secreted GLP-1 reaches the peripheral circulation—considerably less than glucose-dependent insulinotropic peptide (GIP), which exhibits a much greater dynamic range (39). Comparisons of animal models not expressing either the GLP-1 or the GIP receptor suggested to Seeley that only the latter acts systemically (40,41). Rather, he suggested, the predominant GLP-1 effect is in the portal vein, which expresses GLP-1 receptors. Very low intraportal doses of a GLP-1 antagonist, which fail to have effect when given systemically, increase glucose levels.

Central GLP-1 antagonist administration increases blood glucose levels after parenteral glucose (42), suggesting a role of the central GLP-1 system in glucose homeostasis. Central GLP-1 administration also enhances glucose-stimulated insulin secretion. Furthermore, GLP-1 neurons in the NTS project into the hypothalamus, particularly in the arcuate nucleus. In a study of intra-arcuate GLP-1 administration, hepatic glucose production decreased by half (43). The GLP-1 agonist exendin-4, administered peripherally, decreased food intake, an effect blocked by peripheral administration of a GLP-1 antagonist, but central exendin-4 is 100-fold more potent in reducing food ingestion, with a peripheral GLP-1 antagonist failing to reduce the effect (37). In a model with 50% reduction of NTS preproglucagon expression, weight gain is seen, further suggesting a role of central GLP-1 in regulation of food intake. A question being explored pertains to the role of central GLP-1 receptors in mediating the effects of gut-derived GLP-1.

Stephanie Amiel (London, U.K.) discussed further aspects of the central control of appetite. Peripheral signals generated in the gut, pancreas, and liver communicate with the brain, with effects of cognitive and environmental factors; social context; and costs, palatability, and incentive value of food. With use of neural imaging, local increase in glucose uptake and metabolism and in oxygen demand can be imaged with positron-emitting glucose tracers, with water labeled with positron emitters or by magnetic spin, or with change in magnetic resonance signal, all of which can be seen as surrogate markers of regional brain activation.

Although there is no effect of hyperinsulinemia on global brain glucose uptake, there are effects of basal insulin at low levels both in insulin-sensitive and insulin-resistant individuals. Cerebral glucose metabolism, measured using positron emission tomography scanning, was reduced by insulin deficiency so that ~20% of brain glucose uptake is insulin influenced, with lesser effect in individuals with peripheral insulin resistance (46). Basal insulin replacement increases glucose uptake in the ventral striatum, orbital frontal cortex, and insula while being associated with reduction in glucose uptake in the amygdala and cerebellar vermis, suggesting that insulin turns off neurons normally stimulated by fear, vigilance, and anxiety while activating neurons in regions of taste, appetite, and food-seeking and reward behaviors (45,46). In insulin-resistant individuals, insulin-induced neuronal deactivation is not inhibited, whereas sites usually activated by insulin show reduced effect, implying that overeating would occur in situations of stress and anxiety. Functional magnetic resonance imaging shows similar effects in type 2 diabetes (47,48). The effect of insulin resistance extends to brain responses to glucose, insulin, and mixed meals. In early type 2 diabetes, there is inappropriate activation of dopaminergic reward and motivation centers in the fed state and failure to reduce activation in cholinergic self-awareness centers. This may, Amiel suggested, increase appetite, perhaps impairing gut-brain signaling. Whether insulin resistance affects brain insulin uptake or causes altered brain insulin signaling is not known.

Susan Craft (Seattle, WA) discussed the role of insulin in normal brain function and cognition, noting that dysregulation of insulin response and secretion is associated with cognitive impairment. Insulin receptors are distributed in the hippocampus, entorhinal cortex, and frontal cortex, and insulin crosses the blood brain barrier at physiologic levels, increasing brain neurotransmitter levels, glucose utilization, and neuronal firing. At optimal doses, insulin both peripherally and centrally administered enhances memory, with the hippocampus, critical to memory, expressing GLUT4 in response to insulin. States of insulin resistance and hyperinsulinemia, IGT, and type 2 diabetes are associated with increased risk of Alzheimer's disease and of memory impairment. In these states, impaired cerebral glucose metabolism may disrupt regulation of β-amyloid trafficking and clearance, impairing synaptic maintenance and increasing inflammation, perhaps with prolonged peripheral hyperinsulinemia reducing brain insulin uptake and leading to reduced signaling.

