УДК 57.088.6:599.824
https://doi.org/10.20538/1682-0363-2024-2-151-161

Monkeys excluding apes as a model for studies on metabolic syndrome

Orlov S.V.[1, 2], Uspensky Yu.P.[3], Fominykh Yu.A.[3, 4], Kolesnik Yu.A.[1, 2], Panchenko A.V.[1, 2]

[1] *Kurchatov Complex for Medical Primatology, National Research Center Kurchatov Institute*
177, Mira Str., Vesyoloe Village, Adler District, Sochi, Krasnoyarsk Region, 354376, Russian Federation

[2] *Saint Petersburg State University*
7/9, Universitetskaya Embankment, Saint Petersburg, 199034, Russian Federation

[3] *Saint Petersburg State Pediatric Medical University*
2, Litovskaya Str., Saint Petersburg, 194100, Russian Federation

[4] *Almazov National Medical Research Center*
2, Akkuratova Str., Saint Petersburg 197341, Russian Federation

ABSTRACT

Aim. To summarize the results of research on metabolic syndrome in monkeys excluding apes and to conduct a comparison with humans.

A search for full-text publications in PubMed and Scopus databases was carried out using the following keywords: nonhuman primate, monkey, obesity, diabetes mellitus, metabolic syndrome, insulin, atherosclerosis, hypertension. Articles were selected that describe studies involving the following monkey species: cynomolgus monkeys (*Macaca fascicularis*), rhesus macaques (*Macaca mulatta*), baboons (*Papio* sp.), grivets (*Cercopithecus aethiops*), and common marmosets (*Callithrix jacchus*).

The development of various metabolic syndrome criteria was demonstrated in all monkey species reviewed. Many similarities with humans were revealed: macaques with obesity, insulin resistance, and type 2 diabetes mellitus demonstrated an increase in total cholesterol, triglycerides, and free fatty acids and a decrease in the concentration of high-density lipoprotein cholesterol. Obesity and insulin resistance were precursors to impaired carbohydrate metabolism. Blood pressure increased along with the progression of insulin resistance. The similarity of genetic and environmental risk factors between humans and monkeys is important in the development of metabolic syndrome.

The reviewed data suggest that the use of monkeys in biomedical research remains an indispensable resource for the study of pathogenesis and assessment of the efficacy and safety of new therapeutic strategies targeting clinically important metabolic diseases, including obesity, dyslipidemia, atherosclerosis, type 2 diabetes mellitus, and, possibly, other conditions associated with metabolic syndrome.

Keywords: monkeys, model, metabolic syndrome, obesity, diabetes mellitus, arterial hypertension

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The work was conducted as part of the megagrant program of the Government of the Russian Federation under Agreement No. 075-15-2022-1110 of 30.06.2022 and the roadmap of the Kurchatov Complex for Medical Primatology.

For citation: Orlov S.V., Uspensky Yu.P., Fominykh Yu.A., Kolesnik Yu.A., Panchenko A.V. Monkeys excluding apes as a model for studies on metabolic syndrome. *Bulletin of Siberian Medicine.* 2024;23(2):151–161. https://doi.org/10.20538/1682-0363-2024-2-151-161.

✉ *Panchenko Andrey V.,* ando_pan@mail.ru

Низшие обезьяны как модельный объект изучения метаболического синдрома

Орлов С.В.[1, 2], Успенский Ю.П.[3], Фоминых Ю.А.[3, 4], Колесник Ю.А.[1, 2], Панченко А.В.[1, 2]

[1] Курчатовский комплекс медицинской приматологии «Национальный исследовательский центр (НИЦ) «Курчатовский институт»
Россия, 354376, г. Сочи, Адлерский р-н, с. Весёлое, ул. Мира, стр. 177

[2] Санкт-Петербургский государственный университет (СПбГУ)
Россия, 199034, г. Санкт-Петербург, Университетская наб., 7-9

[3] Санкт-Петербургский государственный педиатрический медицинский университет (СПбГПМУ)
Россия, 194100, г. Санкт-Петербург, Литовская ул., 2

[4] Национальный медицинский исследовательский центр (НМИЦ) им. В.А. Алмазова
Россия, 197341, г. Санкт-Петербург, ул. Аккуратова, 2

РЕЗЮМЕ

Цель работы – обобщение результатов исследований по изучению метаболического синдрома на низших обезьянах, проведение сравнительной характеристики с человеком.

Осуществлен поиск полнотекстовых публикаций в базах данных PubMed, Scopus по ключевым словам: nonhuman primate, monkey, obesity, diabetes mellitus, metabolic syndrome, insulin, atherosclerosis, hypertension. Отобраны статьи, описывающие эксперименты с участием следующих видов обезьян: яванские макаки (*Macaca fascicularis*), макаки-резус (*Macaca mulatta*), павианы (*Papio sp.*), африканские зеленые мартышки (*Cercopithecus aethiops*), обыкновенные игрунки (*Callithrix jacchus*).

Развитие различных критериев метаболического синдрома показано у всех рассмотренных видов обезьян. При этом имеется много сходных с людьми черт: у макак с ожирением, инсулинорезистентностью и сахарным диабетом 2-го типа выявляются повышение уровня общего холестерина, триглицеридов и свободных жирных кислот, снижение концентрации холестерина липопротеидов высокой плотности. Предвестником нарушения углеводного метаболизма являются ожирение и инсулинорезистентность, по мере прогрессирования которой также увеличивается артериальное давление. В развитии метаболического синдрома немаловажным является сходство между людьми и обезьянами генетических и средовых факторов.

Возможность использовать обезьян в качестве биомодели человека остается незаменимым ресурсом для изучения патогенеза, оценки эффективности и безопасности новых терапевтических стратегий, направленных на клинически важные метаболические заболевания, включая ожирение, дислипидемию, атеросклероз, сахарный диабет 2-го типа и прочие состояния, ассоциированные с метаболической дисфункцией.

Ключевые слова: обезьяны, модель, метаболический синдром, ожирение, сахарный диабет, артериальная гипертензия

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена в рамках реализации программы мегагрантов Правительства РФ по соглашению от 30.06.2022 № 075-15-2022-1110 и тематического плана Курчатовского комплекса медицинской приматологии.

