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SYMPOSIUM

Nonhuman Primates and Other Animal Models in Diabetes Research

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Abstract

Animal models are important for determining the pathogenesis of and potential treatments for obesity and diabetes. Nonhuman primates (NHPs) are particularly useful for studying these disorders. As in humans, type 2 diabetes mellitus is the most common form of diabetes in NHPs and occurs more often in older obese animals, with a metabolic progression from insulin resistance (IR) and impaired glucose tolerance to overt diabetes. Histopathologic changes in pancreatic islets are also similar to those seen in humans with diabetes. Initially, there is islet hyperplasia with abundant insulin production to compensate for IR, followed by insufficient insulin production with replacement of islets with islet-associated amyloid. Diabetic NHPs also have adverse changes in plasma lipid and lipoprotein concentrations, biomarkers of obesity, inflammation, and oxidative stress, and protein glycation that contribute to the numerous complications of the disease. Furthermore, sex hormones, pregnancy, and environmental factors (e.g., diet and stress) affect IR and can also contribute to diabetes progression in NHPs. Additionally, due to their similar clinical and pathologic characteristics, NHPs have been used in many pharmacological studies to assess new therapeutic agents. For these reasons, NHPs are particularly valuable animal models of obesity and diabetes for studying disease pathogenesis, risk factors, comorbidities, and therapeutic interventions.

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Etiology of Diabetes in Humans

The prevalence of diabetes mellitus has increased exponentially since the 1990s.[1] The American Diabetes Association classifies diabetes mellitus into four categories: type 1 diabetes mellitus (T1DM), in which there is an absolute deficiency of insulin due to autoimmune destruction of the pancreatic β cells; type 2 diabetes mellitus (T2DM), in which there is a relative deficiency of insulin resulting from a progressive insulin secretory defect on a background of insulin resistance (IR); gestational diabetes mellitus (GDM); and other specific types of diabetes.[2] Currently, in the United States, ~8% of the population has diabetes[3] and another 25% has impaired

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Abbreviations: (CB_1) cannabinoid 1, (CVD) cardiovascular disease, (GDM) gestational diabetes mellitus, (GLP-1) glucagon-like peptide-1, (HbA1c) hemoglobin A1c, (HDL) high-density lipoprotein, (IGT) impaired glucose tolerance, (IR) insulin resistance, (LDL) low-density lipoprotein, (NHP) nonhuman primate, (PPAR) peroxisome proliferator-activated receptor, (STZ) streptozotocin, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus, (VLDL) very-low-density lipoprotein.

Keywords: cardiovascular disease, diabetes, metabolic syndrome, nonhuman primates, obesity, therapeutic intervention

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glucose tolerance (IGT), prediabetes, or metabolic syndrome with an increased risk of developing diabetes.[4] The increased prevalence of diabetes, which has occurred in parallel with the increased incidence of obesity,[5] is due to an increase in T2DM, which accounts for 90% to 95% of diabetes cases.[2] The morbidity associated with T2DM results from hyperglycemia-related complications that include both microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (cerebrovascular, coronary artery, peripheral vascular) diseases.[6]

Prediabetic conditions are also associated with increased health risks.[7] For example, obesity not only aggravates, but also precipitates diabetes by increasing IR, which, in turn, increases tissue insulin requirements.[8] This has major health care considerations since >30% of U.S. adults are obese, with another 35% overweight.[5] In addition, the incidence of overweight children/adolescents is now >15% and has quadrupled since the 1980s.[5] Furthermore, half of the obese population, and 25% of the general population, have metabolic syndrome, a condition associated with abdominal obesity, hypertension, increased plasma triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and IR, which increases the risk for cardiovascular disease (CVD).[4,9]

Insulin resistance, a key feature of obesity, represents the earliest metabolic abnormality in the transition from normal to IGT that precedes T2DM development.[10] As IR worsens, insulin secretion increases to help move glucose into target tissues, resulting in compensatory hyperinsulinemia.[8] As the disease progresses, IGT develops with initially only a slight elevation in fasting glucose, followed by overt hyperglycemia as pancreatic exhaustion develops, normal islet architecture is replaced with islet-associated amyloid, and insulin secretion declines.[8]

Type 2 diabetes mellitus is also associated with a specific dyslipidemia [elevated triglycerides, reduced HDL cholesterol, and increased small, dense low-density lipoprotein (LDL) particles] that further increases the risk of developing CVD.[4] Cardiovascular disease, the primary cause of death among persons with diabetes, occurs at an earlier age and results in 2–8-fold greater mortality rates than in persons without diabetes.[7,11] Persons with diabetes also have higher mortality rates after their first myocardial infarction.[12]

Inflammation and oxidative stress are also major contributors to both microvascular and macrovascular diabetic complications. It has been suggested that many mechanisms relating hyperglycemia to vascular disease involve the overproduction of reactive oxygen species.[13–15]

Genetic and Chemically Induced Diabetes in Rodents

To study the development and progression of diabetes at the molecular level in ways not possible in humans, many evaluations have utilized rodent models of T1DM and T2DM. Since rodents do not typically develop spontaneous diabetes, and many are also resistant to the development of diet-induced obesity-mediated T2DM, even though they develop all of the characteristics and comorbidities of metabolic syndrome,[4] researchers have relied on chemical induction of diabetes with streptozotocin (STZ) to produce models of T1DM[16] and development of genetic models of T2DM, such as the ob/ob, Ay/Ay, NZO, KK, and db/db mouse models and the Zucker diabetic fatty, OLETF, GK, and sand rat models.[16]

A number of other species, including cats, dogs, pigs, and nonhuman primates (NHPs) do develop spontaneous diabetes (discussed later), and these animals offer important advantages in studying the characteristics, development, and comorbidities of diabetes in ways not possible in STZ-treated or genetically manipulated rodents.

Naturally Occurring Diabetes in Domestic Animals

Cats that spontaneously develop T2DM are generally obese with body weight inversely proportional to insulin sensitivity.[17,18] Cats that share their environment with humans also have many of the same risk factors for T2DM, including obesity and physical inactivity.[19] Diabetic cats exhibit pathophysiological and clinical derangements similar to those seen in humans with diabetes and experience a prolonged period of prediabetes, which is characterized by obesity and IR.[7,20–24] Cats also develop retinopathy and peripheral neuropathy and, like humans and NHPs, develop islet amyloidosis.[25] Diabetic cats also have dyslipidemia and develop hypertension.

Domesticated dogs also share their environment with humans and are increasingly sedentary and obese. Dogs that develop diabetes are middle-aged and older. However, canine diabetes has a poorly understood pathophysiology and does not fit well into human diabetes classifications. In addition, pancreatitis, acromegaly, and hyperadrenocorticism are often associated with canine diabetes.[26] Some breeds are at increased risk of

developing diabetes, while others are at decreased risk.[27] Dogs better compensate for persistent hyperglycemia than do other species, do not lose appreciable β-cell mass, do not have islet amyloidosis, and less frequently progress to clinically overt diabetes.[27,28] Dogs also do not develop diabetic dyslipidemias, and CVD is not a common complication in dogs. A canine model of T2DM was developed utilizing diet-induced obesity followed by mild chemical β-cell destruction.[29]

Pigs are a good model for human obesity and diabetes because they have a similar omnivorous diet, a predilection for obesity, a similar cardiovascular anatomy, and a similar metabolism and lipoprotein profile.[30] The primary deterrents to use of pig models are expense and size, particularly for the Yorkshire pig, a classic swine model of streptozocin-induced diabetes for studying T1DM.[30] Swine models of T2DM are the Ossabaw pig, which has lived in isolation for several hundred years and has developed the "thrifty genotype,"[31] and the Yucatan minipig, which has altered glucose tolerance and develops obesity and IR when overfed a Western diet.[32,33] Unlike cats and dogs that do not develop diabetic vascular disease, pigs are an important model for this complication. The atherosclerotic lesions found in pigs are in similar anatomic locations as in humans,[34,35] with similar histopathologic characteristics.[36] Pigs with chemically induced diabetes have been used to study the pathogenesis of diabetic cardiovasculopathies.[30]

