ILAR Journal, 2017, Vol. 58, No. 2, 251–268

doi: 10.1093/ilar/ilx031
Article

Use and Importance of Nonhuman Primates in Metabolic Disease Research: Current State of the Field

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Abstract

Obesity and its multiple metabolic sequelae, including type 2 diabetes, cardiovascular disease, and fatty liver disease, are becoming increasingly widespread in both the developed and developing world. There is an urgent need to identify new approaches for the prevention and treatment of these costly and prevalent metabolic conditions. Accomplishing this will require the use of appropriate animal models for preclinical and translational investigations in metabolic disease research. Although studies in rodent models are often useful for target/pathway identification and testing hypotheses, there are important differences in metabolic physiology between rodents and primates, and experimental findings in rodent models have often failed to be successfully translated into new, clinically useful therapeutic modalities in humans. Nonhuman primates represent a valuable and physiologically relevant model that serve as a critical translational bridge between basic studies performed in rodent models and clinical studies in humans. The purpose of this review is to evaluate the evidence, including a number of specific examples, in support of the use of nonhuman primate models in metabolic disease research, as well as some of the disadvantages and limitations involved in the use of nonhuman primates. The evidence taken as a whole indicates that nonhuman primates are and will remain an indispensable resource for evaluating the efficacy and safety of novel therapeutic strategies targeting clinically important metabolic diseases, including dyslipidemia and atherosclerosis, type 2 diabetes, hepatic steatosis, steatohepatitis, and hepatic fibrosis, and potentially the cognitive decline and dementia associated with metabolic dysfunction, prior to taking these therapies into clinical trials in humans.

Key words: baboon; diabetes; dyslipidemia; fatty liver disease; metabolic syndrome; nonhuman primates; obesity; rhesus macaque

Introduction/History

Nonhuman primates (NHPs) have been utilized for over 50 years to investigate the regulation of metabolism and the physiology and secretion of metabolically important pancreatic, gastrointestinal, and adipocyte hormones and have served as critically important models of the pathophysiology and treatment of metabolic diseases, in particular type 2 diabetes and cardiovascular disease. NHPs differ significantly from laboratory rodents and are metabolically more similar to humans in a number of characteristics, including the major site of de novo lipogenesis (liver vs. adipose tissue) and major classes of circulating lipoproteins and in the physiology of thermogenesis and insulin-meditated glucose utilization. The goal of this article is not to provide a comprehensive review of the literature on NHPs in metabolic disease research, but rather to present an overview of the use and importance of NHPs for investigating the etiology, pathophysiology, and treatment of obesity and components of the metabolic syndrome, including lipid disorders, cardiovascular disease, type 2 diabetes, and fatty liver disease. We will also discuss some of the important methodology and approaches employed for metabolic disease research in NHPs and provide several examples where studies in NHPs have provided important advances in the prevention and management of these diseases.

The NHPs most commonly employed for metabolic disease research include rhesus macaques (*Macaca mulatta*), cynomolgus macaques (*Macaca fascicularis*), baboons (*Papio* species), and African Green Monkeys (*Chlorocebus* species), although a number of other species, including marmosets (*Callithrix* species), are sometimes employed. There are currently seven National Primate Research Centers (NPRCs), which include California (Davis), Oregon (Beaverton/Portland), Southwest (San Antonio), Washington (Seattle), Tulane (New Orleans), Yerkes (Emory University, Atlanta), and Wisconsin (Madison), supported by the National Institutes of Health (NIH), several of which currently have programs and research scientists actively engaged in metabolic disease research (NPRC, https://nprcresearch.org/primate/). In addition, there are several of other academic (e.g., Wake Forest University Primate Center) and private (e.g., Crown Biosciences) facilities inside and outside of the United States that maintain colonies of obese and diabetic NHPs for metabolic disease research. The facilities and animals at the US NPRCs are available for collaborative research projects with academic investigators and collaborations and contract studies with pharmaceutical and biotechnology partners. In addition, the NPRCs offer Pilot Research Programs intended to provide funding for investigators new to NHP research who are interested in translating and expanding their experimental findings into NHP models and to generate preliminary data in NHPs needed to apply for larger funding mechanisms.

Endocrine and Metabolic Studies in Nonobese Animals

Studies in nonobese NHPs have been useful for translating physiology in the normal nondisease state from rodent models to primates, including humans. For example, NHPs have been valuable in understanding the regulation of food intake by gastrointestinal peptides, including cholecystokinin (Moran et al. 1993), glucagon-like peptide-1 agonists (Scott and Moran 2007), and peptide-YY (Moran et al. 2005). In addition, the actions and regulation of leptin and its pharmacokinetics have been widely interrogated in rhesus macaques (Adams et al. 2008; Ahren et al. 2000; Ramsey et al. 1998; Tang-Christensen et al. 1999) as well as adiponectin biology in baboons (Tejero et al. 2004a). Studies performed in NHPs have also proven important for establishing the role of the autonomic nervous system in postprandial insulin secretion (D'Alessio et al. 2001) and the regulation of glucagon secretion during insulin-induced hypoglycemia (Havel and Valverde 1996) as well as compensatory insulin secretion in glucocorticoid-induced insulin resistance (Cummings et al. 2013). To highlight the importance of the NHP as a clinically relevant model, several of these studies in NHPs have directly led to very similar studies in humans (Ahren and Holst 2001; Havel and Ahren 1997). Furthermore, studies of long-term energy restriction in aging NHPs (rhesus macaques) performed at the Wisconsin NPRC and the National Institute of Aging, NIH have also been prominent in translating effects on healthy life span and metabolic outcomes originally observed in rodents to primate models (Colman et al. 2009; Kemnitz 2011; Mattison et al. 2012, 2017; Ramsey et al. 2000).

Spontaneous Versus Diet-Induced NHP Models of Metabolic Disease

Obesity and its metabolic sequelae are quite uncommon in NHPs living in the wild as a consequence of high levels of physical activity as well as the energy expended in thermoregulation. In addition, the amount and types of foods that wild animals consume do not typically promote positive energy balance and weight gain, although obesity has been observed in wild NHPs that have access to palatable foods with high caloric content (Kemnitz et al. 2002). In captive animals, the prevalence of obesity increases, even in animals housed in large outdoor enclosures with free access to both physical activity and ad libitum intake of standard laboratory "monkey chow" diets that are typically low in fat and added sugars. However, rates of obesity in NHPs housed in groups in outdoor facilities are considerably lower compared with animals housed indoors in smaller enclosures. Obesity in indoor-housed animals is considerably more prevalent, and many of these animals are often restricted below ad libitum food intake to prevent them from becoming obese.

Due to the longer periods of time for obesity and related metabolic diseases to develop and progress in most NHP species when consuming standard low-fat/low-sugar laboratory NHP diets (~15% of calories from fat and 50–60% of calories from carbohydrates as starch), experimental diets that are high in fat and/or simple sugars are being increasingly used to induce rapid weight gain and accelerate metabolic disease progression in NHPs. One commonly used experimental diet is a high-fat, high-sugar (HFHS) diet, ranging from 30% to 40% of calories from fat and increasing percentages of calories from simple sugars. For example, Higgins and colleagues demonstrated that total and truncal fat mass and fasting plasma triglyceride (TG) concentrations were all more than doubled, and circulating adiponectin concentrations were decreased by ~30% after only 8 weeks of exposure to a HFHS diet in adult male baboons compared with those consuming a standard control diet (Higgins et al. 2010). HFHS diets have also been used in common marmosets (*Callithrix jacchus*), resulting in increased body fat and glucose dysregulation for periods up to 1 year in duration (Wachtman et al. 2011). In a unique NHP model, a similar HFHS diet (~35% of calories from fat and 46% of calories from carbohydrates in the form of sucrose and fructose; TestDiet 5L0P) has been fed to female Japanese macaques to investigate the effects of diet-induced maternal obesity and metabolic perturbations during pregnancy on metabolic disease transmission to their offspring (Aagaard-Tillery et al. 2008; Grant et al. 2012; Pound, Comstock et al. 2014). HFHS diets have been useful

