

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 diabetes³ and another 25% has impaired

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Abbreviations: (CB₁) 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 T1DM¹⁶ 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 cardiovascular pathologies.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 troglodytes*) 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 cynomolgus⁶⁰ 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 postmenopausal¹¹⁶

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 women¹²¹ 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 marmosets¹⁴⁰ 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 PPAR γ 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 PPAR γ 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 PPAR α agonists is of particular importance since, in rodents, PPAR α 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 PPAR α response elements in the rodent and primate apolipoprotein A1 promoters, rodents and primates respond differently, and in opposite directions, to the actions of PPAR α 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 PPAR α activation and shows similar PPAR γ activation,^{144,156} the ability of PPAR α agonism to favorably affect glycemic control independent of associated PPAR γ agonism was confirmed using a highly specific PPAR α 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 PPAR α/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 PPAR α/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 (CB₁) 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 CB₁ receptor antagonist, PF-95453, in obese, insulin-resistant cynomolgus macaques demonstrated that, as in humans, the effects of CB₁ 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 μ g/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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