Для цитирования: Орлов С.В., Успенский Ю.П., Фоминых Ю.А., Колесник Ю.А., Панченко А.В. Низшие обезьяны как модельный объект изучения метаболического синдрома. *Бюллетень сибирской медицины.* 2024;23(2):151–161. https://doi.org/10.20538/1682-0363-2024-2-151-161.

INTRODUCTION

Metabolic syndrome (MS) is a complex of symptoms that combines a number of metabolic disorders, namely insulin resistance, central obesity, atherogenic dyslipidemia, and arterial hypertension. Historically, G. Reaven proposed the term “syndrome X” in 1988, which was later called “MS” to differentiate from syndrome X in cardiology [1]. The first formal definition of MS was proposed in 1998, it was clarified several times, and currently there are main diagnostic criteria for MS (waist circumference or body mass index) and additional ones (fasting glucose level, impaired glucose tolerance, glycated hemoglobin level, low-density lipoprotein cholesterol level, and blood pressure) [2, 3].

When diagnosing MS, Russian experts use the criteria adopted by the Russian Scientific Society of Cardiology, according to which the main criterion for MS is abdominal obesity (waist circumference). Additional criteria (the presence of two or more) include arterial hypertension, increased triglyceride levels, decreased high-density lipoprotein cholesterol, increased low-density lipoprotein cholesterol, fasting hyperglycemia, and impaired glucose tolerance [4]. At the same time, MS is not considered as an independent nosological entity. The pathogenesis of MS includes a variety of genetic and acquired conditions that fall under the definition of insulin resistance and systemic chronic low-grade inflammation. If left untreated, MS is largely associated with an increased risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases [5]. The prevalence of MS ranges from 20 to 25% in adults and from 0 to 19.2% in children, and in patients with T2DM, it reaches 80% [6]. With age, the likelihood of developing metabolic disorders increases [7].

The widespread occurrence of MS and its particular clinical significance predetermine the active study of the pathological physiological mechanisms and morphological manifestations of MS. A large number of experimental models have been created on various animal species. Diabetes and obesity are modeled using high-calorie diets, chemicals, modification of the genetic apparatus of the cell, etc. [8, 9]. A special place among animals used to study the pathogenesis of MS is occupied by monkeys, which, along with humans, belong to the order of primates. This is due to a close genetic relationship with humans and similar physiological changes associated with obesity and metabolic disorders, similar life expectancy, and aging [10, 11].

The laboratory primate model should be considered as an important translational crossover between basic studies in rodent models and clinical studies in humans. Previously, the suborder of monkeys included the broad nosed monkeys (*Platyrrhina*), or New World monkeys, and the narrow nosed monkeys (*Catarrhina*), or Old World monkeys, which include the apes (*Hominoidea*) and humans. Recently, primates have been classified into the suborders *Strepsirrhini* and *Haplorhini*, the latter including tarsiers and monkeys [12]. In English-language literature, the term *Non-human Primates* is usually used, which should be translated from English to Russian as “primates other than humans” according to the taxonomy of the order, and is important to consider when analyzing scientific data.

However, a question arises whether it is possible to generalize such a diverse order when describing it as a human biomodel. It is probably possible but with certain limitations. Thus, it has been shown that waist circumference was positively correlated with systolic and diastolic blood pressure, glucose levels, and insulin resistance in chimpanzees of both sexes, and body weight was correlated with systolic and diastolic blood pressure in female chimpanzees and with triglyceride levels in male chimpanzees. Moreover, waist circumference is more associated with metabolic risk factors than body weight, especially in female chimpanzees [13]. In captive populations of aging adult chimpanzees, T2DM was described based on persistent fasting hyperglycemia, the presence of glycosuria, and the age of the disease onset.

However, cardiac pathology in humans and chimpanzees differs according to histopathological studies of the affected chimpanzee heart. Sudden cardiac death in chimpanzees (as well as gorillas and orangutans) is usually associated with diffuse interstitial myocardial fibrosis of unknown etiology, while in humans most cardiac diseases are known to be associated with atherosclerotic lesions of the coronary arteries. A typical human myocardial infarction caused by coronary thrombosis is rare in these monkey species, despite the human-like blood lipid profiles potentially associated with a high coronary risk. On the contrary, heart attacks in chimpanzees are probably associated with arrhythmias caused by the aforementioned myocardial fibrosis [14].

Apes are currently practically not used in biomedical research for ethical reasons [15]. Therefore, other species of the Haplorhini suborder are of greater interest. Monkeys exhibit the development of various age-related diseases, including cardiovascular diseases, impaired glucose metabolism, redistribution and a general increase in the amount of fat [16]. The development of diabetes and obesity has been described in many monkey species. Among representatives of the Old World, diabetes develops in cynomolgus macaques (*Macaca fascicularis*), rhesus macaques (*Macaca mulatta*), baboons (*Papio sp.*), and African green monkeys or grivets (Cercopithecus aethiops) [17]. Among New World monkeys, diabetes has been described in common marmosets (*Callithrix jacchus*), squirrel monkeys (*Saimiri sciureus*), capuchins (*Cebus apella*) and tamarins (*Saquinus sp.*) [18, 19]. Obese cynomolgus macaques [14] and common marmosets have a number of metabolic parameters similar to those that determine MS in humans [18]. Below we will summarize the data on the criteria for MS in different species of monkeys excluding apes.

OBESITY, DYSLIPIDEMIA

Obesity can be induced in monkeys fed with a hypercaloric diet and is also often observed spontaneously, especially in rhesus monkeys, cynomolgus monkeys, African green monkeys and squirrel monkeys [20]. Hamilton et al. first reported characteristics of spontaneously obese middle-aged male monkeys in the early 1970s. Such rhesus macaques were characterized by hyperinsulinemia, hyperlipidemia, and with prolonged or severe obesity, the development of insulin-dependent DM was observed. It was shown that body weight was not a reliable indicator for determining the severity of obesity, and the amount of fat in an animal body was correlated best with waist circumference (r = 0.981) and the thickness of the skin fold on the anterior chest wall (r = 0.912). "Very obese" rhesus macaques of both sexes had a significant increase in fasting serum insulin levels, elevated insulin values after a glucose challenge, and insulin resistance [21].