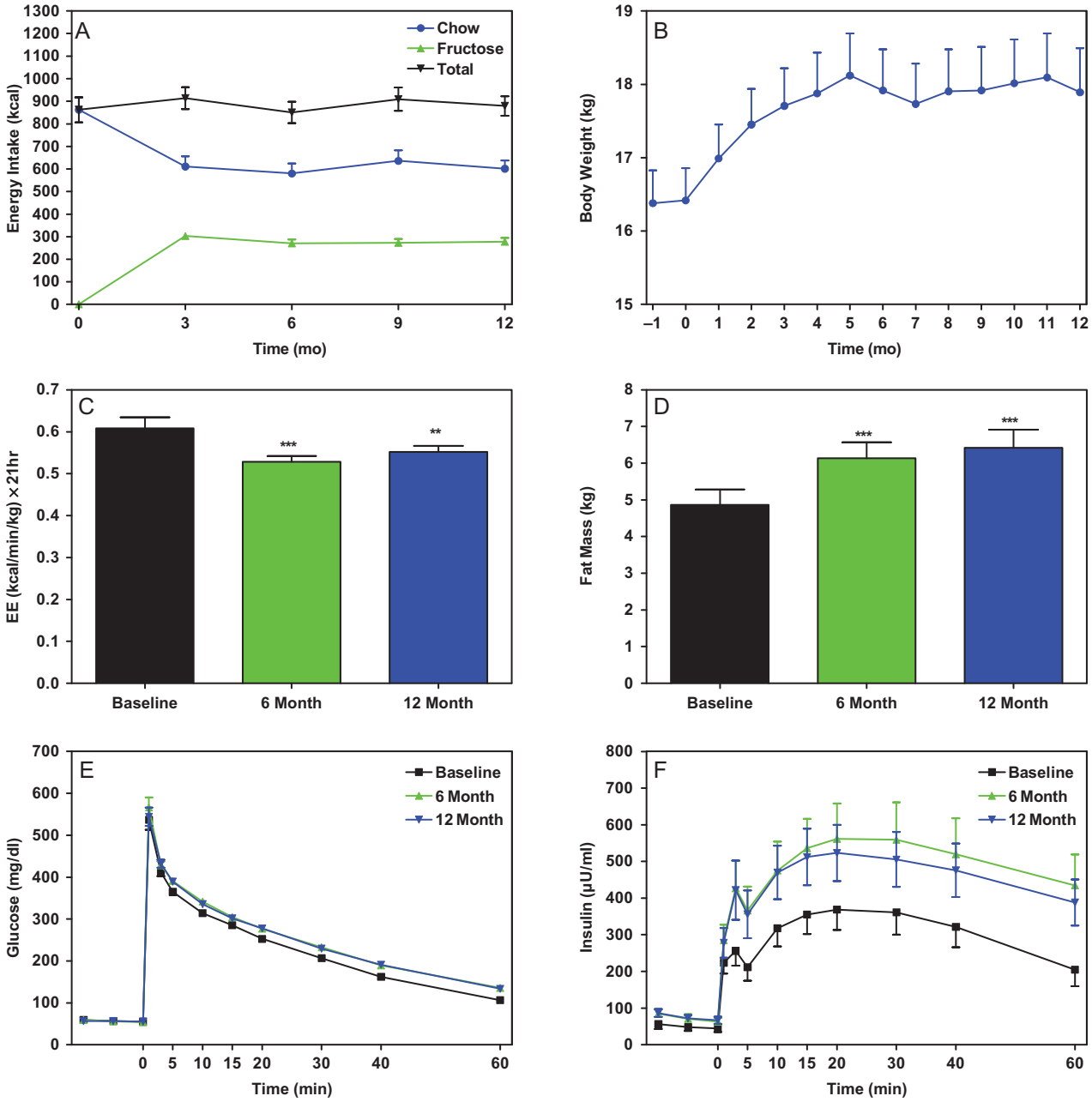

Figure 1 The effect of a high-fructose diet on energy intake from sugar (fructose), chow, and total energy intake (A) body weight (B), energy expenditure (C), and fat mass by DEXA (D) over 12 months in rhesus macaques ($n = 29$) that developed diet-induced metabolic syndrome. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$ versus baseline by linear mixed model. Plasma glucose (E) and insulin (F) responses during intravenous glucose tolerance tests in rhesus macaques at baseline and at 6 and 12 months on the high-sugar (fructose) diet with diet-induced metabolic syndrome. Error bars show SEM. Data are from Bremer et al. 2011.

in investigating the effects of resveratrol supplementation on a number of metabolic outcomes in rhesus macaques, including preservation of β-cell differentiation (Fiori et al. 2013), adipose tissue insulin signaling and inflammation (Jimenez-Gomez et al. 2013), and attenuation of arterial inflammation and aortic wall stiffening (Mattison et al. 2014).

Furthermore, in a well-characterized NHP model of metabolic syndrome, consumption of 300 kcal/day from flavored fructose-sweetened beverages for up to 1 year results in increased energy intake (Figure 1A) and body weight gain (Figure 1B), along with decreased energy expenditure (Figure 1c) and increased fat mass (Figure 1D), impaired glucose tolerance (Figure 1E), and insulin resistance (Figure 1F). These changes are accompanied by dyslipidemia, with hypertriglyceridemia and reduced HDL-C, decreased adiponectin, and elevation of some markers of inflammation in adult male rhesus macaques (Bremer et al. 2011). The animals largely compensate for the energy consumed from the sugar-sweetened beverages by decreasing their intake of the solid chow diet, but remain in positive energy balance consuming ~30 kcal/day more than before the introduction of the beverages. This, combined with an approximately 12% decrease of energy expenditure, leads to the rapid gain of body weight and fat mass. Interestingly, most of the weight gain and accompanying metabolic disarrangements occur during the first 3 to 6 months

on the diet, so long-term dietary interventions are not necessarily required to induce weight gain and components of the metabolic syndrome in this NHP model. Importantly, NHP models with diet-induced metabolic alterations will continue to be the primary source of animals used for metabolic disease research, and most of the research studies discussed in the remainder of this review will be from investigations performed in such models.

Metabolic Syndrome Specific Features

Obesity

As introduced above, there is a significant body of literature clearly demonstrating that NHPs are susceptible to the spontaneous development of obesity and its associated comorbidities (Hansen 2017; Pound, Kievit et al. 2014). Obesity in NHPs is also readily inducible via the consumption of diets high in saturated fats and/or simple sugars. Similar to spontaneous obesity, these diets result in the accumulation of adipose tissue in visceral depots, insulin resistance, hypertension, dyslipidemia, and various other symptoms (Bremer et al. 2011; Chadderdon et al. 2014; Higgins et al. 2010; Kievit et al. 2013; Li et al. 2013). The exposure of both baboons and rhesus macaques to a diet high in simple carbohydrates and saturated fats results in rapid increases in percent body fat; in the case of rhesus macaques, total fat mass increases by an average of 15–20% (Bremer et al. 2011; Li et al. 2013), which is accompanied by the expected dysregulation of lipid and glucose metabolism and other key indicators of negative effects on cardiometabolic health (Bremer et al. 2011; Higgins et al. 2010). Along with an adverse impact on lipid and glucose metabolism, increasing adiposity in NHPs has also been shown to have the same relationships with the expression of adipokines (e.g., leptin and adiponectin) as well as a number of inflammatory cytokines (e.g., TNF-α and IL-6) observed in humans (Bremer et al. 2011; Cole et al. 2003; Comuzzie et al. 2003; Higgins et al. 2010, 2014; Tejero et al. 2008), including an increased recruitment of macrophages into the adipose tissue depots (Tejero et al. 2008).

Along with studies utilizing NHPs to investigate the physiological and metabolic processes underlying obesity and its associated endophenotypes, studies using NHPs have also provided important insights into the genetic and epigenetic factors that also contribute to the risk for developing obesity (Cai et al. 2004; Schwartz 1989; Tejero et al. 2004a, 2004b; Voruganti et al. 2007, 2008). For example, Jaquish and colleagues (Jaquish et al. 1997) reported a genetic contribution accounting for 51% of the total variance in mean adult body weight and 12% of the variance in body weight stability in baboons, demonstrating a substantial genetic component to variations of body weight in these animals, a finding consistent with what has been reported in numerous studies of the genetics of obesity in humans. Additional work in baboons found significant additive genetic heritabilities for serum leptin levels ($h^2 = 0.21$), weight ($h^2 = 0.62$), fat mass ($h^2 = 0.41$), fat free mass ($h^2 = 0.32$), and the ratio of fat free mass ($h^2 = 0.84$) (Comuzzie et al. 2003). Later studies in vervet monkeys have also provided significant insights into the genetic contributions to obesity (Gray et al. 2009; Kavanagh et al. 2007). The interaction of consuming a highly palatable diet and changes of social status on central reward pathways in female rhesus macaques has also recently been reported (Michopoulos et al. 2016), suggesting that it is likely to be a useful model for investigating the interactions between stress, hedonic eating, and the development of obesity (Morris et al. 2015). To summarize, it is clear that the species of NHPs most widely used in biomedical research are highly susceptible to diet-induced obesity and its adverse metabolic sequelae and will be valuable in translating new molecular targets and pharmacologic and surgical therapies from rodents to humans, as well as in understanding their mechanisms in an animal model that more fully recapitulates that pathophysiology of obesity in humans.