Naturally Occurring Diabetes in Nonhuman Primates

A number of NHP species develop obesity and diabetes, as reviewed previously.[37,38] Commonly used species of Old World primates that develop spontaneous diabetes include macaques (*Macaca sp.*),[37,38] vervets (*Chlorocebus aethiops*),[39,40] baboons (*Papio sp.*),[41–44] and mandrills (*Mandrillus sphinx*).[45] New World monkeys that develop spontaneous diabetes include marmosets (*Callithrix jacchus*),[46–48] squirrel monkeys (*Saimiri sciureus*),[49,50] capuchins (*Cebus apella*),[49] and tamarins (*Saquinus sp.*).[49] Chimpanzees (*Pan troglyodytes*) also develop spontaneous diabetes.[51,52]

Categorically, these NHPs all exhibit clinical features of diabetes, including obesity, IR, dyslipidemia, and pancreatic pathology that are similar to those observed in humans[37,49,53] and are therefore excellent models for studying human T2DM. In many NHPs, T2DM is associated with increased age and body weight[37,39,41,42,54–57] and is initially characterized by normal glucose tolerance that is followed by IR, a compensatory increase in insulin secretion, and deterioration of carbohydrate metabolism.[37,56,58,59] As the disease progresses, NHPs develop IGT with a moderate elevation in fasting plasma glucose before becoming overtly hyperglycemic due to a decrease in pancreatic insulin secretion as normal islet architecture is replaced with islet-associated amyloid, resulting in the classic signs of diabetes.[37] Type 1 diabetes mellitus has also been reported in some NHPs but at a much lower frequency,[59] and GDM has been reported in several species,[60,61] with complications similar to those observed in human GDM.[59] As in humans, other atypical forms of diabetes also occur in NHPs.[40]

The most widely studied NHPs that develop spontaneous diabetes are the macaques. Spontaneous diabetes has been demonstrated in cynomolgus macaques (*Macaca fascicularis*),[37,38,62] rhesus macaques (*Macaca mulatta*),[38,49,62] black Celebes macaques (*Macaca nigra*),[53,63–65] bonnet macaques (*Macaca radiata*),[66,67] Formosan rock macaques (*Macaca cyclopis*),[49] and pig-tailed macaques (*Macaca nemestrina*),[49] but the most extensive research regarding the development, characteristics, and comorbidities of diabetes in these animals has been conducted in cynomolgus and rhesus macaques.

Diabetes in cynomolgus macaques was initially reported in the 1980s,[50,68,69] with more detailed characterization in the 1990s.[25,56] Approximately 30% of cynomolgus monkeys >15 years of age (expected life span ~30 years in captivity) have basal and/or postprandial hyperinsulinemia and may also exhibit IGT.[59] Monkeys that progress from IGT to T2DM are typically obese, with body weights and body mass indices outside 95% confidence intervals.[56] However, as their glycemic profile deteriorates, they often lose weight.[56] Type 2 diabetes mellitus monkeys are hyperglycemic and hypertriglyceridemic, yet nonketotic, are severely insulin resistant, and can exhibit increased glycation [hemoglobin A1c (HbA1c)] and delayed glucose clearance for several years before requiring clinical intervention.[56] Obese, insulin-resistant nondiabetic, and T2DM cynomolgus monkeys also exhibit aberrant lipid and lipoprotein metabolism, including increased total cholesterol, triglycerides, and free fatty acids and decreased HDL cholesterol.[37,70] Inflammation and blood pressure also increase during progression from IR to T2DM in these animals.[37]

Diabetes in rhesus macaques was initially described in the 1970s, and the progression from normal to overt T2DM in these animals was characterized by Hansen

and colleagues[58,71] who categorized monkeys into sequential phases of the disease based on age, body weight, glucose clearance, and fasting and secretory insulin levels. These studies showed that T2DM in rhesus monkeys is a progressive disorder with increased basal insulin secretion and impaired insulin response to glucose challenge as the earliest abnormalities. As rhesus monkeys become diabetic, islet amyloid is abundant.[72,73] Rhesus monkeys also exhibit age-related decreases in insulin sensitivity, insulin response to glucose, lean body mass, and energy expenditure,[74,75] and obese animals exhibit increased fasting triglycerides, increased fasting insulin, and impaired insulin responses to glucose.[76] Obesity-related hyperinsulinemia and abnormal glucose tolerance have also been found in feral rhesus monkeys.[77]

Gestational diabetes mellitus has also been described in both cynomolgus[60] and rhesus[61,78] monkeys. Monkeys with GDM have elevated glucose and insulin and deliver macrosomic infants, similar to women with GDM.[60,79] As in humans, there is a risk of T2DM following GDM in monkeys.[59]

Vervet monkeys can become obese, develop IR and dyslipidemia, and progress to T2DM even while consuming a low-fat diet.[39,40] Interestingly, some vervets are insulin sensitive with abundant islet insulin staining but are hyperglycemic. There appears to be a strong heritable pattern in these animals, suggesting the presence of a monogenic form of diabetes, such as maturity-onset diabetes of the young or mitochondrial diabetes.[40]

Baboons have been used extensively to study CVD and also for obesity and diabetes research. Clinical and pathologic signs of T2DM in baboons are similar to those observed in macaques and humans,[41] and many glycemic and obesity parameters are heritable.[42,43] The baboon has therefore been characterized as a model for studying the genetics of obesity, with many obesity-related phenotypes already collected with genotyping in progress.[44]

Marmosets are small (~400 g) South American primates that develop obesity.[47,48] Marmosets mature rapidly and are considered aged at ~8 years, making diseases of old age easier to study in these animals.[46–48] Obese marmosets have increased body fat with little change in lean mass, elevated glucose and HbA1c, and increased triglycerides and very-low-density lipoprotein (VLDL) cholesterol, consistent with other models of obesity,[47] and could be considered diabetic if urinary glucose or pancreatic pathology were available.

Type 2 diabetes mellitus has also been described in aging captive chimpanzees based on persistent fasting hyperglycemia and glycosuria.[51] Reference intervals for fasting plasma glucose and HbA1c for healthy-nondiabetic, prediabetic, and diabetic chimpanzees show a positive correlation and have demonstrated that the overall incidence of T2DM in chimpanzees is nearly five times greater in aged animals than in the general population.[52]

Induction of Diabetes in Nonhuman Primates

While NHPs are ideal models for studying spontaneous diabetes development, the time course of progression is extensive and the percentage of animals progressing to overt diabetes is small. The ability to induce T1DM with STZ and to enhance the progression of overweight animals to overt T2DM with high-carbohydrate and high-fat diets increases the utility of these models dramatically.

Streptozotocin is a specific β-cell toxin that generates a reproducible form of diabetes with limited side effects.[16] In cynomolgus macaques and other NHPs, STZ treatment results in a marked hyperglycemia and dyslipidemia, with changes in pancreatic islets that are characteristic of T1DM.[59,80–83] Streptozotocin-induced diabetic monkeys are generally not insulin resistant but, depending on the extent of islet damage, often require exogenous insulin.[84]

Many NHPs develop diet-induced obesity when fed diets high in fat and/or sugars (sucrose or fructose) or when allowed to eat to caloric excess,[37] and as in humans, this diet-induced obesity leads to development of metabolic syndrome and to progression from IR and IGT to T2DM.[4,37] For example, cynomolgus and rhesus macaques fed diets high in fructose or containing trans-fatty acids gain weight or central adiposity and develop dyslipidemia,[37,85] and administration of a Western (high-fat/high-cholesterol) diet induces atherosclerosis and obesity in these animals.[50,86,87] Baboons fed high-sucrose/high-fat diets gain adiposity and develop features of metabolic syndrome within 8 weeks of exposure,[88] suggesting that they may represent a clinically relevant animal model for studying the progression of obesity to T2DM.[88] Marmosets fed diets high in fat and/or monosaccharides develop metabolic syndrome and, when fed a glucose-enriched diet, develop an obese phenotype and a prolonged hyperglycemic state as early as 16 weeks, with subsequent pancreatic islet hyperplasia and increased atherosclerotic lesion development.[89]

Pathologies and Comorbidities of Diabetes in Nonhuman Primates

Due to the similar clinical and pathologic characteristics of diabetes in humans and NHPs, and the fact that NHPs are good models to study aging and atherosclerosis,[50,87,90] NHPs are useful for studying not only diabetes characteristics and development, but also comorbidities.