In another study, in rhesus monkeys, waist circumference correlated best with body fat content (r = 0.90). There was also a strong linear relationship between waist circumference and plasma insulin levels (r = 0.66), impaired glucose tolerance (r = –0.53), but not with blood glucose levels, lipoprotein fractions or free fatty acids [22]. The pattern of abdominal fat distribution in the body of an obese person is similar [21].

Since obesity plays a key role in the progression of insulin resistance, MS, and T2DM, measuring body fat in animals is important [23]. Obesity is associated with increased levels of leptin in the blood of cynomolgus and rhesus macaques, as well as baboons. Leptin concentrations were often elevated in T2DM in rhesus and cynomolgus monkeys and were significantly correlated with body weight (r = 0.72). Moreover, leptin levels increased proportionately with insulin resistance and obesity in macaques, but decreased slightly with the development of T2DM and associated fat loss [17].

Leptin levels correlate positively with insulin concentration and body fat, with which adiponectin levels correlate negatively [14]. In a study on a population of African green monkeys of 98 males and 157 non-pregnant females, waist circumference was correlated with increased blood triglyceride concentrations. Moreover, females had a higher concentration of triglycerides than males and had a high risk of central obesity and a poor lipid profile [24]. Monkeys with diabetes with relative insulinopenia had elevated levels of cholesterol and triglycerides, which was associated with impaired activity of lipoprotein lipase, an insulin-dependent enzyme playing an important role in the catabolism of very low-density lipoproteins rich in triglycerides and to a lesser extent – low-density lipoproteins. In addition, in T2DM, the content of free fatty acids increases [17].

The development of obesity is accompanied by nonspecific tissue damage in the form of lipidosis and liver glycogenosis, as well as fatty infiltration of many organs [25]. Numerous studies of atherogenesis in monkeys exposed to a high-fat high-cholesterol diet demonstrated changes in the lipid profile similar to those in humans. Significant individual differences in the development of dyslipidemia and atherosclerosis were also established. In particular, no atherosclerotic changes were practically observed in some individuals, despite severe hypercholesterolemia [26]. The fatal fasting syndrome has been described in obese macaques, which is manifested by sudden death without previous signs of illness, often following short periods of anorexia or 20–30% body weight loss over a period of several days to two weeks. The pathogenesis of this syndrome has not been fully studied [27].

Baboons are considered as a model object for studying the genetics of obesity, in particular, genotyping and phenotypic characterization of a colony of baboons (more than 16,000 individuals traced in seven generations) is being carried out at the Southwest National Primate Research Center of the USA [28]. With increasing weight, animals showed an increase in body fat, waist circumference, and leptin concentration in the blood. Body composition analysis carried out using the bioelectrical impedance method showed that when female baboons reach 20 kg (average adult weight is 19 kg), and males reach 38 kg (average adult weight is 31 kg), the amount of body fat is 20%. Many indicators of carbohydrate metabolism and obesity (body weight, insulin, glucose, C-peptide, triglycerides, adiponectin) are largely hereditary [28, 29].

FASTING HYPERGLYCEMIA, IMPAIRED GLUCOSE TOLERANCE, T2DM

As in humans, rhesus macaques, cynomolgus macaques, and baboons have an association of T2DM with age and body weight, mainly due to obesity. About 30% of cynomolgus macaques over 15 years of age have basal and / or postprandial hyperinsulinemia [17]. In rhesus monkeys, insulin sensitivity decreases with age [30]. However, obesity alone is not enough to predict the development of T2DM. T2DM is a progressive disease in macaques. It is initially characterized by normal glucose tolerance and insulin resistance with compensatory hyperinsulinemia. All monkeys with progressive development of T2DM were obese, but some obese monkeys maintained normal glucose tolerance [31].

Cynomolgus and rhesus monkeys have insulin resistance and hyperinsulinemia for a long time before the development of overt DM [32]. Subsequently, amyloid is deposited, and the number of β-cells decreases in the pancreatic islets. Insulin secretion cannot be maintained at an elevated level, the concentration of circulating insulin decreases, and impaired glucose tolerance develops. The mechanisms are identical to those in humans [33]. As obesity, insulin resistance and T2DM progress, postprandial glucose levels increase earlier than fasting glucose concentrations [17]. Glycation increases due to non-enzymatic binding of glucose to amino acid groups of proteins. As in humans, in monkeys with hyperglycemia, the blood levels of fructosamine (a product of albumin glycation) and glycated hemoglobin increase [10, 34].

Finally, when endocrine pancreatic function is insufficient, animals with T2DM may have elevated fasting insulin levels, but they cannot respond adequately to glucose administration, and fasting glucose levels increase. Calorie restriction and the use of oral hypoglycemic drugs are effective for some time, but over time, exogenous insulin is often required [35]. Grivets are susceptible to developing obesity and diabetes when kept in captivity. Females are especially at risk for central obesity and a poor lipid profile. Females with elevated levels of glycated hemoglobin had impaired glucose tolerance and central obesity, but not insulin resistance. A strong hereditary pattern was found suggesting the presence of a monogenic form of diabetes, such as MODY diabetes mellitus or mitochondrial diabetes [36].

The determination of reference values for biochemical parameters for all monkey species (Tables 1–3) used in biomedical research is still an important issue. For example, blood glucose concentrations may be affected by the status of the animal before blood collection, the procedure itself (stress, sedation, anesthesia), handling of blood samples (duration and temperature of storage, bacterial contamination), and the reliability of the determination method used. The tables provide data reflecting the differences and partial registration of indicators in different studies. In monkeys, fasting glucose concentrations are 20–30 mg / dl lower (conversion: 1.1–1.7 mmol / l) than in humans, and fasting glucose concentrations in the range of 100–126 mg / dl (conversion: 5.6–7.0 mmol / l) clearly indicate diabetes [17, 34]. Fasting glucose concentration differs depending on the stage of carbohydrate metabolism disorder and increases significantly in overt T2DM.