Metabolic Syndrome Components

Visceral Adiposity

In some of the earliest studies on obesity in adult rhesus macaques it was reported that the distribution patterns of adipose tissue in the obese animals closely reflects the adipose tissue distribution in many obese humans, with increased adipose tissue mass preferentially distributed in the abdominal region (Kemnitz et al. 1989), a pattern later confirmed in baboons and vervet monkeys as well (Morris et al. 2015). In addition to the demonstration that NHPs tend to accumulate fat centrally, as seen in humans with metabolic syndrome, this accumulation is also associated with the same adverse effects on glucose and lipid metabolism accompanying the metabolic syndrome in humans. Kemnitz and Francken (Kemnitz and Francken 1986) divided a cohort of rhesus macaques into nonobese, moderately obese, and very obese (30–61% body fat), and reported strong correlations of body adiposity with fasting insulin and TG concentrations despite similar food intake between the groups. Likewise, results from studies in baboons and vervet monkeys support the relationship between increasing fat accumulation, particularly centrally deposited fat, and increasing insulin resistance and adverse lipid profiles (Chavez et al. 2008, 2009; Comuzzie et al. 2003; Kavanagh et al. 2007). However, in a study by Bodkin and colleagues (Bodkin et al. 1993), they reported that although there is a linear relationship between the development of insulin resistance and body fat percentage in rhesus macaques, there did not appear to be a clear relationship between of degree of central obesity and the severity of insulin resistance. These findings suggest that although body fat percentage (i.e., obesity) is an important contributor to the development of insulin resistance, a number of other factors are involved as well (Bodkin et al. 1993; Tigno et al. 2004). With the increased availability and use of advanced imaging techniques (e.g., computerized tomography and magnetic resonance imaging) for assessing and distinguishing between subcutaneous and visceral abdominal fat distribution in NHPs, the role of intra-abdominal fat deposition in contributing to the metabolic sequelae of inflammation, insulin resistance, and hepatic fat accumulation will be more clearly defined.

Glucose Intolerance/Insulin Resistance

Plasma glucose concentrations in normal-weight rhesus macaques are somewhat lower (averaging 60–80 mg/dL) than those typically measured in humans (Bremer et al. 2011). This is likely due to an overnight fast being a fairly long fasting period for these relatively smaller (10–15 kg) animals. Normal fasting plasma glucose in baboons, which are larger (25–35 kg) animals, is closer to that in humans (averaging 80–100 mg/dL) (Higgins et al. 2010). Fasting plasma glucose concentrations do not typically increase noticeably in diet-induced obese NHPs unless they develop overt type 2 diabetes (with fasting glucose concentrations >125 mg/dL). For example, impaired fasting glucose levels with intermediate glucose concentrations of 100–125 mg/dL were observed after 6 months in rhesus macaques that later developed diabetes after

12 months on a high-sugar (fructose beverage) diet (Bremer et al. 2011). Impaired glucose tolerance during a dynamic intravenous glucose tolerance test (IVGTT) is also observed in rhesus macaques with diet-induced obesity/metabolic syndrome with a relatively modest (~20%) increase of the glucose area under the curve (AUC) over a 60-minute period following i.v. glucose administration (Bremer et al. 2011). In contrast, larger compensatory increases of plasma insulin excursions (ΔAUC insulin +75%) maintain glucose tolerance in the presence of marked insulin resistance. Interestingly, a paradoxical improvement (i.e., lowering) of glucose excursions during a standard meal test was observed in rhesus macaques with glucocorticoid (dexamethasone)-induced insulin resistance (Cummings et al. 2013). This improvement is likely the result of an overcompensation of meal-induced insulin secretion, which at least in part may be mediated by increased glucose-dependent insulinotropic polypeptide, as postprandial glucose-dependent insulinotropic polypeptide release was approximately doubled when the animals received dexamethasone (Cummings et al. 2013).

Obese NHPs are insulin resistant as demonstrated by the use of hyperinsulinemic-euglycemic clamps, IVGTTs, and fasting insulin concentrations (see below). The natural history and progression of obesity and insulin resistance to type 2 diabetes in rhesus macaques has been well described by Barbara Hansen and colleagues (Hansen and Bodkin 1986, 1990). As alluded to above, the harbinger of metabolic disease in diet-induced obesity, and metabolic syndrome is the hypersecretion of insulin, manifested by fasting hyperinsulinemia and increased first- and second-phase insulin secretion during an IVGTT (Bremer et al. 2011). Insulin resistance as assessed by fasting hyperinsulinemia occurs very early (within the first 4 weeks) during the progression of diet-induced metabolic syndrome, at a time when there has only been a small amount of proportional weight gain (PJ Havel, JL Graham, AA Bremer, unpublished data). Furthermore, the prevention of insulin resistance in diet-induced obese and insulin-resistant rhesus macaques by dietary omega-3 fatty acids from fish oil and an improvement in metabolic responses to pharmacological interventions is evident by both reductions of fasting plasma insulin concentrations and reduced first- and second-phase glucose-induced insulin secretion during dynamic metabolic testing (e.g., IVGTTs) (Bremer et al. 2014; Swarbrick et al. 2009).

Dyslipidemia/Hyperlipidemia and Atherosclerosis

There is a long history of using NHPs to study the effects of diet on lipid and lipoprotein risk factors for cardiovascular disease, particularly atherosclerosis. Seminal studies started during the 1960s by Dr. Henry McGill and colleagues in San Antonio established the relationship between diet and serum cholesterol levels and experimental atherosclerosis in baboons (Strong and McGill 1967; Strong et al. 1966). This work was continued by Dr. John VandeBerg and co-workers (Babiak et al. 1985; Mott et al. 1992; Shi et al. 2014). The most frequently used animal model to study the pathophysiology and potential treatment of atherosclerosis and other cardiometabolic outcomes is the mouse. Although mice do not normally develop atherosclerosis, genetic deletions of ApoE or the LDL receptor in mice result in the development of atherosclerosis, and these models have been extensively used to investigate the molecular mechanisms of plaque development (reviewed in Getz and Reardon 2012). However, despite the insight into the pathways contributing to the development of atherosclerosis obtained from rodent models, there are several important differences in lipoprotein metabolism between mice and humans that underscore the importance of performing atherosclerosis research in animal models (i.e., NHPs) more similar to humans.

Dyslipidemia, particularly increased circulating TGs and low levels of HDL-C, are hallmark components of the metabolic syndrome. Importantly, NHP models demonstrate patterns of lipid dysregulation that are very similar to those in humans (Shamekh et al. 2011). For example, in a recent study comparing detailed plasma lipid profiles in four species of lean and dyslipidemic NHPs versus several nonprimate models (including several strains of mice, rats, rabbits, pigs, and dogs) with those in dyslipidemic humans concluded that the NHP species more closely matched the fasting lipid profiles and responses to statin treatment to dyslipidemic humans than any of the other models (Yin et al. 2012). Specifically, NHPs were more similar to humans in the total amount of cholesterol present in the non-HDL-C fractions (i.e., LDL-C and VLDL-C), which are associated with the development of atherosclerotic plaques (Yin et al. 2012). Therapeutically, nondiabetic hyperlipidemic rhesus macaques respond to treatment with a fibrate drug (fenofibrate), which acts in part via activation of PPARα, with decreases of TG and LDL-C and an increase of HDL-C, similar to the responses observed in humans (Winegar et al. 2001).