In both humans and NHPs, histopathologic changes within the pancreas are restricted to the islets of Langerhans, with morphologic changes varying with diabetes type and stage of development. Islets from nondiabetic monkeys are generally cellular, with abundant immunostaining for both insulin and glucagon[25,37,59] and resemble in distribution and cellular composition islets from nondiabetic humans.[91]

The histopathologic features of T1DM in humans and NHPs are islet inflammation, which occurs through an autoimmune mechanism, lymphocyte infiltration, and selective β-cell destruction, with subsequent islet loss and reduced insulin staining.[92] In cynomolgus monkeys with T1DM, although insulin staining is significantly reduced, glucagon staining remains robust.[59] Islet amyloid does not play a role in the pathogenesis of T1DM.[37]

The histopathologic features of T2DM in humans and NHPs include islet hyperplasia and hypertrophy, islet amyloidosis, and variable insulin staining, depending on the stage of disease development.[25,37,56,59] Early in the disease, the pancreas responds to peripheral IR by increasing insulin production, and this manifests as an increased number of islets that stain intensely for insulin.[40] With continued insulin demands, amylin, which is cosecreted with insulin, accumulates, amyloid formation ensues, and the degree of islet mass replaced by amyloid correlates with both increasing IR and worsening glycemic control.[25,56,73,93] Islet amyloidosis is found in ~90% of humans with T2DM and has been documented in macaques, vervets, and baboons.[25,40,72,94–97] Type 2 diabetes mellitus monkeys with less islet amyloid and greater insulin staining generally do not require insulin therapy.[37,56] However, once islets are replaced with amyloid, less insulin staining is discernable and exogenous insulin therapy is required.[37] Despite abundant amyloid infiltration and markedly reduced insulin staining in advanced T2DM, glucagon staining remains abundant.[40]

Macrovascular disease is the leading cause of death in humans with both T1DM and T2DM, with increased progression of atherosclerosis resulting in CVD.[6,98,99] Atherosclerosis is increased in NHPs with both naturally occurring diabetes and chemically induced diabetes,[50,64,86] and when monkeys are fed an atherogenic diet, their dyslipidemia resembles that of humans with diabetes consuming a Western diet.[86] In naturally occurring diabetic primates, atherosclerotic plaques appear as fibrofatty expansions of the tunica intima with large foci of necrosis and inflammation evident in unstable lesions.[50,64] Over time, unstable plaques may rupture and thrombose, resulting in acute myocardial or cerebral infarction.[100] Although atherosclerotic plaques form in the arteries of T2DM cynomolgus monkeys fed a chow diet, little atherosclerosis forms in chow-fed nondiabetic monkeys.[64]

Microvascular disease is an ischemic process that results from endothelial and smooth muscle dysfunction in combination with vascular wall remodeling.[101] In developed countries, diabetic nephropathy is the most common cause of end-stage renal disease, and this condition also occurs in diabetic macaques.[102,103] Diabetic retinopathy and peripheral neuropathy are also occasionally seen in diabetic macaques.[104,105]

Physiological Interventions in Nonhuman Primates

In addition to similarities in development and characteristics of obesity, IR, metabolic syndrome, and T2DM in humans and NHPs, many physiological factors that predispose humans to T2DM also predispose NHPs to the disease. Key examples are outlined here.

Sex hormones affect body weight, fat distribution, and IR and influence the risk of diabetes and CVD in both humans and NHPs.[37,46,59,106–110] Nonhuman primates are uniquely important models in this area of research because their reproductive physiology is similar to humans. Old World monkeys and great apes, for example, are the only species with a menstrual cycle similar to humans.[111] This is important when assessing insulin action, because women have decreased insulin sensitivity during the luteal phase and improved sensitivity during the follicular phase of the normal menstrual cycle,[112] and similar findings have been reported in rhesus monkeys.[106]

Natural menopause has also been reported in cynomolgus and rhesus macaques, chimpanzees, and baboons,[78,113–116] and as in nondiabetic women,[117] the postmenopausal state is associated with increased IR in postmenopausal[116]

and ovariectomized NHPs.[118,119] In general, an increase in body weight and a redistribution of body fat occurs postmenopausally,[120] which may contribute to increased IR. Supplemental estrogens prevent weight gain in postmenopausal women[121] and monkeys[118,119] by reducing abdominal fat and improving insulin sensitivity.[81,122,123] Estrogen treatment in postmenopausal monkeys also improves lipoprotein profiles.[90,124]

Psychosocial stress also contributes to IR and risk of developing T2DM in humans and NHPs.[62,125–128] In NHPs, housing situations can be stressful, and this varies by species. For example, when living under crowded social conditions, young vervet and patas monkeys, species that emphasize avoidance and spatial dispersion as social strategies,[129] are more insulin resistant than their noncrowded counterparts.[37] By contrast, for macaques and baboons that live in large aggregations, interventions that disrupt their species-typical lifestyle are more stressful and can induce metabolic abnormalities.[130]

Caloric restriction can be a successful adjunct for management of metabolic abnormalities associated with T2DM in both humans and NHPs.[131–135] Indeed, a consistent physiological change observed with caloric restriction in cynomolgus and rhesus monkeys is a lowering of plasma glucose and insulin and an increase in insulin sensitivity.[136–139]

Early life experiences also effect subsequent development of metabolic syndrome in marmosets[140] and cynomolgus monkeys.[141] For example, in marmosets, a fetal programming paradigm, developed using a brief antenatal exposure to dexamethasone, did not affect weight gain during the gestational period, but offspring of mothers treated late in pregnancy showed higher rates of weight gain postnatally and elevated glucose concentrations by 24 months.[140] In cynomolgus monkeys, infants reared by mothers consuming animal-based protein (casein and whey) gained less weight and had better glycemic and lipid profiles than those reared by mothers consuming plant-based protein (soy).[141]

Pharmacologic Interventions in Nonhuman Primates

Because development and characteristics of obesity, IR, metabolic syndrome, and T2DM in humans and NHPs are similar, obese insulin-resistant and diabetic NHPs are ideal animal models for studying potential therapeutic interventions. Indeed, NHPs have been used to study the consequences of drugs that directly increase insulin production, increase insulin sensitivity, reduce hepatic glucose production, reduce appetite, increase energy expenditure, and alter lipid metabolism, and there has been a high translation of efficacy (as well as nonefficacy) in NHPs to efficacy (and nonefficacy) in the clinic.[38] Key examples are outlined here.

Peroxisome proliferator-activated receptor (PPAR) γ is a nuclear receptor found in tissues important to insulin action and is the therapeutic target of the glitazone class of antidiabetic agents.[142–146] Peroxisome proliferator-activated receptor γ is highly expressed in brown and white adipose tissue and is thought to trigger adipocyte differentiation, promote lipid storage, and modulate insulin action.[147,148] Improved glycemic control has been reported in patients treated with the PPARγ agonists rosiglitazone and pioglitazone[149,150] and also in cynomolgus[37,151,152] and rhesus[153,154] monkeys. The fluid retention and edema that occur in humans after treatment with PPARγ agonists also occur in NHPs, rendering NHPs important models of tolerability for this class of therapeutics.[152]

Peroxisome proliferator-activated receptor α is highly expressed in liver, skeletal muscle, and heart; is activated by various naturally occurring lipids; potentiates fatty acid oxidation; modulates lipoprotein metabolism; and is the therapeutic target of the fibrate class of antidyslipidemic agents.[143–145] Use of NHPs in studying PPARα agonists is of particular importance since, in rodents, PPARα agonists induce peroxisomal fatty acid oxidation enzymes, leading to peroxisomal proliferation, hepatomegaly, and hepatic carcinomas,[142,144] an effect that does not occur in either humans or NHPs.[142,144] Furthermore, due to differences in the PPARα response elements in the rodent and primate apolipoprotein A1 promoters, rodents and primates respond differently, and in opposite directions, to the actions of PPARα agonists on HDL metabolism.[142,144]