Table 1

Some anthropometric and biochemical parameters of *M. mulatta* monkeys with metabolic disorders

Diet	Number and characteristics of animals	Fasting glucose, mmol / l	HbA1c	TC, mmol / l	TG, mmol / l	Insulin, μU / ml	Waist circumference, cm	Ref.
Standard*	4 obese males	3.5 ± 0.2	–	3.67 ± 0.34	0.99 ± 0.17	164.7 ± 37.9**	74.9 ± 5.4	[21]
	4 obese females	3.3 ± 0.2	–	4.09 ± 0.23	0.91 ± 0.02	109.7 ± 16.3**	58.4 ± 3.1	
	3 males without obesity	3.2 ± 0.2	–	2.61 ± 0.36	0.42 ± 0.05	26.2 ± 11.8**	36.5 ± 1.6	
	3 females without obesity	2.9 ± 0.1	–	3.49 ± 0.62	0.52 ± 0.08	48.2 ± 11.5**	36.3 ± 4.2	
Standard*	18 males with MS	4.46 ± 0.21	–	3.31 ± 0.19	1.04 ± 0.15	58.9 ± 15.8	52.14 ± 2.35	[37]
	17 control males	3.90 ± 0.10	–	3.50 ± 0.16	0.58 ± 0.05	18.5 ± 3.6	41.97 ± 2.49	

Table 1 (continued)

Diet	Number and characteristics of animals	Fasting glucose, mmol / l	HbA1c	TC, mmol / l	TG, mmol / l	Insulin, μU / ml	Waist circumference, cm	Ref.
Standard***	«Full health» stage. 12 males, 3.0–8.9 years old	3.7 ± 0.1	–	–	–	42.0 ± 3.0	– (4-16% of body fat	[31]
	The stage of severe hyperinsulinemia. 6 males, 14.3–19.6 years old, obese	4.4 ± 0.2	–	–	–	415.0 ± 84.2	– (25–44% of body fat)	
	The stage of overt diabetes. 7 males, 14.8–21.3 years old, obese	10.8 ± 1.1	–	–	–	45.0 ± 5.1	– (18–30% of body fat)	

* body weight in obese males exceeded by 207% and in females – by 173% the body weight of animals without obesity. ** converted from pmol / l (1 pmol / l = 0.144 μU / ml). *** Among 42 males aged 3–28 years, weighing 5.0–31.7 kg (28 animals were initially obese), 8 stages of carbohydrate and lipid metabolism disorders were identified from the "full health" stage to the "overt diabetes" stage, the latter was characterized by weight loss and severe glycosuria.

Table 2

Some anthropometric and biochemical parameters of *M. fascicularis* monkeys with metabolic disorders

Diet	Number and characteristics of animals	Fasting glucose, mmol / l	HbA1c	TC, mmol / l	TG, mmol / l	Insulin, μU / ml	Waist circumference, cm	Ref.
High in carbohydrates and low in cholesterol	Control – 7 males and 5 females	3.06 ± 0.13*	–	3.52 ± 0.18*	2.22 ± 0.31*	12.8 ± 2.2	–	[17]
	5 males and 3 females with hyperinsulinemia	3.83 ± 0.25*	–	3.65 ± 0.33*	1.76 ± 0.16*	56.5 ± 10.4	–	
	3 males and 7 females with impaired glucose tolerance	3.44 ± 0.22*	–	3.91 ± 0.77*	1.89 ± 0.33*	15.1 ± 1.6	–	
	4 males, 1 female with hyperinsulinemia and impaired glucose tolerance**	4.95 ± 0.57*	–	3.36 ± 0.52 8	5.69 ± 1.71*	62.7 ± 13.5	–	
Standard*	24 control males	3.19 ± 0.09 *	3.8 ± 0.3 %	2.77 ± 0.1*	0.80 ± 0.10*	11.4 ± 0.9	–	[17]
	17 males and 8 females with type 2 diabetes mellitus	14.44 ± 1.21 *	10.7± 1.4 %	4.24 ± 0.39*	9.13 ± 1.24*	90.6 ± 18.5	–	

* converted from mg / dl (glucose: 1 mmol / l = 18.018 mg / dl; TC: 1 mmol / l = 38.66 mg / dl, TG: 1 mmol / l = 88.5 mg / dl). ** animals in this group were obese, exceeding by 40% the average body weight of animals in other groups.

Table 3

Some anthropometric and biochemical parameters of *Cercopithecus aethiops* monkeys with metabolic disorders

Diet	Number and characteristics of animals	Fasting glucose, mmol / l	HbA1c	TC, mmol / l	TG, mmol / l	Insulin, μU / ml	Waist circumference, cm	Ref.
Standard*	157 females, general population	3.35 ± 0.13*	5.,48 ± 0.15 %	3.96 ±0.07*	1.00 ± 0.05*	27.7 ± 1.7	37.8 ± 0.39	[24]
	Control, 4 females	3.36 ± 0.26*	5.27 ± 0.19 %	–	1.27 ± 0.27*	20.8 ± 5.2	38.37 ± 0.36	
	Impaired glucose tolerance, 3 females	5.81 ± 0.41*	8.30 ± 0.40 %	–	3.05 ± 1.04*	26.5 ± 2.8	43.33 ± 2.17	

* converted from mg / dl (glucose: 1 mmol / l = 18.018 mg / dl; TC: 1 mmol / l = 38.66 mg / dl, TG: 1 mmol / l = 88.5 mg / dl).

ARTERIAL HYPERTENSION, CARDIOVASCULAR PATHOLOGY

Diagnosis of spontaneous arterial hypertension is challenging in monkeys. Awake animals must be restrained during the procedure, which is a stressful factor that increases blood pressure. The use of sedatives is usually accompanied by changes in blood pressure. And the use of telemetry systems is limited by the need for surgical implantation and the service life of the system itself [38]. Spontaneous arterial hypertension develops in rhesus monkeys and grivets [39]. Two models of hypertension in baboons showed a doubling of the number of fatty streaks in the abdominal aorta, iliofemoral artery, brachial artery, and coronary arteries after 13 months, regardless of plasma lipid levels [40].