Although hyperlipidemia, especially increases of circulating TGs, occurs in NHP species spontaneously as the animals age and metabolic dysfunction progresses (Hannah et al. 1991), the onset and severity of dyslipidemia can be accelerated by feeding the animals diets high in fat, sugar, or both fat and sugar. Rhesus macaques fed an ad libitum chow diet accompanied by 500 mL/day of a flavored beverage sweetened with 15% fructose providing 300 kcal/day (~30% of energy requirements) (Bremer et al. 2011) provide a good example of the onset and progression of dyslipidemia in a NHP model of diet-induced metabolic syndrome. In that model, fasting TG concentrations increase from an average pre-diet baseline level of ~80 mg/dL into the metabolic syndrome range (>150 mg/dL) within 1 month on the high-fructose diet (PJ Havel, JL Graham, AA Bremer, unpublished data; Havel et al. 2017). Fasting plasma TG remains elevated in the animals maintained on the high-sugar diet for 6 and 12 months and is accompanied by a ~15% decrease of plasma HDL-C concentrations (Bremer et al. 2011). Low HDL-C concentrations are one of the key-defined components of metabolic syndrome in humans. Furthermore, the increase in fasting TG and decrease in HDL-C levels are much more marked in animals that develop overt diabetes after 1 year on the high-fructose diet; this is indicative of diabetic dyslipidemia, as has been previously reported during the natural history of the progression from insulin resistance to overt type 2 diabetes in middle-age rhesus macaques (Hannah et al. 1991). In addition, plasma concentrations of apolipoprotein-C3, which inhibits TG clearance via inhibitory actions on lipoprotein lipase and activation of hepatic de novo lipogenesis (Zheng 2014), increase rapidly by ~40% within 1 month on a high-fructose diet and remain elevated during chronic fructose consumption (Bremer et al. 2014). Interestingly, the increases of ApoC3 in fructose-fed rhesus macaques are highly predictive ($r = 0.74$, $p < 0.0001$) of the increases of fasting plasma TG, while the concurrent increases of Apo-E and fasting insulin concentrations are not (PJ Havel, JL Graham, AA Bremer, unpublished data; Havel et al. 2017). The adverse effects of high-sugar diets on ApoC3 as a lipoprotein risk factor for cardiovascular disease in rhesus macaques are therefore similar to those observed in humans (Stanhope et al. 2013, 2015). In addition to the more well-known lipid and lipoprotein risk factors for cardiovascular disease, it has been shown that several specific forms of sphingolipids/ceramides are increased in obese and diabetic rhesus macaques

consuming a high-fat/high-fructose diet and that some of these increases appear to be related to alterations of glucose homeostasis (Brozinick et al. 2013).

Blood Pressure/Hypertension

Elevated blood pressure is a key component of the metabolic syndrome, and NHP models have successfully been used to evaluate the hemodynamic effects of existing and novel therapies aimed at treating hypertension, a common cause of morbidity and mortality in humans. Importantly, the use of NHPs in preclinical studies permits continuous cardiovascular telemetry and the assessment of hemodynamic parameters that are often not practical to perform in humans. Implantable telemetry devices have successfully been used in NHP models (Chaves et al. 2006; Kievit et al. 2013; Regan et al. 2009) and permit the recording of arterial blood pressure, heart rate, the PR interval, the QRS interval, and the QT interval in freely moving animals, thus preventing the confounding influence of anesthesia. The QT interval in NHP can also be corrected for heart rate using methods established in beagles using telemetry (Miyazaki and Tagawa 2002). Furthermore, the log(QT) can be expressed as a function of the log(HR) for each animal with an implantable telemetry device and fit with a linear regression analysis (Miyazaki and Tagawa 2002).

As an example of the utility of using NHPs in the evaluation of hypertension, extensive preclinical studies in the cynomolgus monkey were recently performed to demonstrate the early clinical profile of a highly selective and potent oral inhibitor of aldosterone synthase (CYP11B2) (Bogman et al. 2017). The findings of this study not only support investigating the suppression of aldosterone production as a treatment option for hypertension in humans, but further suggest that selective inhibitors of aldosterone synthase can be developed using NHPs as the relevant preclinical model to mechanistically investigate the antihypertensive effects of aldosterone inhibition. Moreover, the cynomolgus monkey model has been used successfully to characterize inhibitors of CYP11B1 and CYP11B2, and cynomolgus monkey CYP11B assays have been shown to be suitable surrogates for the human enzymes (Cerny et al. 2015). The effects of other pharmacological agents, for example, pioglitazone to reduce blood pressure (Kemnitz et al. 1994) and a melanocortin-4 receptor agonist to increase blood pressure (Kievit et al. 2013), have also been studied in NHP models.

Diabetes Mellitus

Type 1 Diabetes

Although much of the current focus on diabetes is centered on type 2 diabetes, there is also a rising incidence of type 1 diabetes in many countries around the world. Not only is the incidence increasing, there has also been a shift towards a younger age of onset (Dahlquist 2006). One hypothesis for this observation is that obesity and increased early growth rates lead to pancreatic hyperfunction and increased presentation of autoantigens from ß-cells, potentially accelerating an autoimmune response (Dahlquist 2006). However, other hypotheses exist and myriad other factors (besides diet and obesity) are most likely involved. Furthermore, the incidence rate for type 1 diabetes varies markedly between countries; it is highest in Scandinavian countries, followed by European countries, North America, and Australia, and lowest in Asian countries. The reasons for this geographic variation in incidence rates remain unresolved, but may be related to genetic susceptibility (e.g., HLA-DR-DQ genotypes) and environmental and lifestyle factors, including diet, hygiene, and childhood infections (Katsarou et al. 2017). Nevertheless, the growing prevalence of type 1 diabetes warrants the development and use of animal models sufficiently close to humans in which the pathogenesis and complications of type 1 diabetes can be fully investigated.

While autoimmune diabetes is not well recognized in NHPs, chemically induced islet lesions using the β-cell toxin streptozotocin (STZ), or surgical pancreatectomy (both partial and total), have long been used to produce and model type 1 diabetes in a number of NHP species, including rhesus macaques (Pitkin and Reynolds 1970), baboons, cynomolgus macaques, and vervet monkeys (Frost et al. 2015; Graham et al. 2012; McCulloch et al. 1988; Zhu et al. 2014). In addition, STZ-induced diabetic vervet monkeys have been demonstrated to be a useful animal model of type 1 diabetes (Kavanagh et al. 2011). NHP models of type 1 diabetes are also a valuable tool for understanding mechanisms underlying diabetic complications such as diabetic nephropathy (Birrell et al. 2002; Rincon-Choles et al. 2012) and neuropathy (Pare et al. 2007), common to both type 1 and type 2 diabetes in humans, as well as new therapeutic approaches for the treatment of diabetic complications. For example, the vervet monkey model of type 1 diabetes has also been used to demonstrate brain-wide insulin resistance, tau phosphorylation changes, and hippocampal neprilysin and amyloid-beta alterations similar to what has been reported in humans (Morales-Corraliza et al. 2016). Moreover, NHP models of type 1 diabetes have been useful for investigating cell-based therapies, including pancreatic islet transplantation (Pathiraja et al. 2017; Zhu et al. 2014), the viability and glucose-lowering effects of islet allografts (Thomas et al. 2001) and xenografts (Kirchhof et al. 2004), and novel gene therapy approaches (Chen et al. 2014) for the management of type 1 diabetes.

Type 2 Diabetes

Diabetes secondary to insulin resistance and inadequate β-cell/islet compensation has been reported to spontaneously develop in a number of captive NHP species (Pound, Kievit et al. 2014). There is a high prevalence of type 2 diabetes in *Macaca nigra* (Howard 1986) as well as a significant prevalence in rhesus macaques (*Macaca mulatta*) (Hansen 1996). The progression of obesity accompanied by insulin resistance and hyperinsulinemia to inadequate islet compensation leading to β-cell failure and overt diabetes in aging rhesus macaques has also been well characterized in longitudinal studies and is similar to the progression observed in cross-sectional studies in humans (Hansen 1989; Kahn and Porte 2003). Furthermore, the presence of islet amyloidosis characteristic of type 2 diabetes in humans is also observed in diabetic monkeys, implicating a similar etiology of islet lesions in monkeys and humans (Clark et al. 2001; de Koning et al. 1993; Spijker et al. 2015).