In clinical studies, fibrates such as fenofibrate and bezafibrate reduce plasma triglycerides, reduce VLDL and LDL cholesterol, increase HDL cholesterol through increases in apolipoprotein A1 production, and favorably affect atherosclerotic progression and cardiovascular outcomes.[142,144,155–160] Similarly, in vervets, fenofibrate increases HDL cholesterol and decreases triglycerides,[161] and in obese rhesus monkeys, fenofibrate lowers plasma triglycerides and LDL cholesterol, increases HDL cholesterol, and ameliorates hyperinsulinemia.[143] Although fenofibrate

is not specific for PPARα activation and shows similar PPARγ activation,[144,156] the ability of PPARα agonism to favorably affect glycemic control independent of associated PPARγ agonism was confirmed using a highly specific PPARα agonist, CP-900691.[162] In addition to reducing plasma triglycerides and triglyceride-rich lipoproteins and elevating HDL cholesterol in diabetic cynomolgus monkeys, CP-900691 also improved glycemic control and reduced exogenous insulin requirement.[162]

Mixed PPARα/γ agonists have also been evaluated in NHP models of T2DM and have recapitulated the combined efficacy of rosiglitazone and fenofibrate.[151,163] For example, in prediabetic rhesus monkeys, the mixed PPARα/γ agonist, TAK-559, increased HDL cholesterol and reduced plasma triglycerides, triglyceride-rich lipoproteins, hyperinsulinemia, and IR after 12 weeks of treatment.[164]

The endocannabinoid system plays a key role in energy homeostasis by modulating both food intake and energy expenditure.[165–170] Cannabinoid 1 (CB_1) receptor antagonists exhibit pharmacological properties favorable to treatment of obesity and diabetes,[171,172] but the relative contribution of their effects on appetite and energy expenditure are uncertain and difficult to assess clinically. Studies evaluating the CB_1 receptor antagonist, PF-95453, in obese, insulin-resistant cynomolgus macaques demonstrated that, as in humans, the effects of CB_1 receptor blockade on energy metabolism in monkeys involve both drug-dependent reductions in food intake and food intake-independent effects on energy expenditure.[173]

Oversecretion of glucagon in the postabsorptive state leads to nocturnal hyperglycemia, and there is evidence that increased glucagon contributes to T2DM in humans through altered glucose sensing and β-cell function defects.[174] In addition to its insulinotropic effects, the incretin hormone, glucagon-like peptide-1 (GLP-1) also suppresses glucagon release, both of which occur in a glucose-dependent manner, resulting in lower plasma glucose without increased risk of hypoglycemia.[174] This favorable action, which was initially reported in rodents, baboons, and humans, has resulted in the use of GLP-1 analogs (e.g., exenatide) clinically.[174,175] In one study, exenatide, administered subcutaneously to cynomolgus macaques for 2 weeks at clinically relevant doses (1 μg/kg three times daily), reduced glucose excursion and increased insulin responses to intravenously administered glucose in insulin-resistant monkeys and markedly reduced insulin requirements in diabetic monkeys (unpublished observations of Wagner and Harwood).

Summary

With the increased incidence of human obesity and diabetes, animal models are especially relevant to studying the interactions among obesity, IR, aging, and associated comorbidities. Nonhuman primates are particularly important models because the metabolic progression from IR through IGT to overt diabetes, the pathological changes that occur in the pancreatic islets as diabetes develops, and the comorbidities that manifest as a consequence of disease progression are all comparable to characteristics of the disease in humans. Additionally, studies of atherosclerosis progression (as well as CVD risk factor intervention studies) and studies of other lesion development such as diabetic microangiopathies, retinopathies, nephropathies, and vasculitides are all quite plausible in NHPs. In addition, the similar pathogenetic characteristics and accompanying risk factors observed in both humans and NHPs make NHPs unique models for studying early development and environmental factors that affect obesity and diabetes and for studying potential pharmacological interventions. Nonhuman primates therefore represent important animal models for studying disease development, pathogenesis, risk factors, comorbidities, and potential therapies.

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References:

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012;35 Suppl 1:S64–71.
3. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
4. Harwood HJ Jr. Treating the metabolic syndrome: acetyl-CoA carboxylase inhibition. Expert Opin Ther Targets. 2005;9(2):267–81.
5. Centers for Disease Control and Prevention. National health and nutrition examination survey. http://www.cdc.gov/nchs/nhanes.htm.

6. Bierman EL. George Lyman Duff Memorial Lecture. Atherogenesis in diabetes. Arterioscler Thromb. 1992;12(6):647–56.
7. Cefalu WT. Animal models of type 2 diabetes: clinical presentation and pathophysiological relevance to the human condition. ILAR J. 2006;47(3):186–98.
8. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104(6):787–94.
9. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med. 2003;163(4):427–36.
10. DeFronzo RA. Pathogenesis of type 2 diabetes: Metabolic and molecular implications for identifying diabetes genes. Diabetes Rev. 1997;5(3):177–269.
11. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241(19):2035–8.
12. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes. 1992;41(6):715–22.
13. Pennathur S, Heinecke JW. Mechanisms of oxidative stress in diabetes: implications for the pathogenesis of vascular disease and antioxidant therapy. Front Biosci. 2004;9:565–74.
14. Rowe PA, Kavanagh K, Zhang L, Harwood HJ Jr, Wagner JD. Short-term hyperglycemia increases arterial superoxide production and iron dysregulation in atherosclerotic monkeys. Metabolism. 2011;60(8):1070–80.
15. Brownlee M. The pathogenesis of diabetic complications: a unifying mechanism. Diabetes. 2005;54:1615–25.
16. Kaneko JJ. Carbohydrate metabolism. In: Loeb WF, Quimby FW, eds. The clinical chemistry of laboratory animals. 2nd ed. Philadelphia: Taylor and Francis; 1999.
17. Hoenig M, Thomaseth K, Waldron M, Ferguson DC. Insulin sensitivity, fat distribution, and adipocytokine response to different diets in lean and obese cats before and after weight loss. Am J Physiol Regul Integr Comp Physiol. 2007;292(1):R227–34.
18. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J Clin Invest. 1997;100(5):1166–73.
19. Henson MS, O'Brien TD. Feline models of type 2 diabetes mellitus. ILAR J. 2006;47(3):234–42.
20. Johnson KH, Hayden DW, O'Brien TD, Westermark P. Spontaneous diabetes mellitus-islet amyloid complex in adult cats. Am J Pathol. 1986;125(2):416–9.
21. Johnson KH, O'Brien TD, Betsholtz C, Westermark P. Islet amyloid, islet-amyloid polypeptide, and diabetes mellitus. N Engl J Med. 1989;321(8):513–8.
22. O'Brien TD, Hayden DW, Johnson KH, Stevens JB. High dose intravenous glucose tolerance test and serum insulin and glucagon levels in diabetic and non-diabetic cats: Relationships to insular amyloidosis. Vet Pathol. 1985;22(3):250–61.
23. O'Brien TD, Hayden DW, Johnson KH, Fletcher TF. Immuno-histochemical morphometry of pancreatic endocrine cells in diabetic, normoglycaemic glucose-intolerant and normal cats. J Comp Pathol. 1986;96(4):357–69.
24. O'Brien TD, Butler PC, Westermark P, Johnson KH. Islet amyloid polypeptide: A review of its biology and potential roles in the pathogenesis of diabetes mellitus. Vet Pathol. 1993;30(4):317–32.
25. O'Brien TD, Wagner JD, Litwak KN, Carlson CS, Cefalu WT, Jordan K, Johnson KH, Butler PC. Islet amyloid and islet amyloid polypeptide in cynomolgus macaques (Macaca fascicularis): an animal model of human non-insulin-dependent diabetes mellitus. Vet Pathol. 1996;33(5):479–85.
26. Hoenig M. Comparative aspects of diabetes mellitus in dogs and cats. Mol Cell Endocrinol. 2002;197(1-2):221–9.
27. Marmor M, Willeberg P, Glickman LT, Priester WA, Cypess RH, Hurvitz AI. Epizootiologic patterns of diabetes mellitus in dogs. Am J Vet Res. 1982;43(3):465–70.
28. Verkest KR, Rand JS, Fleeman LM, Morton JM. Spontaneously obese dogs exhibit greater postprandial glucose, triglyceride, and insulin concentrations than lean dogs. Domest Anim Endocrinol. 2012;42(2):103–12.
29. Ionut V, Liu H, Mooradian V, Castro AV, Kabir M, Stefanovski D, Zheng D, Kirkman EL, Bergman RN. Novel canine models of obese prediabetes and mild type 2 diabetes. Am J Physiol Endocrinol Metab. 2010;298(1):E38–48.
30. Bellinger DA, Merricks EP, Nichols TC. Swine models of type 2 diabetes mellitus: Insulin resistance, glucose tolerance, and cardio-vascular complications. ILAR J. 2006;47(3):243–58.
31. Prentice AM, Rayco-Solon P, Moore SE. Insights from the developing world: Thrifty genotypes and thrifty phenotypes. Proc Nutr Soc. 2005;64(2):153–61.
32. Phillips RW, Panepinto LM, Spangler R, Westmoreland N. Yucatan miniature swine as a model for the study of human diabetes mellitus. Diabetes. 1982;31(Suppl 1 Pt 2):30–6.
33. Phillips RW, Panepinto LM. Swine as a model for human diabetes. In: Swine in biomedical research. Vol. 1. New York: Plenum Press; 1986.
34. Gerrity RG, Naito HK, Richardson M, Schwartz CJ. Dietary induced atherogenesis in swine. Morphology of the intima in prelesion stages. Am J Pathol. 1979;95(3):775–92.
35. Prescott MF, Hasler-Rapacz J, von Linden-Reed J, Rapacz J. Familial hypercholesterolemia associated with coronary atherosclerosis in swine bearing different alleles for apolipoprotein B. Ann N Y Acad Sci. 1995;748:283–93.
36. Prescott MF, McBride CH, Hasler-Rapacz J, Von Linden J, Rapacz J. Development of complex atherosclerotic lesions in pigs with inherited hyper-LDL cholesterolemia bearing mutant alleles for apolipoprotein B. Am J Pathol. 1991;139(1):139–47.
37. Wagner JD, Kavanagh K, Ward GM, Auerbach BJ, Harwood HJ Jr, Kaplan JR. Old world nonhuman primate models of type 2 diabetes mellitus. ILAR J. 2006;47(3):259–71.
38. Wagner JD, Cann JA, Zhang L, Harwood HJ Jr. Diabetes and obesity research using nonhuman primates. In: Abee CR, Mansfield K, Tardif SD, Morris T, eds. Nonhuman primates in biomedical research Volume 2: Diseases. 2nd ed. 2012. Elsevier. Chapter 14, pp 699–732.
39. Kavanagh K, Fairbanks LA, Bailey JN, Jorgensen MJ, Wilson M, Zhang L, Rudel LL, Wagner JD. Characterization and heritability of obesity and associated risk factors in vervet monkeys. Obesity (Silver Spring). 2007;15(7):1666–74.
40. Cann JA, Kavanagh K, Jorgensen MJ, Mohanan S, Howard TD, Gray SB, Hawkins GA, Fairbanks LA, Wagner JD. Clinico-pathologic characterization of naturally occurring diabetes mellitus in vervet monkeys. Vet Pathol. 2010;47(4):713–8.
41. Stokes WS. Spontaneous diabetes mellitus in a baboon (Papio cynocephalus anubis). Lab Anim Sci. 1986;36(5):529–33.
42. Cai G, Cole SA, Tejero ME, Proffitt JM, Freeland-Graves JH, Blangero J, Comuzzie AG. Pleiotropic effects of genes for insulin resistance on adiposity in baboons. Obes Res. 2004;12(11):1766–72.