Features of Alzheimer's disease, defined by deficits in memory and at least one other area of cognition, are seen in one-half of the population by age 85 years, with impaired ability to carry out daily functions. This is progressive, with pathologic features of synaptic loss followed by atrophy and cerebral volume loss and with histologic findings of neurofibrillary tangles comprised of hyperphosphorylated τ protein and neuritic plaques of aggregated β-amyloid. Impaired cerebral glucose metabolism, with hypometabolism at rest in the frontal, temporal-parietal, and cingulated regions, associated with Alzheimer's disease, features demonstrable years before clinical onset. A study of healthy adults with newly diagnosed IGT or mild type 2 diabetes and with normal cognition on testing showed a pattern of brain glucose metabolism similar to that in Alzheimer's disease (49). Craft commented that "the more insulin resistant they were, the more their brains looked like those of patients with Alzheimer's disease."

β-Amyloid aggregates in plaques, but soluble β-amyloid oligomers also are present in Alzheimer's disease and appear to be neurotoxic and to inhibit memory, somewhat analogous to findings with islet amyloid and the β-cell. Insulin regulates levels of β-amyloid by promoting its intracellular release from neurons because degradation of β-amyloid is mediated by insulin-degrading enzyme, with activity inversely proportional to insulin levels. Exposure to β-amyloid causes insulin receptors to be translocated intracellularly from dendritic membranes, suggesting that β-amyloid may lead to central insulin resistance. Insulin reduces β-amyloid oligomer–induced synapse loss, while insulin resistance disrupts β-amyloid regulation. Sucrose-fed insulin-resistant animals have greater brain amyloid burden and impaired memory. Greater levels of dietary saturated fat intake in midlife are associated with increased age-related cognitive impairment and Alzheimer's disease risk, while mono- and polyunsaturated fats and complex carbohydrate appear to be protective.

Craft reviewed a study comparing eucaloric diets (one with 45% fat, 25% saturated fat, and high glycemic index and the other with 25% fat, 7% saturated fat, and low glycemic index) in 70-year-old adults undergoing lumbar puncture at baseline and week 4. The diets increased versus decreased insulin resistance and LDL cholesterol levels, respectively, and

spinal fluid β-amyloid increased versus decreased, with corresponding changes in the inflammatory marker F2-isoprostane.

Could reduced brain insulin signaling play a role in Alzheimer's disease? Spinal fluid insulin levels and brain insulin expression are reduced in Alzheimer's disease. Craft described her studies with intranasal insulin, noting that perivascular channels along the olfactory and trigeminal nerves allow insulin administered in this fashion to reach the brain in 15–30 min. There is also axonal transport along the olfactory neurons. In the *db/db* diabetic mouse model, intranasal insulin reduces brain atrophy, improves memory, and increases downstream insulin signaling molecules. Craft presented findings from the recently completed Study of Nasal Insulin to Fight Forgetfulness (SNIFF) in which 104 adults having Alzheimer's disease or preclinical Alzheimer's disease were administered with placebo or with intranasal insulin at doses of 10 or 20 units twice daily. Recent memory improved at the lower dose, and a functional impairment measure improved at both doses, with cerebral glucose metabolism as assessed with positron emission tomography scan showing worsening with placebo over 16 weeks while no change occurred in either insulin-treated group. A number of related strategies are being explored for Alzheimer's disease treatment. Thiazolidinedione treatment may be beneficial; pioglitazone improves memory and lowers spinal fluid Aβ42 in insulin-resistant adults without Alzheimer's disease. There is growing literature on the benefit of exercise in prevention of Alzheimer's disease. Intriguingly, because the GLP-1 receptor is present in the hippocampus GLP-1 mimetics have been studied; both peripheral and central administration in animal models reduce the memory impairment induced by a high-fat diet and prevent streptozotocin-induced increases in β-amyloid.

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