Diabetes associated with insulin resistance can also be induced by administering nicotinic acid to baboons with reduced β-cell mass produced with a low dose of STZ (McCulloch et al. 1991). However, this model is less representative of type 2 diabetes in humans due to the chemically induced islet lesion. Importantly, the more usual progression from prediabetes to overt diabetes with fasting hyperglycemia (>125 mg/dL) can be hastened in NHPs by feeding the animals a HFHS or high-sugar diets. For example, ~15% (4 of 29) of rhesus macaques fed a high-sugar diet from fructose-sweetened beverages develop type 2 diabetes within 1 year on the diet (Bremer et al. 2011). The monkeys that developed diabetes had higher fasting insulin concentrations, impaired glucose-stimulated insulin secretion during an IVGTT,

and lower adiponectin levels than the monkeys that only became more insulin resistant with compensatory increases in fasting insulin concentrations and glucose-stimulated insulin secretion during the 1-year dietary intervention period. While the diabetic animals exhibited a marked decline in glucose-stimulated insulin secretion with the onset and progression of diabetes, the insulin-resistant nondiabetic animals also demonstrated a decrease of glucose-stimulated insulin secretion between 6 and 12 months on the diet, indicative of a progression towards inadequate β-cell compensation and suggesting that many more of these monkeys would likely have developed overt diabetes if they had continued to consume the high-sugar diet for a longer period of time. This scenario is very similar to what is observed in the natural progression of prediabetes to overt type 2 diabetes in humans (Kahn and Porte 2003). To summarize, it is clear that NHPs develop both spontaneous and diet-induced type 2 diabetes that is quite similar to the pathophysiology of the disease in humans, making them the most representative translational model for investigating its etiology, prevention, and therapeutic management.

Gestational Diabetes and Fetal Programming

NHP models have also been used to better elucidate the mechanisms underlying how poor maternal health affects fetal programming and imparts risk for future metabolic disease in the offspring (Friedman 2015). Specifically, the Japanese macaque model referenced above has demonstrated that consumption of a maternal Western-style diet causes placental dysfunction, tissue-specific changes in the mitochondria in the offspring, widespread inflammation, hepatic steatosis, and broad developmental changes in the liver, skeletal muscle, brain, and pancreas (reviewed in Friedman 2015). Furthermore, these in utero perturbations are accompanied by significant and persistent changes in the epigenome, the microbiome, and offspring behavior (Friedman 2015). The observation that these abnormalities in the offspring persist even after being weaned to a healthy diet after lactation further suggests that gestational and lactational dietary exposures are significant and possibly permanent contributors to the offspring's health and may initiate the development of pathways that drive health risks. Furthermore, this NHP model evaluating the impact of a western-style diet and maternal obesity on metabolic systems in the offspring has demonstrated the impact of maternal diet on fetal nonalcoholic fatty liver disease (NAFLD). Importantly, NAFLD is the most common liver disease in children and adults and the leading cause of liver transplantation (Pacifico et al. 2008; Welsh et al. 2013) and is a frequent comorbidity of obesity and type 2 diabetes.

Fatty Liver Disease

As introduced above, NAFLD, along with its sequelae, including nonalcoholic steatohepatitis (NASH), has emerged as the most prevalent liver disease, and new approaches for managing NAFLD and NASH are needed. As far back as the mid-1970s it was noted that NHPs, like humans, were susceptible to the accumulation of excess lipids in the liver (Kritchevsky et al. 1973). More recently, however, studies in a number of NHP species have focused specifically on the pathogenesis of NAFLD and NASH (Bose et al. 2010; Cydylo et al. 2017; Kamath et al. 2011; Kavanagh et al. 2013; Nagarajan et al. 2008). For example, Bose and colleagues (Bose et al. 2010) reported that dedifferentiation of adipocytes is associated with changes in monocyte chemoattractant protein-1 and overall insulin resistance and that such changes could potentially contribute to the development of NAFLD. Other studies in the baboon model (Kamath et al. 2011) demonstrated that defects in hepatic long-chain fatty acid metabolism along with increased hepatic TG accumulation resulted in significant hepatic insulin resistance; these studies also demonstrated that liver fat accumulation was associated with both hepatic and peripheral insulin resistance and suggest that insulin resistance could be a major contributor leading to fatty liver in these animals. In addition, the common marmoset exhibits increased hepatocellular lipid accumulation and a number of indices in inflammation, indicating they are also likely to be a valuable NHP model of NAFLD/NASH (Kramer et al. 2015).

Recent studies in vervet monkeys have shown that dietary exposure to fructose also leads to increased fat in the liver and hepatic damage (Kavanagh et al. 2013) and even fibrosis (Cydylo et al. 2017). In addition, histopathology of the liver of aged bonnet macaques shows diffused microvesicular and macrovesicular fatty changes; perivenular, portal, and perisinusoidal fibrosis with fatty degeneration of hepatocytes; and immunostaining consistent with NAFLD, suggesting that aged bonnet monkeys may also serve as a unique animal model for studies related to NAFLD (Nagarajan et al. 2008). Diets high in fructose-containing sugars have also been reported to increase liver fat in several studies in humans (Maersk et al. 2012; Schwarz et al. 2015). Rhesus macaques fed a high-sugar diet from beverages sweetened with fructose or high fructose corn syrup exhibit liver TG content that is increased 5- to 10-fold compared with normal-weight chow-fed control animals within 2 to 3 months on the diet (PJ Havel, JL Graham, AA Bremer, unpublished data), suggesting that this diet-induced NHP model will be useful for studies investigating the pathophysiology and treatment of NAFLD. Importantly, a significant advantage of using NHP models in the study of NAFLD/NASH is the ability to perform serial laparoscopic liver biopsies, not only for liver fat content, but also to assess fibrosis and the expression of genes and proteins potentially involved in de novo lipogenesis, impaired fat oxidation, and inflammation. NHPs can also be used as a model to investigate the effects of liver transplantation (Luo et al. 1998).

Specific Approaches

Clamps/IVGTTs

Measurements and accurate assessments of glucose tolerance and insulin sensitivity are central in the investigational evaluation of metabolic status in humans and in studies in NHP models of metabolic disease. Hyperinsulinemic-euglycemic clamps, often considered to be the optimal method for assessing insulin sensitivity, have successfully been used in NHP species (Kavanagh et al. 2007; Lee et al. 2011; Standaert et al. 2002). In addition, a hyperinsulinemic, hypoglycemic clamp approach has been utilized to study the influence of the autonomic nervous system in regulating increased glucagon secretion during hypoglycemic counterregulation in rhesus macaques (Havel and Valverde 1996). In addition to clamps, intravenous glucose tolerance tests (IVGTTs) with Minimal Model analysis originally developed and validated for use in dogs and humans (Ader et al. 1985; Pacini and Bergman 1986) have been used to compare parameters of insulin sensitivity and glucose effectiveness in control and energy-restricted rhesus macaques (Gresl et al. 2003). IVGTTs can also be used to assess insulin sensitivity based on a calculated index of insulin sensitivity (ISI) using the slope of glucose disappearance and the insulin AUC in rhesus

macaques. This method has been validated against the deuterated glucose disposal technique (Beysen et al. 2007) and is highly correlated with the ISI index from the IVGTT in rhesus macaques ($r = 0.97$, $p < 0.001$, PJ Havel, JL Graham, AA Bremer, unpublished data). IVGTTs have been used to assess the effects of a high-sugar diet on the progression of insulin resistance and type 2 diabetes in a rhesus macaque model of metabolic syndrome (Bremer et al. 2011) as well as measures of improved insulin sensitivity in response to insulin sensitizers or weight loss (Kemnitz et al. 1994; Kievit et al. 2013). As observed with type 2 diabetes in humans (Kahn and Porte 2003), glucose-stimulated insulin secretion deteriorates over time, and first-phase insulin secretion is largely absent in rhesus macaques chronically fed a high-sugar diet during the progression to overt diabetes (Bremer et al. 2011).

Several surrogate measures of S_I, including the fasting insulin concentration, the homeostasis assessment model, and the quantitative insulin-sensitivity check index, have been compared with hyperinsulinemic-euglycemic clamps in a large number ($n = 199$) of lean and obese rhesus macaques (Lee et al. 2011). Fasting insulin (1/fasting insulin) levels had the highest correlation with the clamp S_I, which is not completely surprising since, in the nondiabetic state, these surrogate markers are largely determined by fasting insulin concentrations. Changes of fasting insulin levels also changed in parallel with the insulin AUC and S_I index in fructose-fed rhesus macaques (Bremer et al. 2011) and predicted the protection against diet-induced insulin resistance in animals receiving omega-3 fatty acids from fish oil (Bremer et al. 2014) or treatment with antisense oligonucleotides targeting protein-tyrosine phosphatase-1ß (Swarbrick et al. 2009). Therefore, fasting insulin concentrations can be used as an index of insulin sensitivity in NHP studies in which clamps and glucose tolerance tests are not logistically possible. In addition to clamps and IVGTTs, oral glucose tolerance tests and meal tolerance tests, either by orogastric gavage or free-fed in chair-trained animals, can be used to assess glucose tolerance, insulin secretion, and nutrient-induced pancreatic and gastrointestinal hormone release before and during interventions in NHPs (Cummings et al. 2013; D'Alessio et al. 2001; Dunning et al. 2003).