43. Tejero ME, Voruganti VS, Rodríguez-Sánchez IP, Proffitt JM, Blangero J, Cox LA, Mahaney MC, Rogers J, VandeBerg JL, Cole SA, Comuzzie AG. Genetics of variation in adiponectin in pedigreed baboons: evidence for pleiotropic effects on adipocyte volume and serum adiponectin. Heredity (Edinb). 2008;100(4):382–9.
44. Comuzzie AG, Cole SA, Martin L, Carey KD, Mahaney MC, Blangero J, VandeBerg JL. The baboon as a nonhuman primate model for the study of the genetics of obesity. Obes Res. 2003;11(1):75–80.
45. Pirarat N, Kesdangsakolwut S, Chotiapisitkul S, Assarasakorn S. Spontaneous diabetes mellitus in captive Mandrillus sphinx monkeys: a case report. J Med Primatol. 2008;37(3):162–5.
46. Abbott DH, Foong SC, Barnett DK, Dumesic DA. Nonhuman primates contribute unique understanding to anovulatory infertility in women. ILAR J. 2004;45(2):116–31.
47. Tardif SD, Power ML, Ross CN, Rutherford JN, Layne-Colon DG, Paulik MA. Characterization of obese phenotypes in a small nonhuman primate, the common marmoset (callithrix jacchus). Obesity (Silver Spring). 2009;17(8):1499–505.
48. Tardif SD, Mansfield KG, Ratnam R, Ross CN, Ziegler TE. The marmoset as a model of aging and age-related diseases. ILAR J. 2011;52(1):54–65.
49. Bodkin NL. The rhesus monkey (Macaca mulatta):a unique and valuable model for the study of spontaneous diabetes mellitus and associated conditions. In: Sima AF, Shafrir E, eds. Animal models in diabetes: a primer. Singapore: Taylor & Francis; 2000.
50. Clarkson TB, Koritnik DR, Weingand KW, Miller LC. Nonhuman primate models of atherosclerosis: Potential for the study of diabetes mellitus and hyperinsulinemia. Metabolism. 1985;34(12 Suppl 1):51–9.
51. Rosenblum IY, Barbolt TA, Howard CF Jr. Diabetes mellitus in the chimpanzee (Pan troglodytes). J Med Primatol. 1981;10(2-3):93–101.
52. McTighe MS, Hansen BC, Ely JJ, Lee DR. Determination of hemoglobin A1c and fasting blood glucose reference intervals in captive chimpanzees (Pan troglodytes). J Am Assoc Lab Anim Sci. 2011;50(2):165–70.
53. Howard CF Jr, Yasuda M. Diabetes mellitus in nonhuman primates: Recent research advances and current husbandry practices. J Med Primatol. 1990;19(7):609–25.
54. Hamilton CL, Ciaccia P. The course of development of glucose intolerance in the monkey (Macaca mulatta). J Med Primatol. 1978;7(3):165–73.
55. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes. 2001;50(5):1126–33.
56. Wagner JD, Carlson CS, O'Brien TD, Anthony MS, Bullock BC, Cefalu WT. Diabetes mellitus and islet amyloidosis in cynomolgus monkeys. Lab Anim Sci. 1996;46(1):36–41.
57. Banks WA, Altmann J, Sapolsky RM, Phillips-Conroy JE, Morley JE. Serum leptin levels as a marker for a syndrome X-like condition in wild baboons. J Clin Endocrinol Metab. 2003;88(3):1234–40.
58. Hansen BC, Bodkin NL. Heterogeneity of insulin responses: Phases leading to type 2 (non-insulin-dependent) diabetes mellitus in the rhesus monkey. Diabetologia. 1986;29(10):713–9.
59. Wagner JD, Cline JM, Shadoan MK, Bullock BC, Rankin SE, Cefalu WT. Naturally occurring and experimental diabetes in cynomolgus monkeys: A comparison of carbohydrate and lipid metabolism and islet pathology. Toxicol Pathol. 2001;29(1):142–8.
60. Wagner JD, Jayo MJ, Bullock BC, Washburn SA. Gestational diabetes mellitus in a cynomolgus monkey with group A streptococcal metritis and hemolytic uremic syndrome. J Med Primatol. 1992;21(7-8):371–4.
61. Kessler MJ, Howard CF Jr, London WT. Gestational diabetes mellitus and impaired glucose tolerance in an aged Macaca mulatta. J Med Primatol. 1985;14(5):237–44.
62. Bauer SA, Arndt TP, Leslie KE, Pearl DL, Turner PV. Obesity in rhesus and cynomolgus macaques: a comparative review of the condition and its implications for research. Comp Med. 2011;61(6):514–26.
63. Howard CF Jr. Diabetes in Macaca nigra: metabolic and histologic changes. Diabetologia. 1974;10 Suppl:671–7.
64. Howard CF. Atherosclerosis and insulin in primates with diabetes mellitus. Metabolism. 1985;34(12 Suppl 1):60–6.
65. Riley WJ, Maclaren NK. Islet cell autoantibodies. In: Samols E, ed. The endocrine pancreas. New York: Raven Press; 1991.
66. Kaufman D, Smith EL, Gohil BC, Banerji M, Coplan JD, Kral JG, Rosenblum LA. Early appearance of the metabolic syndrome in socially reared bonnet macaques. J Clin Endocrinol Metab. 2005;90(1):404–8.
67. Kaufman D, Banerji MA, Shorman I, Smith EL, Coplan JD, Rosenblum LA, Kral JG. Early-life stress and the development of obesity and insulin resistance in juvenile bonnet macaques. Diabetes. 2007;56(5):1382–6.
68. Tanaka Y, Ohto H, Kohno M, Cho F, Honjo S. Spontaneous diabetes mellitus in cynomolgus monkeys (macaca fascicularis). Jikken Dobutsu. 1986;35(1):11–9.
69. Yasuda M, Takaoka M, Fujiwara T, Mori M. Occurrence of spontaneous diabetes mellitus in a cynomolgus monkey (Macaca fascicularis) and impaired glucose tolerance in its descendants. J Med Primatol. 1988;17(6):319–32.
70. Bagdade JD, Wagner JD, Rudel LL, Clarkson TB. Accelerated cholesteryl ester transfer and altered lipoprotein composition in diabetic cynomolgus monkeys. J Lipid Res. 1995;36(4):759–66.
71. Hansen BC, Bodkin NL. Beta-cell hyperresponsiveness: Earliest event in development of diabetes in monkeys. Am J Physiol. 1990;259(3 Pt 2):R612–7.
72. De Koning EJ, Bodkin NL, Hansen BC, Clark A. Diabetes mellitus in Macaca mulatta monkeys is characterised by islet amyloidosis and reduction in beta-cell population. Diabetologia. 1993;36(5):378–84.
73. Clark A, Nilsson MR. Islet amyloid: a complication of islet dysfunction or an aetiological factor in type 2 diabetes? Diabetologia. 2004;47(2):157–69.
74. Ramsey JJ, Laatsch JL, Kemnitz JW. Age and gender differences in body composition, energy expenditure, and glucoregulation of adult rhesus monkeys. J Med Primatol. 2000;29(1):11–9.
75. Tigno XT, Gerzanich G, Hansen BC. Age-related changes in metabolic parameters of nonhuman primates. J Gerontol A Biol Sci Med Sci. 2004;59(11):1081–8.
76. Kemnitz JW, Francken GA. Characteristics of spontaneous obesity in male rhesus monkeys. Physiol Behav. 1986;38(4):477–83.
77. Howard CF Jr, Kessler MJ, Schwartz S. Carbohydrate impairment and insulin secretory abnormalities among Macaca mulatta from Cayo Santiago. Am J Primatol. 1986;11(2):147–62.
78. Kemnitz JW, Gibber JR, Lindsay KA, Eisele SG. Effects of ovarian hormones on eating behaviors, body weight, and glucoregulation in rhesus monkeys. Horm Behav. 1989;23(2):235–50.
79. Skyler JS, O'Sullivan MJ, Holsinger KK. The relationship between maternal glycemia and macrosomia. Diabetes Care. 1980;3(3):433–4.
80. Litwak KN, Cefalu WT, Wagner JD. Streptozotocin-induced diabetes mellitus in cynomolgus monkeys: Changes in carbohydrate metabolism, skin glycation, and pancreatic islets. Lab Anim Sci. 1998;48(2):172–8.