Lesions of the main blood vessels cause death in people with T2DM and are associated with the progression of atherosclerosis leading to coronary heart disease and stroke [41]. Atherosclerotic manifestations are significantly more common in monkeys with spontaneous or drug-induced diabetes [26]. Cynomolgus macaques show an increase in blood pressure and inflammatory markers as they progress from insulin resistance to T2DM [19]. Rhesus macaques are some of many animal models for diabetic peripheral neuropathy and retinopathy [42], and glomerular dilation, glomerulosclerosis, and thickening of the glomerular basement membrane with hypertrophy have been described at the hyperinsulinemia stage of prediabetes [43]. Cynomolgus macaques with severe dyslipidemia, DM, and proteinuria showed left ventricular diastolic dysfunction with preserved ejection fraction and impaired cardiac reserve in dobutamine stress test, indicating the high translational potential of this model for humans [44]. This allows us to consider monkeys as a model for studying the role of insulin resistance in the development and progression of diabetic vascular diseases.

MS MODELING

In a study by a Chinese team [37], 408 adult *Macaca mulatta* males from three nurseries in China were screened. In accordance with the criteria for predisposition to MS in humans [3], the following ones were identified (three positive out of five): 1) blood pressure ≥ 120 / 75 mm Hg; 2) waist circumference ≥ 37 cm; 3) fasting plasma glucose ≥ 3.8 mmol / l; 4) fasting plasma triglycerides ≥ 0.45 mmol / l and above the 80th percentile; 5) HDL-C ≤ 1.10 mmol / l or below the 20th percentile. According to the selection method, the animals predisposed to metabolic syndrome had significantly higher blood pressure, fasting plasma glucose, waist circumference, and body weight than the controls. However, there were no differences between these groups in terms of triglycerides, HDL-C, LDL-C, total cholesterol or insulin [37].

After observing animals with a predisposition to MS, the authors proposed the following criteria to diagnose MS (≥ 3 positive out of five): 1) waist circumference ≥ 40 cm and waist-to-hip ratio ≥ 0.9; 2) fasting plasma glucose ≥ 4.40 mmol / l; 3) fasting plasma triglycerides ≥ 0.90 mmol / l; 4) HDL-C ≤ 1.55 mmol / l; 5) blood pressure ≥ 130 / 80 mm Hg. Eighteen monkeys met these criteria, among which one, four, and thirteen monkeys had a combination of 5, 4, and 3 positive MS criteria, respectively. The two most prevalent criteria were increased waist circumference (94%) and arterial hypertension (73%). The remaining criteria were found in combinations of varying frequency [37]. This pattern is similar to the one observed in humans [45].

DM MODELING

Historically, the most common methods for inducing diabetes have been partial or total pancreatectomy or the administration of alloxan, which causes rapid and complete loss of beta cells, soon after which hyperglycemia develops. The main factor limiting the use of alloxan is concomitant damage to the kidneys, adrenal glands, thyroid gland, pituitary gland, and liver [25]. A more specific beta cell toxin is streptozotocin, an antibiotic derived from *Streptomyces aromogenes*.

In monkeys, the administration of streptozotocin leads to severe hyperglycemia and dyslipidemia, which have some similarities with both type 1 and type 2 DM, however, changes in the pancreatic islets are more characteristic of type 1 DM [25]. The extent of damage to the islets of Langerhans varies, with some monkeys requiring more than one dose of streptozotocin to develop hyperglycemia. Animals do not develop insulin resistance unless it is combined with obesity or older age; correction insulin doses are 1.0–5.0 U / kg of body weight per day [46]. Plasma cholesterol and triglyceride levels increase slightly when hyperglycemia is adequately controlled [47].

DISCUSSION

The development of metabolic disorders in monkeys has many similarities with humans. Cynomolgus macaques with obesity, insulin resistance, and T2DM have the same changes in the lipid profile as patients with T2DM, namely increased total cholesterol, triglycerides, and free fatty acids and decreased HDL-C concentrations [17]. T2DM is a progressive disease in both monkeys and humans [31]. As insulin resistance progresses, blood pressure also increases. The association of MS with systemic inflammation is important. C-reactive protein synthesized by the liver during the acute-phase inflammatory response correlates with insulin resistance and obesity, as well as with an increased risk of developing T2DM and related cardiovascular diseases [48].

In cynomolgus macaques, the increase in C-reactive protein is stepwise when comparing control, insulin-resistant, and T2DM animals [17]. In grivets at high risk of MS, there is constant activation of the immune system associated with an increase in the proinflammatory cytokine interleukin (IL)-6 and mediated by resident gram-negative microbial communities that are formed in the visceral adipose tissue in both lean and obese individuals [49].

In addition to the similarity of pathogenetic characteristics in the development of MS, the similarity of genetic and environmental factors is also important. Since such factors are difficult to control in clinical practice, models of metabolic disorders in monkeys become unique in the context of studying the influence of genetic and environmental factors (diet, stress) on the development of obesity, DM, and MS. In controlled colonies of animals with a known pedigree, it becomes possible to study gene – environment interactions [24, 50].

Heredity has a strong effect on the body weight of baboons ($h^2 = 0.9$). Obviously, there appears to be a set of genes associated with insulin resistance that are also likely to affect obesity-related phenotypes, which confirms a common genetic basis for the development of insulin resistance and obesity [51]. Glucose transporter 4 (GLUT4) mRNA expression is under significant genetic influence and correlates with plasma insulin levels and body weight. This indicates a common genetic regulation of these phenotypic traits [28]. Diet is an important environmental factor influencing carbohydrate metabolism and obesity. Calorie restriction is beneficial for macaques since a positive effect is observed, namely a decrease in glucose and insulin levels and an increase in insulin sensitivity [52].

When keeping monkeys in captivity, it is routine practice to provide food *ad libitum*. Monkeys in groups have a certain social hierarchy (for example, a dominant or subordinate role), which determines differences in feeding behavior. The composition of the feed also matters. Many standard feeds (Purina, Teklad, etc.) use soybeans containing isoflavones (genistein, daidzein, etc.) as the main source of protein. Isoflavones are plant phytoestrogenic compounds that have an estrogenic or antiestrogenic effect, affecting the hormonal and metabolic parameters of animals. Adequate isoflavone intake level has not been established for monkeys [53].