Imaging in NHPs for Metabolic Studies

Cutting-edge imaging technology is increasingly being applied in a wide-range of studies on metabolic and cardiovascular disease processes and outcomes. NHPs represent an optimal animal model to study these diseases based on their physiological and metabolic similarity to humans. In addition, their anatomical structure and relatively larger body size also make them well-suited for a number of imaging modalities. Below we review a selection of published studies that demonstrate the range of imaging studies being performed across a variety of NHP species in metabolic disease research.

Body composition in animals can be assessed via several techniques. Somatometry, the least invasive method, can provide an estimate of the body composition based on measures like crown-rump length, skin fold thickness, body weight, and body scores (with an NHP-specific rating of obesity on a scale of 1–5) but is susceptible to variation when compared with imaging-based technologies (Colman et al. 1999; Sharma et al. 1996). Dual-energy X-ray absorptiometry (DEXA) scanning has also been used to assess body composition, including lean body mass versus fat mass and bone mineral density in a number of studies in NHPs. For example, in rhesus macaques consuming a standard primate chow diet ad libitum along with 300 kcal/day of flavored sugar (fructose)-sweetened beverages for 1 year, the fructose-fed animals gained an average of approximately 1.5 kg of body weight, mainly during the first 3 to 6 months on the diet. DEXA scanning for body composition revealed that the weight gain consisted almost entirely in increased body fat mass, which was increased by ~1.5 kg during the time on the diet (Bremer et al. 2011). An important limitation of DEXA scanning for body composition is that although it can localize fat mass to the truncal region, it does not distinguish whether the truncal fat is distributed within intra- or extra-abdominal fat regions. However, computerized tomography and MRI modalities can be used to differentiate and quantify visceral and subcutaneous fat depots. In one important study in older female rhesus macaques, DEXA was used to measure total body fat and MRI was used to assess subcutaneous and visceral fat, while magnetic resonance spectroscopy was used to quantify intra-hepatic and intra-myocellular lipid deposition (Chu et al. 2013). Subcutaneous fat area was associated with indices of insulin resistance, but not after adjustment for total fat mass. Interestingly, although visceral fat area was greater than subcutaneous fat area in these animals, intra-hepatic fat accumulation was most closely correlated with indices of impaired insulin sensitivity, whereas visceral fat and muscle fat content were not (Chu et al. 2013).

An additional noninvasive technique that has demonstrated to be very informative is contrast-enhanced ultrasound. The vascular endothelium plays a major role in the development of atherosclerotic plaques often found in metabolic disease in many species. Obesity, insulin resistance, and increased levels of oxidative stress result in increased perfusion rates and vascular inflammation, eventually leading to vascular dysfunction and atherosclerotic lesions in several NHP species (for some examples, see Chadderdon et al. 2014; Frias et al. 2011; Mattison et al. 2014; Shi et al. 2005; Shively and Clarkson 1988; Zheng 2014). Recent advances in ultrasound imaging techniques have also allowed for detecting vascular inflammation using targeted microbubbles (molecular imaging). For example, a recent study by Chadderdon and colleagues (Chadderdon et al. 2014) demonstrated endothelial inflammation that increased over the course of 2 years in rhesus macaques consuming a diet high in fat and simple carbohydrates. Furthermore, contrast-enhanced ultrasound with microbubbles specifically targeted to P-selectin and VCAM-1 showed that the development of insulin resistance in the animals coincided with the development of vascular inflammation, carotid intimal thickness, and body weight (Chadderdon et al. 2014).

Ultrasound is also used to investigate the elasticity of certain tissues in a technique called shear-wave elasticity (for review, see Nowicki and Dobruch-Sobczak 2016). Each tissue has a specific stiffness that can be altered when lesions or scar tissue is present, allowing for quantitative assessment of tissue damage in a noninvasive manner. Although current use in NHPs is in its initial phases, shear-wave ultrasound in humans has proven very valuable to quantify and monitor the development of NAFLD (Palmeri et al. 2011) and adipose tissue (Sasso et al. 2016). The application of this technique in NHPs will likely be valuable for investigating the development, progression, and treatment of NAFLD and hepatic fibrosis. The field of molecular imaging using techniques such as contrast-enhanced ultrasound, shear-wave ultrasound, SPECT, and other imaging modalities is an important area to expand, as these techniques are readily applicable to the study of obesity in humans and allow for noninvasive measurements in a longitudinal fashion.

Other studies have examined cardiovascular function in both diabetic and nondiabetic cynomolgus macaques. Using echocardiographic instrumentation, Gu and colleagues (Gu et al. 2015) demonstrated that significant differences in cardiac function were evident between the two groups, with the diabetic animals exhibiting significant left ventricular (LV) diastolic dysfunction, which included higher end-systolic volume and lower end-diastolic volume and decreased ejection fraction as well as a greater left arterial maximal dimension. Their detailed statistical analysis of the data collected clearly demonstrated a pattern of myocardial ischemia and cardiac remodeling very similar to that observed in humans with LV dysfunction (Gu et al. 2015). Importantly, the use of NHPs allows investigators to concurrently obtain tissue samples (e.g., heart, vasculature, liver, kidney, etc.) at the time of imaging that can be used to better assess the anatomical changes observed with advanced imaging studies. In another imaging study on cardiac remodeling in baboons exposed to intrauterine growth restriction (IUGR), Kuo and colleagues (Kuo et al. 2017) used MRI to assess the cardiac changes in offspring of animals exposed to a 30% maternal caloric restriction. Comparing juvenile IUGR animals with age- and sex-matched controls, the investigators reported that the IUGR animals displayed both impaired systolic and diastolic cardiac function, including ejection fraction, 3-dimensional sphericity indices, LV wall thickness, and average filling rate. Perhaps most interesting result was that the cardiac characteristics of the juvenile IUGR animals were consistent with the same traits assessed in a cohort of geriatric baboons (Kuo et al. 2017). Based on these findings, it is plausible that IUGR in this NHP model may lead to accelerated cardiac remodeling (Kuo et al. 2017).

In addition, Kochunov and colleagues (Kochunov et al. 2017) have utilized perfusion-weighted MRI to assess changes in cerebral blood flow in response to alterations in glucose levels in baboons. Following a 20-minute baseline assessment, they exposed baboons to a hyperglycemic challenge over the course of 40 minutes with scans taken every 7 seconds to map changes in cerebral blood flow (CBF). As a result, they were able to map changes in CBF across four clusters consisting of the cerebral cortex, thalamus, hypothalamus, and mesencephalon. Interestingly, they found that CBF in the hypothalamus followed rises in systemic glucose levels, while CBF declined in the other brain regions. Furthermore, CBF in the hypothalamus was the first of the four regions to return to baseline following exposure to hyperglycemia (Kochunov et al. 2017).

Energy Expenditure and Calorimetry

Monitoring and accurate assessments of energy expenditure and metabolic rate are important components of metabolic phenotyping studies in NHPs, particularly those assessing the efficacy and mechanisms of pharmacological or (bariatric) surgical interventions designed to produce weight loss in the management of obesity, particularly since both the interventions themselves and the changes of weight can influence energy expenditure. The two major approaches for assessing energy expenditure in NHPs are the calorimetry chamber technique for measuring oxygen consumption and carbon dioxide production and the doubly-labeled water technique, which measures stable isotopic dilution to estimate carbon dioxide production (Yamada et al. 2013). In addition, a multisensory activity monitor using accelerometry and skin temperature responses (Sensewear, BodyMedia, Inc) placed in specially designed jackets has been used to estimate resting and total energy expenditure in baboons (Casiraghi et al. 2013). However, an advantage of indirect calorimetry is that the respiratory quotient as well as rates of carbohydrate and lipid oxidation can be calculated from measurements of oxygen consumption and carbon dioxide production. For example, specifically designed metabolic chambers were used to measure 24-hour energy expenditure in rhesus macaques before and during consumption of a high-sugar (fructose) diet and demonstrated that 24-hour energy expenditure was decreased with the development of diet-induced obesity and metabolic syndrome in this model (Bremer et al. 2011). Indirect calorimetry and doubly-labeled water have also been used to assess the influences of age and sex on energy expenditure and the effects of long-term caloric restriction in rhesus macaques (Blanc et al. 2003; Raman et al. 2007; Ramsey et al. 1997, 2000; Yamada et al. 2013). Furthermore, these techniques have been used to demonstrate that oxytocin administration increases energy expenditure in diet-induced obese rhesus macaques (Blevins et al. 2015).