81. Contreras JL, Smyth CA, Curiel DT, Eckhoff DE. Nonhuman primate models in type 1 diabetes research. ILAR J. 2004;45(3):334–42.
82. Gaur LK, Nepom GT, Lernmark A. Low-dose streptozotocin induces sustained hyperglycemia in Macaca nemestrina. Autoimmunity. 2001;33(2):103–14.
83. V on Herrath M, Nepom GT. Animal models of human type 1 diabetes. Nat Immunol. 2009;10(2):129–32.
84. Saisho Y, Butler AE, Manesso E, Galasso R, Zhang L, Gurlo T, Toffolo GM, Cobelli C, Kavanagh K, Wagner JD, Butler PC. Relationship between fractional pancreatic beta cell area and fasting plasma glucose concentration in monkeys. Diabetologia. 2010;53(1):111–4.
85. Kavanagh K, Jones KL, Sawyer J, Kelley K, Carr JJ, Wagner JD, Rudel LL. Trans fat diet induces abdominal obesity and changes in insulin sensitivity in monkeys. Obesity (Silver Spring). 2007;15(7):1675–84.
86. Litwak KN, Cefalu WT, Wagner JD. Chronic hyperglycemia increases arterial low-density lipoprotein metabolism and atherosclerosis in cynomolgus monkeys. Metabolism. 1998;47(8):947–54.
87. Cefalu WT, Wagner JD. Aging and atherosclerosis in human and nonhuman primates. Age. 1997;20:15–28.
88. Higgins PB, Bastarrachea RA, Lopez-Alvarenga JC, Garcia-Forey M, Proffitt JM, Voruganti VS, Tejero ME, Mattern V, Haack K, Shade RE, Cole SA, Comuzzie AG. Eight week exposure to a high sugar high fat diet results in adiposity gain and alterations in metabolic biomarkers in baboons (Papio hamadryas sp.). Cardiovasc Diabetol. 2010;9:71.
89. Wachtman LM, Kramer JA, Miller AD, Hachey AM, Curran EH, Mansfield KG. Differential contribution of dietary fat and monosaccharide to metabolic syndrome in the common marmoset (Callithrix jacchus). Obesity (Silver Spring). 2011;19(6):1145–56.
90. Wagner JD. Effects of ERT and HRT on cardiovascular risk factors and coronary artery atherosclerosis. Menopausal Med. 2001;10:12–5.
91. Cabrera O, Berman DM, Kenyon NS, Ricordi C, Berggren PO, Caicedo A. The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proc Natl Acad Sci U S A. 2006;103(7):2334–9.
92. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293–300.
93. Hull RL, Westermark GT, Westermark P, Kahn SE. Islet amyloid: A critical entity in the pathogenesis of type 2 diabetes. J Clin Endocrinol Metab. 2004;89(8):3629–43.
94. Cromeens DM, Stephens LC. Insular amyloidosis and diabetes mellitus in a crab-eating macaque (Macaca fascicularis). Lab Anim Sci. 1985;35(6):642–5.
95. Howard CF Jr, Van Bueren A. Changes in islet cell composition during development of diabetes in Macaca nigra. Diabetes. 1986;35(2):165–71.
96. Hubbard GB, Steele KE, Davis KJ 3rd, Leland MM. Spontaneous pancreatic islet amyloidosis in 40 baboons. J Med Primatol. 2002;31(2):84–90.
97. Ohagi S, Nishi M, Bell GI, Ensinck JW, Steiner DF. Sequences of islet amyloid polypeptide precursors of an Old World monkey, the pig-tailed macaque (Macaca nemestrina), and the dog (Canis familiaris). Diabetologia. 1991;34(8):555–8.
98. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22(2):233–40.
99. Danaei G, Lawes CM, Vander Hoorn S, Murray CJ, Ezzati M. Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. Lancet. 2006;368(9548):1651–9.
100. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481–8.
101. Matrougui K. Diabetes and microvascular pathophysiology: role of epidermal growth factor receptor tyrosine kinase. Diabetes Metab Res Rev. 2010;26(1):13–6.
102. Brown WV. Microvascular complications of diabetes mellitus: renal protection accompanies cardiovascular protection. Am J Cardiol. 2008;102(12A):10L–13L.
103. Cusumano AM, Bodkin NL, Hansen BC, Iotti R, Owens J, Klotman PE, Kopp JB. Glomerular hypertrophy is associated with hyperinsulinemia and precedes overt diabetes in aging rhesus monkeys. Am J Kidney Dis. 2002;40(5):1075–85.
104. Johnson MA, Lutty GA, McLeod DS, Otsuji T, Flower RW, Sandagar G, Alexander T, Steidl SM, Hansen BC. Ocular structure and function in an aged monkey with spontaneous diabetes mellitus. Exp Eye Res. 2005;80(1):37–42.
105. Kim SY, Johnson MA, McLeod DS, Alexander T, Hansen BC, Lutty GA. Neutrophils are associated with capillary closure in spontaneously diabetic monkey retinas. Diabetes. 2005;54(5):1534–42.
106. Bruns CM, Kemnitz JW. Sex hormones, insulin sensitivity, and diabetes mellitus. ILAR J. 2004;45(2):160–9.
107. Kemnitz JW, Holston KA, Colman RJ. Nutrition, aging and reproduction in rhesus monkeys. In: Hansel W, Bray GA, Ryan DH, eds. Pennington center nutrition series. Part IV. Evolution of research methods in nutrition and reproduction. Nutrition and reproduction Vol. 8. Baton Rouge: Louisiana State University Press; 1998.
108. Wagenknecht LE, Langefeld CD, Scherzinger AL, Norris JM, Haffner SM, Saad MF, Bergman RN. Insulin sensitivity, insulin secretion, and abdominal fat: The Insulin Resistance Atherosclerosis Study (IRAS) Family Study. Diabetes. 2003;52(10):2490–6.
109. Arifin E, Shively CA, Register TC, Cline JM. Polycystic ovary syndrome with endometrial hyperplasia in a cynomolgus monkey (Macaca fascicularis). Vet Pathol. 2008;45(4):512–5.
110. Fujisawa S, Atsumi T, Kadoma Y. Metabolic abnormalities among free-ranging Macaca mulatta on Cayo Santiago: comparisons with Macaca mulatta at Sabana Seca. Am J Primatol. 1990;21(3):189–200.
111. Weinbauer GF, Niehoff M, Niehaus M, Srivastav S, Fuchs A, Van Esch E, Cline JM. Physiology and endocrinology of the ovarian cycle in macaques. Toxicol Pathol. 2008;36(7S):7S–23S.
112. Valdes CT, Elkind-Hirsch KE. Intravenous glucose tolerance test-derived insulin sensitivity changes during the menstrual cycle. J Clin Endocrinol Metab. 1991;72(3):642–6.
113. Chen LD, Kushwaha RS, McGill HC Jr, Rice KS, Carey KD. Effect of naturally reduced ovarian function on plasma lipoprotein and 27-hydroxycholesterol levels in baboons (Papio sp.). Atherosclerosis. 1998;136(1):89–98.
114. Gilardi KV, Shideler SE, Valverde CR, Roberts JA, Lasley BL. Characterization of the onset of menopause in the rhesus macaque. Biol Reprod. 1997;57(2):335–40.
115. Gould KG, Flint M, Graham CE. Chimpanzee reproductive senescence: A possible model for evolution of the menopause. Maturitas. 1981;3(2):157–66.
116. Kavanagh K, Koudy Williams J, Wagner JD. Naturally occurring menopause in cynomolgus monkeys: Changes in hormone, lipid, and carbohydrate measures with hormonal status. J Med Primatol. 2005;34(4):171–7.