Another environmental factor is stressful conditions of captivity. Thus, when kept in conditions of relative social crowding, grivets (*Chlorocebus aethiops*) and African red monkeys (*Erythrocebus patas*) coped significantly worse with glucose challenge test compared to their counterparts kept in smaller groups [17]. This factor may not be important for monkeys that live in large groups. For such species (for example, rhesus macaques), repeated reorganizations of the established social group are more stressful.

Primate models of MS are more adequate compared to rodents. For example, peroxisome proliferator-activated receptors (PPARs) have differences in expression levels and binding to regulatory elements in the apolipoprotein A1 (ApoA1) promoter between rodents and monkeys, which leads to opposite effects of PPAR agonists on ApoA1 production and HDL metabolism [54]. Thus, primate models have made a significant contribution to understanding the fundamental basis of the development of MS.

CONCLUSION

The ability to use monkeys as human biomodels remains an indispensable resource for studying the pathogenesis and assessing the efficacy and safety of new therapeutic strategies targeting clinically important metabolic diseases, including obesity, dyslipidemia, atherosclerosis, type 2 diabetes mellitus, and, possibly, other conditions associated with metabolic dysfunction.

REFERENCES

1. Cheng T.O. Cardiac syndrome X versus metabolic syndrome X. *Int. J. Cardiol.* 2007;119(2):137–138. DOI: 10.1016/j.ijcard.2006.06.062.
2. Dobrowolski P., Prejbisz A., Kuryłowicz A., Baska A., Burchardt P., Chlebus K. et al. Metabolic syndrome – a new definition and management guidelines. A joint position paper by the Polish Society of Hypertension, Polish Society for the Treatment of Obesity, Polish Lipid Association, Polish Association for Study of Liver, Polish Society of Family Medicine, Polish Society of Lifestyle Medicine, Division of Prevention and Epidemiology Polish Cardiac Society, "Club 30" Polish Cardiac Society, and Division of Metabolic and Bariatric Surgery Society of Polish Surgeons. *Arch. Med. Sci.* 2022;18(5):1133–1156. DOI: 10.5114/aoms/152921.
3. Alberti K.G.M.M., Eckel R.H., Grundy S.M., Zimmet P.Z., Cleeman J.I., Donato K.A. et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120(16):1640–1645. DOI: 10.1161/CIRCULATIONAHA.109.192644.

4. McCracken E., Monaghan M., Sreenivasan S. Pathophysiology of the metabolic syndrome. *Clinics in Dermatology*. 2018;36(1):14–20. DOI: 10.1016/j.clindermatol.2017.09.004.
5. Ivanov S.V., Uspensky Yu.P., Fomin Yu.A. Metabolic syndrome: from anthropoid primate to human. *Experimental and Clinical Gastroenterology.* 2017;143(7):135–140 (in Russ.).
6. Belete R., Ataro Z., Abdu A., Sheleme M. Global prevalence of metabolic syndrome among patients with type I diabetes mellitus: a systematic review and meta-analysis. *Diabetology & Metabolic Syndrome*. 2021;13(1):25. DOI: 10.1186/s13098-021-00641-8.
7. Ladabaum U., Mannalithara A., Myer P.A., Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. *Am. J. Med*. 2014;127(8):717–727.e12. DOI: 10.1016/j.amjmed.2014.02.026.
8. Kennedy A.J., Ellacott K.L.J., King V.L., Hasty A.H. Mouse models of the metabolic syndrome. *Disease Models & Mechanisms*. 2010;3(3–4):156–166. DOI: 10.1242/dmm.003467.
9. Romero-Nava R., García N., Aguayo-Cerón K.A., Sánchez Muñoz F., Huang F., Hong E. et al. Modifications in GPR21 and GPR82 genes expression as a consequence of metabolic syndrome etiology. *J. Recept. Signal Transduct Res*. 2021;41(1):38–44. DOI: 10.1080/10799893.2020.1784228.
10. Wagner J.D., Bagdade J.D., Litwak K.N., Zhang L., Bell-Farrow A.D., Wang Z.Q. et al. Increased glycation of plasma lipoproteins in diabetic cynomolgus monkeys. *Lab. Anim. Sci.* 1996;46(1):31–35.
11. Pound L.D., Kievit P., Grove K.L. The nonhuman primate as a model for type 2 diabetes. *Curr Opin. Endocrinol Diabetes Obes.* 2014;21(2):89–94. DOI: 10.1097/MED.0000000000000043.
12. Mammal Diversity Database. Zenodo. 2023 [Internet, cited 24 Jul 2023]. URL: https://zenodo.org/record/4139722. DOI: 10.5281/ZENODO.4139722.
13. Andrade M.C., Higgins P.B., Mattern V.L., Garza M.A.D.L., Brasky K.M., Voruganti V.S. et al. Morphometric Variables related to metabolic profile in captive chimpanzees (*Pan troglodytes*). *Comp. Med.* 2011;61(5):457–461.
14. Chen Y., Ogawa H., Narita H., Ohtoh K., Yoshida T., Yoshikawa Y. Ratio of leptin to adiponectin as an obesity index of cynomolgus monkeys (*Macaca fascicularis*). *Exp. Anim.* 2003;52(2):137–143. DOI: 10.1538/expanim.52.137.
15. Aguilera B., Perez Gomez J., DeGrazia D. Should biomedical research with great apes be restricted? A systematic review of reasons. *BMC Med. Ethics.* 2021;22(1):15. DOI: 10.1186/s12910-021-00580-z.
16. Chiou K.L., Montague M.J., Goldman E.A., Watowich M.M., Sams S.N., Song J. et al. Rhesus macaques as a tractable physiological model of human ageing. *Philos. Trans. R Soc. Lond. B, Biol. Sci.* 2020;375(1811):20190612. DOI: 10.1098/rstb.2019.0612.
17. Wagner J.D., Kavanagh K., Ward G.M., Auerbach B.J., Harwood H.J., Kaplan J.R. Old world nonhuman primate models of type 2 diabetes mellitus. *ILAR Journal*. 2006;47(3):259–71. DOI: 10.1093/ilar.47.3.259.
18. Tardif S.D., Mansfield K.G., Ratnam R., Ross C.N., Ziegler T.E. The marmoset as a model of aging and age-related diseases. *ILAR Journal.* 2011;52(1):54–65. DOI: 10.1093/ilar.52.1.54.
19. Harwood H.J., Listrani P., Wagner J.D. Nonhuman primates and other animal models in diabetes research. *J. Diabetes Sci. Technol*. 2012;6(3):503–514.
20. Vaughan K.L., Mattison J.A. Obesity and aging in humans and nonhuman primates: A mini-review. *Gerontology*. 2016;62(6):611–617. DOI: 10.1159/000445800.
21. Kemnitz J.W., Goy R.W., Flitsch T.J., Lohmiller J.J., Robinson J.A. Obesity in male and female rhesus monkeys: Fat distribution, glucoregulation, and serum androgen level. *J. Clin. Endocrinol. Metab*. 1989;69(2):287–293. DOI: 10.1210/jcem-69-2-287.
22. Bodkin N.L., Hannah J.S., Ortmeyer H.K., Hansen B.C. Central obesity in rhesus monkeys: association with hyperinsulinemia, insulin resistance and hypertriglyceridemia? *Int. J. Obes. Relat. Metab. Disord.* 1993;17(1):53–61.
23. Cefalu W.T., Wagner J.D. Aging and atherosclerosis in human and nonhuman primates. *AGE*. 1997;20(1):15–28. DOI: 10.1007/s11357-997-0002-4.
24. Kavanagh K., Fairbanks L.A., Bailey J.N., Jorgensen M.J., Wilson M., Zhang L. et al. Characterization and heritability of obesity and associated risk factors in vervet monkeys. *Obesity*. 2007;15(7):1666–1674. DOI: 10.1038/oby.2007.199.
25. Wagner J.D., Cann J.A., Zhang L., Harwood H.J. Diabetes and obesity research using nonhuman primates. In: Nonhuman primates in biomedical research. Elsevier, 2012:699–732. DOI: 10.1016/B978-0-12-381366-4.00014-6.
26. Shelton K.A., Clarkson T.B., Kaplan J.R. Nonhuman primate models of atherosclerosis. In: Nonhuman primates in biomedical research. Elsevier, 2012:385–411. DOI: 10.1016/B978-0-12-381366-4.00008-0.
27. Donnelly T.M. Diagnosis: Fatal fasting syndrome of obese macaques. *Lab. Anim.* 2003;32(7):24–25. DOI: 10.1038/laban0803-24.
28. Cox L.A., Comuzzie A.G., Havill L.M., Karere G.M., Spradling K.D., Mahaney M.C. et al. Baboons as a model to study genetics and epigenetics of human disease. *ILAR J.* 2013;54(2):106-21. DOI: 10.1093/ilar/ilt038.
29. Tejero M.E., Voruganti V.S., Rodríguez-Sánchez I.P., Proffitt J.M., Blangero J., Cox L.A. et al. Genetics of variation in adiponectin in pedigreed baboons: evidence for pleiotropic effects on adipocyte volume and serum adiponectin. *Heredity (Edinb).* 2008;100(4):382–389. DOI: 10.1038/sj.hdy.6801089.
30. Tigno X.T., Gerzanich G., Hansen B.C. Age-related changes in metabolic parameters of nonhuman primates. *J. Gerontol. A Biol. Sci. Med. Sci.* 2004;59(11):1081–1088. DOI: 10.1093/gerona/59.11.1081.
31. Hansen B.C., Bodkin N.L. Heterogeneity of insulin responses: phases leading to Type 2 (non-insulin-dependent) diabetes mellitus in the rhesus monkey. *Diabetologia*. 1986;29(10):713–719. DOI: 10.1007/BF00870281.
32. Bodkin N.L. The rhesus monkey (*Macaca mulatta*): A unique and valuable model for the study of spontaneous diabetes mellitus and associated conditions. In: Sima A.F., Shafrir E., editors. Animal models in diabetes: A primer. Singapore: Taylor & Francis, Inc., 2000:309–325.