Examples of the Use of Nonhuman Primate Models in Pharmaceutical Target Validation

In this section, we will highlight a number of selected examples in which studies performed in NHP models have been valuable as translational studies of novel therapeutics for metabolic diseases. Specifically, NHPs have been used to evaluate the pharmacological profiles of several new compounds for the treatment of type 2 diabetes, including the insulin secretogogue nateglinide (Dunning et al. 2003) and gemigliptin (LC15-0444), a novel dipeptidyl peptidase-4 inhibitor (Kim et al. 2016). NHP models are also useful to assess potential toxicities in new and approved agents for the treatment of type 2 diabetes. For example, glucagon-like peptide-1 (GLP-1) receptor agonists have been implicated in preclinical and clinical studies as a potential risk factor for acute pancreatitis; however, chronic dosing of cynomolgus macaques with dulaglutide did not induce inflammatory or preneoplastic changes in the exocrine pancreas (Vahle et al. 2015a). Moreover, the lack of an effect of dulaglutide on thyroid C cells in cynomolgus macaques is consistent with other studies in NHPs using GLP-1 receptor agonists and suggests that NHPs are less sensitive than rodents to the induction of proliferative changes in thyroid C cells by GLP-1 receptor agonists (Vahle et al. 2015b), again underscoring the importance of using animal models more directly relevant to humans to evaluate novel therapies for metabolic diseases.

As an example of therapeutic validation, the administration of an antisense oligonucleotide (ASO) targeting protein tyrosine phosphatase 1β in liver and adipose tissue to obese insulin-resistant rhesus macaques lowered plasma TG concentrations and increased insulin sensitivity as demonstrated by decreases of fasting insulin concentrations and an ISI index determined from insulin responses during IVGTTs (Swarbrick et al. 2009). Interestingly, treatment with the protein tyrosine phosphatase 1β ASO also resulted in increased circulating adiponectin levels, mainly consisting of the more bioactive high-molecular-weight form of adiponectin within 4 weeks, suggesting one potential mechanism contributing to the insulin sensitizing effects of the treatment (Swarbrick et al. 2009). Moreover, with respect to the management of dyslipidemia, a recent study demonstrated that antagonism of a microRNA expressed in the liver (mIR-33) in vervets targeting genes involved in lipogenesis and fatty acid oxidation improved the ratio of HDL-C to VLDL-C through modulating oxysterol-binding protein like 6, providing a potentially novel

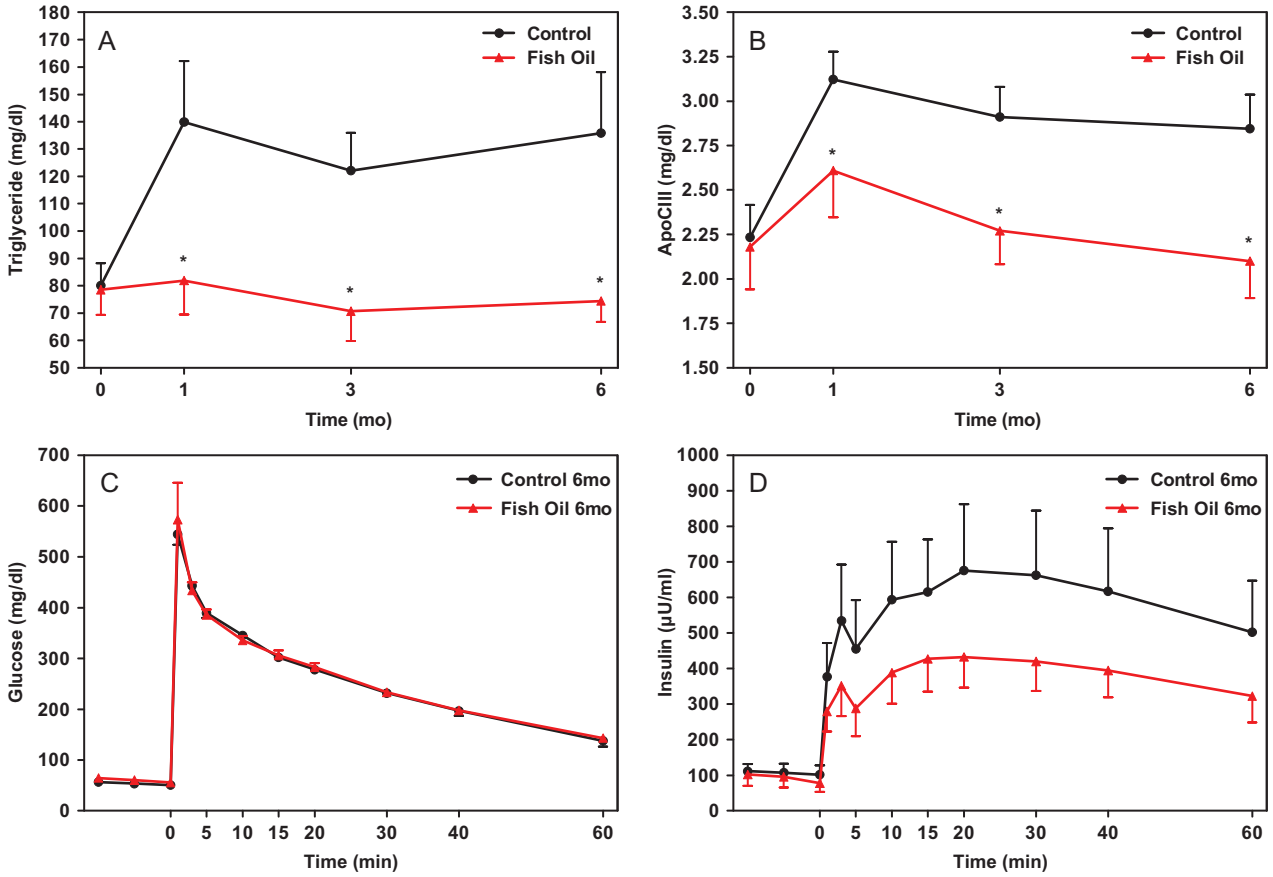

Figure 2 The effect of fish oil on fasting plasma triglyceride (A) and apolipoprotein-CIII (B) concentrations in rhesus macaques fed a high-fructose diet for 6 months. *$P \leq 0.05$ between control and fish oil-treated groups by linear mixed model. Plasma glucose (C) and insulin (D) responses during an intravenous glucose tolerance test (IVGTT) in control monkeys and monkeys supplemented with fish oil after 6 months on the high-fructose diet. Glucose excursions (C) did not differ between the two treatment groups; however, glucose-induced insulin secretion (D) during the IVGTT was significantly increased after 6 months on fructose compared with the fish oil-treated animals. Control group, $n = 9$; fish oil group, $n = 10$. Error bars show SEM. Data are from Bremer et al. 2014.

therapeutic to treat dyslipidemia in humans (Ouimet et al. 2016; Rayner et al. 2011). Furthermore, supplementation with 4 g/day of whole fish oil largely prevents the increases of plasma TG (Figure 2A) and apolipoprotein-C3 (Figure 2B) concentrations and the development of insulin resistance (Figure 2, C and D) (Bremer et al. 2014) observed in the fructose-fed rhesus macaque model of metabolic syndrome (Bremer et al. 2011). In addition, a high dose of omega-3 FA-ethyl esters of EPA and DHA from fish oil has previously been shown to interrupt the formation of vascular lesions and thrombi, without marked effects on platelet function, in baboons (Harker et al. 1991). These results suggest that the doses of omega-3 fatty acids used in many studies in humans are too low and indicate that diet-induced NHP models of metabolic dysfunction will be valuable for identifying the bioactive components and mechanisms by which marine-derived omega-3 fatty acids exert their beneficial metabolic effects on dyslipidemia and insulin resistance (Lorente-Cebrian et al. 2013) and potentially fatty liver disease as well (de Castro and Calder 2017).