117. Lindheim SR, Buchanan TA, Duffy DM, Vijod MA, Kojima T, Stanczyk FZ, Lobo RA. Comparison of estimates of insulin sensitivity in pre- and postmenopausal women using the insulin tolerance test and the frequently sampled intravenous glucose tolerance test. J Soc Gynecol Investig. 1994;1(2):150–4.

118. Wagner JD, Martino MA, Jayo MJ, Anthony MS, Clarkson TB, Cefalu WT. The effects of hormone replacement therapy on carbohydrate metabolism and cardiovascular risk factors in surgically postmenopausal cynomolgus monkeys. Metabolism. 1996;45(10):1254–62.

119. Wagner JD, Cefalu WT, Anthony MS, Litwak KN, Zhang L, Clarkson TB. Dietary soy protein and estrogen replacement therapy improve cardiovascular risk factors and decrease aortic cholesteryl ester content in ovariectomized cynomolgus monkeys. Metabolism. 1997;46(6):698–705.

120. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr. 1992;55(5):950–4.

121. Haarbo J, Marslew U, Gotfredsen A, Christiansen C. Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. Metabolism. 1991;40(12):1323–6.

122. Matute ML, Kalkhoff RK. Sex steroid influence on hepatic gluconeogenesis and glycogen formation. J Lab Clin Med. 1971;78(6):997–8.

123. Mauro L, Salerno M, Panno ML, Bellizzi D, Sisci D, Miglietta A, Surmacz E, Andò S. Estradiol increases IRS-1 gene expression and insulin signaling in breast cancer cells. Biochem Biophys Res Commun. 2001;288(3):685–9.

124. Wagner JD, Kaplan JR, Burkman RT. Reproductive hormones and cardiovascular disease mechanism of action and clinical implications. Obstet Gynecol Clin North Am. 2002;29(3):475–93.

125. Björntorp P. Neuroendocrine perturbations as a cause of insulin resistance. Diabetes Metab Res Rev. 1999;15(6):427–41.

126. Rosmond R. Stress induced disturbances of the HPA axis: a pathway to type 2 diabetes? Med Sci Monit. 2003;9(2):RA35–9.

127. Chrousos GP. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Obes Relat Metab Disord. 2000;24 Suppl 2:S50–5.

128. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. Psychosom Med. 2004;66(3):316–22.

129. Kaplan JR. Dominance and affiliation in the Cercopithecini and Papionini: a comparative examination. Monogr Primatol. 1987;10:127–50.

130. Kaplan JR, Manuck SB. Status, stress, and atherosclerosis: the role of environment and individual behavior. Ann N Y Acad Sci. 1999;896:145–61.

131. Bodkin NL, Alexander TM, Ortmeyer HK, Johnson E, Hansen BC. Mortality and morbidity in laboratory-maintained rhesus monkeys and effects of long-term dietary restriction. J Gerontol A Biol Sci Med Sci. 2003;58(3):212–9.

132. Cefalu WT, Wang ZQ, Bell-Farrow AD, Collins J, Morgan T, Wagner JD. Caloric restriction and cardiovascular aging in cynomolgus monkeys (Macaca fascicularis): metabolic, physiologic, and atherosclerotic measures from a 4-year intervention trial. J Gerontol A Biol Sci Med Sci. 2004;59(10):1007–14.

133. Gresl TA, Colman RJ, Roecker EB, Havighurst TC, Huang Z, Allison DB, Bergman RN, Kemnitz JW. Dietary restriction and glucose regulation in aging rhesus monkeys: a follow-up report at 8.5 yr. Am J Physiol Endocrinol Metab. 2001;281(4):E757–65.

134. Hansen BC, Bodkin NL, Ortmeyer HK. Calorie restriction in nonhuman primates: Mechanisms of reduced morbidity and mortality. Toxicol Sci. 1999;52(2 Suppl):56–60.

135. Wagner JD, Bagdade JD, Litwak KN, Zhang L, Bell-Farrow AD, Wang ZQ, Cefalu WT. Increased glycation of plasma lipoproteins in diabetic cynomolgus monkeys. Lab Anim Sci. 1996;46(1):31–5.

136. Bodkin NL, Ortmeyer HK, Hansen BC. Long-term dietary restriction in older-aged rhesus monkeys: effects on insulin resistance. J Gerontol A Biol Sci Med Sci. 1995;50(3):B142–7.

137. Kemnitz JW, Elson DF, Roecker EB, Baum ST, Bergman RN, Meglasson MD. Pioglitazone increases insulin sensitivity, reduces blood glucose, insulin, and lipid levels, and lowers blood pressure, in obese, insulin-resistant rhesus monkeys. Diabetes. 1994;43(2):204–11.

138. Lane MA, Black A, Handy A, Tilmont EM, Ingram DK, Roth GS. Caloric restriction in primates. Ann N Y Acad Sci. 2001;928:287–95.

139. Wang ZQ, Floyd ZE, Qin J, Liu X, Yu Y, Zhang XH, Wagner JD, Cefalu WT. Modulation of skeletal muscle insulin signaling with chronic caloric restriction in cynomolgus monkeys. Diabetes. 2009;58(7):1488–98.

140. Nyirenda MJ, Carter R, Tang JI, de Vries A, Schlumbohm C, Hillier SG, Streit F, Oellerich M, Armstrong VW, Fuchs E, Seckl JR. Prenatal programming of metabolic syndrome in the common marmoset is associated with increased expression of 11beta-hydroxysteroid dehydrogenase type 1. Diabetes. 2009;58(12):2873–9.