33. Kahn S.E., Prigeon R.L., Schwartz R.S., Fujimoto W.Y., Knopp R.H., Brunzell J.D. et al. Obesity, body fat distribution, insulin sensitivity and islet β-cell function as explanations for metabolic diversity. *J. Nutr*. 2001;131(2):354S–360S. DOI: 10.1093/jn/131.2.354S.
34. Cefalu W.T., Wagner J.D., Bell-Farrow A.D. Role of glycated proteins in detecting and monitoring diabetes in cynomolgus monkeys. *Lab. Anim. Sci*. 1993;43(1):73–77.
35. Hansen B.C. Investigation and treatment of type 2 diabetes in nonhuman primates. In: Joost H.G., Al-Hasani H., Schürmann A., editors. Animal models in diabetes research. Totowa, NJ: Humana Press; 2012:177–185. DOI: 10.1007/978-1-62703-068-7_11.
36. Cann J.A., Kavanagh K., Jorgensen M.J., Mohanan S., Howard T.D., Gray S.B. et al. Clinicopathologic characterization of naturally occurring diabetes mellitus in vervet monkeys. *Vet. Pathol*. 2010;47(4):713–718. DOI: 10.1177/0300985810370011.
37. Zhang X., Zhang R., Raab S., Zheng W., Wang J., Liu N. et al. Rhesus macaques develop metabolic syndrome with reversible vascular dysfunction responsive to pioglitazone. *Circulation*. 2011;124(1):77–86. DOI: 10.1161/CIRCULATIONAHA.110.990333.
38. Mitchell A.Z., McMahon C., Beck T.W., Sarazan R.D. Sensitivity of two noninvasive blood pressure measurement techniques compared to telemetry in cynomolgus monkeys and beagle dogs. *J. Pharmacol. Toxicol. Methods*. 2010;62(1):54–63. DOI: 10.1016/j.vascn.2010.04.005.
39. Vemuri R., Ruggiero A., Whitfield J.M., Dugan G.O., Cline J.M., Block M.R. et al. Hypertension promotes microbial translocation and dysbiotic shifts in the fecal microbiome of nonhuman primates. *Am. J. Physiol. Heart Circ. Physiol*. 2022;322(3):H474–485. DOI: 10.1152/ajpheart.00530.2021.
40. McGill H.C., Carey K.D., McMahan C.A., Marinez Y.N., Cooper T.E., Mott G.E. et al. Effects of two forms of hypertension on atherosclerosis in the hyperlipidemic baboon. *Arteriosclerosis*. 1985;5(5):481–493. DOI: 10.1161/01.ATV.5.5.481.
41. Danaei G., Lawes C.M.M., Vander Hoorn S., Murray C.J.L., Ezzati M. Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. *Lancet*. 2006;368(9548):1651–1659. DOI: 10.1016/S0140-6736(06)69700-6.
42. Simmons H.A. Age-associated pathology in rhesus macaques (*Macaca mulatta*). *Vet. Pathol.* 2016;53(2):399–416. DOI: 10.1177/0300985815620628.
43. Cusumano A.M., Bodkin N.L., Hansen B.C., Iotti R., Owens J., Klotman P.E. et al. Glomerular hypertrophy is associated with hyperinsulinemia and precedes overt diabetes in aging rhesus monkeys. *Am. J. Kidney Dis*. 2002;40(5):1075–1085. DOI: 10.1053/ajkd.2002.36348.
44. Wikstrom J., Liu Y., Whatling C., Gan L.M., Konings P., Mao B. et al. Diastolic dysfunction and impaired cardiac output reserve in dysmetabolic nonhuman primate with proteinuria. *J. Diabetes Complications*. 2021;35(4):107881. DOI: 10.1016/j.jdiacomp.2021.107881.
45. Franco O.H., Massaro J.M., Civil J., Cobain M.R., O'Malley B., D'Agostino R.B. Trajectories of entering the metabolic syndrome: The Framingham Heart Study. *Circulation*. 2009;120(20):1943–1950. DOI: 10.1161/CIRCULATIONAHA.109.855817.
46. Saisho Y., Butler A.E., Manesso E., Galasso R., Zhang L., Gurlo T. et al. Relationship between fractional pancreatic beta cell area and fasting plasma glucose concentration in monkeys. *Diabetologia*. 2010;53(1):111–114. DOI: 10.1007/s00125-009-1552-z.
47. Wagner J.D., Cline J.M., Shadoan M.K., Bullock B.C., Rankin S.E., Cefalu W.T. Naturally occurring and experimental diabetes in cynomolgus monkeys: a comparison of carbohydrate and lipid metabolism and islet pathology. *Toxicol. Pathol*. 2001;29(1):142–148. DOI: 10.1080/019262301301418955.
48. Lau D.C.W., Dhillon B., Yan H., Szmitko P.E., Verma S. Adipokines: molecular links between obesity and atheroslcerosis. *Am. J. Physiol. Heart Circ. Physiol*. 2005;288(5):H2031-H2041. DOI: 10.1152/ajpheart.01058.2004.
49. Ruggiero A.D., Vemuri R., DeStephanis D., Brock A., Block M.R., Chou J. et al. Visceral adipose microbial and inflammatory signatures in metabolically healthy and unhealthy nonhuman primates. *Obesity (Silver Spring)*. 2023;31(10):2543–2556. DOI: 10.1002/oby.23870.
50. Comuzzie A.G., Cole S.A., Martin L., Carey K.D., Mahaney M.C., Blangero J. et al. The baboon as a nonhuman primate model for the study of the genetics of obesity. *Obes. Res.* 2003;11(1):75–80. DOI: 10.1038/oby.2003.12.
51. Cai G., Cole S.A., Tejero M.E., Proffitt J.M., Freeland-Graves J.H., Blangero J. et al. , Comuzzie A.G. Pleiotropic effects of genes for insulin resistance on adiposity in baboons. *Obes. Res.* 2004;12(11):1766–1772. DOI: 10.1038/oby.2004.219.
52. Kemnitz J.W. Calorie restriction and aging in nonhuman primates. *ILAR J.* 2011;52(1):66–77.
53. Power M.L., Toddes B., Koutsos L. Nutrient requirements and dietary husbandry principles for captive nonhuman primates. In: Nonhuman primates in biomedical research. Elsevier; 2012:269–286. DOI: 10.1016/B978-0-12-381365-7.00010-8.
54. Willson T.M., Brown P.J., Sternbach D.D., Henke B.R. The PPARs: From orphan receptors to drug discovery. *J. Med. Chem.* 2000;43(4):527–550. DOI: 10.1021/jm990554g.