A clear example of how the use of an NHP model can provide important new insights into our understanding of molecular pathways of potential pharmacological interest is demonstrated by a study by Lin and colleagues (Lin et al. 2008) evaluating the potential role of TrkB in appetite regulation. Previous studies in rodents had reported that either peripheral or central stimulation of TrkB by its natural ligands, BDNF or NT4, reduced body weight and food intake. However, Lin and colleagues (Lin et al. 2008) found that while central administration of TrkB produced an anorexigenic effect leading to weight loss as seen in rodents, peripheral administration produced an orexigenic effect resulting in increased appetite and weight gain. As a result, these experiments in baboons revealed the dual nature of the control of TrkB signaling in energy homeostasis and pathways that could be targeted for the treatment of either wasting disorders or obesity. This discrepancy between the mechanism of action of a therapeutic between rodent and NHP models has also been observed for other proteins, including orexin. For example, a study by Ramsey and colleagues (Ramsey et al. 2005) demonstrated that injection of orexin A into the central nervous system of rhesus macaques resulted in significant decreases of food intake, contrary to the increase of food intake that is observed after a central injection of orexin A in rats.

The melanocortin receptor 4 pathway has been an intriguing target for the treatment of obesity because of its crucial role in the homeostatic regulation of energy balance via effects on food intake and energy expenditure. Activation of this pathway with melanocortin receptor 4 agonists can result in decreased food intake and weight loss, but is often associated with detrimental side effects such as increased skin pigmentation and elevations of blood pressure and heart rate (Greenfield et al. 2009). However, peptide-based agonists that retain similar biological properties as the endogenous hormone alpha-MSH can induce weight loss through a combination of decreasing food

intake and increasing energy expenditure in obese NHPs without producing adverse cardiovascular effects (Chen et al. 2015; Kievit et al. 2013). One such drug, setmelanotide, is currently in clinical development for the treatment of metabolic disorders resulting from specific genetic deficiencies (Kuhnen et al. 2016).

Advantages and Limitations of NHP Models

Important advantages of NHP models include their close genetic identity and physiological similarity to humans. The baboon and rhesus macaque genomes have been sequenced, and this information can be used in target identification and validation studies. Another advantage of studies in NHPs compared with humans is that diet and pharmacological interventions can be well controlled, whereas compliance with dietary and drug treatment regimens is generally quite poor in free-living human subjects. In fact, in dietary studies in NHPs, compliance with the dietary regimen can be known with near certainty. In addition, biopsies of a variety of tissues including intra-abdominal adipose tissue, liver, and kidney can be sequentially performed in studies of NHPs, particularly when minimally invasive approaches (e.g., laparoscopic biopsies) are employed. In contrast, in humans, these samples can be obtained only in cross-sectional studies, usually at a single time point during elective abdominal or bariatric surgery, seriously limiting subject selection as well as the ability to assess the longitudinal effects of different interventions. Tissues samples that cannot be accessed and studied in humans, including specific CNS regions involved in energy balance, memory, and cognition (e.g., hypothalamus, hippocampus and cortex), large blood vessels, kidney, and pancreatic islets, can also be obtained at the time of necropsy in NHP studies that are designed to have a terminal endpoint.

The major disadvantages of using NHPs versus other animal models include the limited number of animals available for study and the expense of maintaining colonies of NHPs and in performing experimental procedures in the animals. In addition, there are a relatively small number of facilities that have the resources and technical expertise required to provide support for NHP research (e.g., the NPRCs). However, research studies utilizing other larger animal species such as pigs and dogs (which are less closely related to humans) are also quite expensive and require larger and more sophisticated facilities for maintaining and studying these animals than those required for studies performed only in rodent models.

Conclusions Regarding the Importance/Value and Future of NHPs in Metabolic Disease Research

Given the enormous impact of metabolic disease on human health, and the investment in metabolic disease research by the private and public sectors, reliable preclinical models of human physiology and disease are needed. Importantly, NHPs provide such a model. First, compared with rodents, NHPs exhibit greater similarity to human physiology and susceptibility to metabolic diseases (Gibbs et al. 2007; Rogers and Gibbs 2014) and have been shown to be susceptible to adult-onset obesity, accompanied by insulin resistance, dyslipidemia, hypertension, and type 2 diabetes (Bodkin et al. 1996; Hansen and Bodkin 1993). Second, the genomes of several NHP species commonly used in biomedical research have been sequenced (Gibbs et al. 2007; Pennisi 2007), enabling comparative genetic studies with humans. For example, the human and rhesus macaque genomes are ~93% similar, and each species is believed to have shared a common ancestor ~25 million years ago (Gibbs et al. 2007). In contrast, and again underscoring the importance of NHPs in biomedical research, rodents are believed to have separated from humans more than 70 million years ago (Gibbs et al. 2004; Kumar and Hedges 1998). Third, NHPs have successfully been used to study complex human metabolic traits, and the results derived from studies in NHPs have paralleled the results of later studies performed in humans (Ahren and Holst 2001; Havel and Ahren 1997), reinforcing the utility of NHPs as a preclinical animal model for investigating the physiology of human metabolism and the pathophysiology of metabolic dysfunction. Furthermore, NHP models provide unique advantages over rodent models for not only understanding human physiology, but also establishing the safety and efficacy of novel therapeutic compounds in humans.

As discussed above, studies using NHPs are enhanced by collaborations with investigators and access to facilities that have the requisite expertise and resources to effectively and ethically perform research in NHPs. While experimental investigations involving NHP species can often be more technically complex when compared with studies in rodent models, they remain far less expensive than performing similar clinical trials in humans (Courtine et al. 2007). As has been noted by others (Courtine et al. 2007), the financial cost associated with a single human clinical trial could support many studies in NHPs. In turn, these studies are likely to lead to greater and more rapid advances in the evaluation and translation of novel therapies, maximizing the cost/benefit ratio and the return on the initial investments. Importantly, highly significant efficacy and safety concerns that were not detected in rodent studies may be subsequently identified in preclinical studies in NHPs, thereby protecting valuable time and financial resources and potentially adverting adverse events incurred in the performance of unsuccessful clinical trials in human subjects.

An important future direction for the use of NHPs is the investigation of the relationships between diet-induced metabolic dysfunction, cognitive decline, and dementia (including Alzheimer's dementia), since both insulin resistance without hyperglycemia and overt diabetes are being increasingly recognized as important independent risk factors for cognitive impairment and its decline with aging (Diehl et al. 2017; Neergaard et al. 2017; Pugazhenthi et al. 2016). Insulin resistance occurs in the brain, and insulin signaling is impaired with the progression of diabetes in rodents (Agrawal et al. 2014). Furthermore, the administration of glucagon-like-peptide agonists has beneficial effects on the central nervous system in rodents (Agrawal et al. 2014) and in humans (Talbot 2014; Tramutola et al. 2017). Importantly, insulin signaling in the brain is involved in both cognitive function (Kullmann et al. 2016) and in the central regulation of metabolism, including hepatic glucose production and peripheral glucose disposal (Schwartz et al. 2013). The decline of cognitive function in NHPs has also been well described (Eberling et al. 1997; Moss et al. 2007; Peters et al. 1996). There is evidence that feeding a HFHS diet for 2 years can activate pathways involved in oxidative stress, apoptosis, and inflammation (e.g., NF-κB) in the cortex of middle-age male rhesus macaques (Bernier et al. 2016). Conversely, ongoing studies at the Wisconsin Primate Center have demonstrated that prolonged caloric restriction can protect against age-related diseases, including inflammation in the central nervous system (Sridharan et al. 2013), supporting the hypothesis that nutritional status modulates the health of the central nervous system. Important for understanding relationships between structure and function, both cognitive function and markers of synaptic morphology and plasticity can be studied in the same animal using NHP models (Hara et al. 2012, 2014,

2016; Morrison and Baxter 2012). As such, performing these types of studies in NHP with diet-induced metabolic dysfunction/metabolic syndrome, including insulin resistance, glucose intolerance, and dyslipidemia, will be important in understanding the impact of dietary components (both harmful and protective) and their metabolic sequelae in the etiology, prevention, and treatment of cognitive decline and dementia in humans.

Acknowledgments/Grant Support

Dr. Havel acknowledges technical and logistical support from James Graham, Ross Allen, Sarah Davis, Jenny Short, and the Primate Services and Primate Medicine Units of the California National Primate Research Center (base grant no. OD-0111107) and research funding from the American Diabetes Association and NIH grants AT-002599, AT-003645, DK-095960, HL-121324, and U24-DK-092993 and from Bristol Myers Squibb, Princeton, NJ. We thank Dr. Jon Ramsey (UC, Davis) for his input on the Energy Expenditure/Calorimetry section.

Disclaimer

The contents of this article represent the authors' views and do not constitute an official position of the National Institutes of Health or the United States Government.

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