141. Wagner JD, Jorgensen MJ, Cline JM, Lees CJ, Franke AA, Zhang L, Ayers MR, Schultz C, Kaplan JR. Effects of soy vs. casein protein on body weight and glycemic control in female monkeys and their offspring. Am J Primatol. 2009;71(9):802–11.

142. Corton JC, Anderson SP, Stauber A. Central role of peroxisome proliferator-activated receptors in the actions of peroxisome proliferators. Annu Rev Pharmacol Toxicol. 2000;40:491–518.

143. Winegar DA, Brown PJ, Wilkison WO, Lewis MC, Ott RJ, Tong WQ, Brown HR, Lehmann JM, Kliewer SA, Plunket KD, Way JM, Bodkin NL, Hansen BC. Effects of fenofibrate on lipid parameters in obese rhesus monkeys. J Lipid Res. 2001;42(10):1543–51.

144. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J Med Chem. 2000;43(4):527–50.

145. Harwood HJ Jr, Hamanaka ES. Modulators of dyslipidemia. Emerg Drug. 1998;3:147–72.

146. Picard F, Auwerx J. PPAR(gamma) and glucose homeostasis. Annu Rev Nutr. 2002;22:167–97.

147. Lee CH, Olson P, Evans RM. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. Endocrinology. 2003;144(6):2201–7.

148. Torra IP, Chinetti G, Duval C, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors: From transcriptional control to clinical practice. Curr Opin Lipidol. 2001;12(3):245–54.

149. Goldstein BJ. Rosiglitazone. Int J Clin Pract. 2000;54(5):333–7.

150. Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. Diabetologia. 2000;43(3):278–84.

151. Gee MK, Zhang L, Rankin SE, Collins JN, Kauffman RF, Wagner JD. Rosiglitazone treatment improves insulin regulation and dyslipidemia in type 2 diabetic cynomolgus monkeys. Metabolism. 2004;53(9):1121–5.

152. Kavanagh K, Brown KK, Berquist ML, Zhang L, Wagner JD. Fluid compartmental shifts with efficacious pioglitazone therapy in overweight monkeys: implications for peroxisome proliferator-activated receptor-gamma agonist use in prediabetes. Metabolism. 2010;59(6):914–20.

153. Kemnitz JW, Roecker EB, Weindruch R, Elson DF, Baum ST, Bergman RN. Dietary restriction increases insulin sensitivity and lowers blood glucose in rhesus monkeys. Am J Physiol. 1994;266(4 Pt 1):E540–7.

154. Ortmeyer HK, Bodkin NL, Haney J, Yoshioka S, Horikoshi H, Hansen BC. A thiazolidinedione improves *in vivo* insulin action on skeletal muscle glycogen synthase in insulin-resistant monkeys. Int J Exp Diabetes Res. 2000;1(3):195–202.

155. Faergeman O. Hypertriglyceridemia and the fibrate trials. Curr Opin Lipidol. 2000;11(6):609–14.

156. Jones AB. Peroxisome proliferator-activated receptor (PPAR) modulators: diabetes and beyond. Med Res Rev. 2001;21(6):540–52.

157. Castrillo A, Tontonoz P. PPARs in atherosclerosis: the clot thickens. J Clin Invest. 2004;114(11):1538–40.

158. Li AC, Binder CJ, Gutierrez A, Brown KK, Plotkin CR, Pattison JW, Valledor AF, Davis RA, Willson TM, Witztum JL, Palinski W, Glass CK. Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPARalpha, beta/delta, and gamma. J Clin Invest. 2004;114(11):1564–76.

159. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet. 2001;357(9260):905–10.

160. Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, Richmond W, Mather H, Sharp P, Feher MD. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. Diabetes Care. 1998;21(4):641–8.

161. Wallace JM, Schwarz M, Coward P, Houze J, Sawyer JK, Kelley KL, Chai A, Rudel LL. Effects of peroxisome proliferator-activated receptor alpha/delta agonists on HDL-cholesterol in vervet monkeys. J Lipid Res. 2005;46(5):1009–16.

162. Wagner JD, Shadoan MK, Zhang L, Ward GM, Royer LJ, Kavanagh K, Francone OL, Auerbach BJ, Harwood HJ Jr. A selective peroxisome proliferator-activated receptor alpha agonist, CP-900691, improves plasma lipids, lipoproteins, and glycemic control in diabetic monkeys. J Pharmacol Exp Ther. 2010;333(3):844–53.

163. Cox PJ, Ryan DA, Hollis FJ, Harris AM, Miller AK, Vousden M, Cowley H. Absorption, disposition, and metabolism of rosiglitazone, a potent thiazolidinedione insulin sensitizer, in humans. Drug Metab Dispos. 2000;28(7):772–80.

164. Ding SY, Tigno XT, Braileanu GT, Ito K, Hansen BC. A novel peroxisome proliferator--activated receptor alpha/gamma dual agonist ameliorates dyslipidemia and insulin resistance in prediabetic rhesus monkeys. Metabolism. 2007;56(10):1334–9.

165. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev. 2006;27(1):73–100.

166. Nogueiras R, Veyrat-Durebex C, Suchanek PM, Klein M, Tschöp J, Caldwell C, Woods SC, Wittmann G, Watanabe M, Liposits Z, Fekete C, Reizes O, Rohner-Jeanrenaud F, Tschöp MH. Peripheral, but not central, CB1 antagonism provides food intake-independent metabolic benefits in diet-induced obese rats. Diabetes. 2008;57(11):2977–91.

167. Nogueiras R, Diaz-Arteaga A, Lockie SH, Velásquez DA, Tschop J, López M, Cadwell CC, Diéguez C, Tschöp MH. The endo-cannabinoid system: Role in glucose and energy metabolism. Pharmacol Res. 2009;60(2):93–8.

168. Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong WI, Bátkai S, Marsicano G, Lutz B, Buettner C, Kunos G. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J Clin Invest. 2008;118(9):3160–9.

169. Cota D, Sandoval DA, Olivieri M, Prodi E, D'Alessio DA, Woods SC, Seeley RJ, Obici S. Food intake-independent effects of CB1 antagonism on glucose and lipid metabolism. Obesity (Silver Spring). 2009;17(8):1641–5.

170. Quarta C, Bellocchio L, Mancini G, Mazza R, Cervino C, Braulke LJ, Fekete C, Latorre R, Nanni C, Bucci M, Clemens LE, Heldmaier G, Watanabe M, Leste-Lassere T, Maitre M, Tedesco L, Fanelli F, Reuss S, Klaus S, Srivastava RK, Monory K, Valerio A, Grandis A, De Giorgio R, Pasquali R, Nisoli E, Cota D, Lutz B, Marsicano G, Pagotto U. CB(1) signaling in forebrain and sympathetic neurons is a key determinant of endocannabinoid actions on energy balance. Cell Metab. 2010;11(4):273–85.

171. Butler H, Korbonits M. Cannabinoids for clinicians: the rise and fall of the cannabinoid antagonists. Eur J Endocrinol. 2009;161(5):655–62.

172. Akbas F, Gasteyger C, Sjödin A, Astrup A, Larsen TM. A critical review of the cannabinoid receptor as a drug target for obesity management. Obes Rev. 2009;10(1):58–67.

173. Wagner JD, Zhang L, Kavanagh K, Ward GM, Chin JE, Hadcock JR, Auerbach BJ, Harwood HJ Jr. A selective cannabinoid-1 receptor antagonist, PF-95453, reduces body weight and body fat to a greater extent than pair-fed controls in obese monkeys. J Pharmacol Exp Ther. 2010;335(1):103–13

174. Dunning BE, Foley JE, Ahrén B. Alpha cell function in health and disease: influence of glucagon-like peptide-1. Diabetologia. 2005;48(9):1700–13.

175. D'Alessio DA, Vogel R, Prigeon R, Laschansky E, Koerker D, Eng J, Ensinck JW. Elimination of the action of glucagon-like peptide 1 causes an impairment of glucose tolerance after nutrient ingestion by healthy baboons. J Clin Invest. 1996;97(1):133–8.