Authors' contribution

Orlov S.V., Uspensky Yu.P., Fominykh Yu.A., Panchenko A.V. – conception and design, analysis and interpretation of the data. Panchenko A.V., Kolesnik Yu.A. – drafting of the manuscript. All the authors conducted critical revision of the manuscript, made comments, and approved the final version of the manuscript for publication.

Authors' information

Orlov Sergey V. – Dr. Sci. (Med.), Professor, Corresponding Member of the Russian Academy of Sciences, Saint Petersburg State University; Scientific Supervisor, Kurchatov Complex for Medical Primatology, National Research Center Kurchatov Institute, Sochi, https://orcid.org/0000-0001-6080-8042

Uspensky Yuri P. – Dr. Sci. (Med.), Professor, Head of the Department of Intermediate-Level Therapy named after Professor V.A. Waldman, Saint Petersburg State Pediatric Medical University, Saint Petersburg, https://orcid.org/0000-0001-6434-1267

Fominykh Yulia A. – Dr. Sci. (Med.), Professor, Department of Intermediate-Level Therapy named after Professor V.A. Waldman, Saint Petersburg State Pediatric Medical University; Deputy Dean for Academic and Methodological Work, Almazov NMRC, Saint Petersburg, https://orcid.org/0000-0002-2436-3813.

Kolesnik Yulia A. – Researcher, Saint Petersburg State University; Laboratory of Pathological Anatomy, Kurchatov Complex for Medical Primatology, National Research Center Kurchatov Institute, Sochi, https://orcid.org/0000-0001-9440-5145

Panchenko Andrey V. – Dr. Sci. (Med.), Principle Researcher, Laboratory of Molecular Biology, Kurchatov Complex for Medical Primatology, National Research Center Kurchatov Institute, Sochi, ando_pan@mail.ru, https://orcid.org/0000-0002-5346-7646

(✉) **Panchenko Andrey V.,** ando_pan@mail.ru

Received 11.10.2023;
approved after peer review 20.10.2023;
accepted 02.11.2023