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Hyperlipidemia and Atherosclerosis: Experimental Models

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ABSTRACT

Cardiovascular diseases are the leading cause of death worldwide, and atherosclerosis is considered as the primary pathological process responsible for their development. Numerous studies have shown that high levels of low-density lipoproteins in the blood are one of the most significant risk factors for the development of atherosclerosis. Various models using both small and large animals, including genetically modified models – transgenic and knockout animals – are used to study the atherogenic process. Studies on hyperlipidemia and atherosclerosis commonly combine an atherogenic diet with genetic manipulations. However, none of the available models is ideal, as each has its own advantages and limitations in reproducing the lipoprotein profile and the extent of atherosclerosis compared to human cases.

This review presents literature data on modern models of hyperlipidemia in the most frequently studied laboratory animals: mice, rats, and rabbits.

Keywords: hyperlipidemia, atherosclerosis, experimental models

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Гиперлипидемия и атеросклероз: экспериментальные модели

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РЕЗЮМЕ

Известно, что сердечно-сосудистые заболевания являются основной причиной смертности во всем мире, а главным патологическим процессом, определяющим их развитие, считается атеросклероз. Многочисленные исследования показали, что высокие уровни липопротеинов низкой плотности в крови представляют собой один из наиболее значимых факторов риска развития атеросклеротического поражения артерий. Для изучения атерогенного процесса применяются различные модели как мелких, так и крупных животных, в том числе генетически модифицированных – трансгенных и нокаутированных.

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Как правило, в исследованиях гиперлипидемии и атеросклероза часто используют сочетанное применение атерогенной диеты и генетических манипуляций. Ни одна из предложенных к настоящему времени моделей не является идеальной, поскольку каждая имеет свои преимущества и ограничения в воспроизведении профиля липопротеинов и степени атеросклеротического поражения сосудистой стенки. В связи с этим выбор адекватной модели важен для каждого конкретного исследования.

В настоящем обзоре приведены литературные данные о современных моделях гиперлипидемии на наиболее часто используемых лабораторных животных – мышах, крысах и кроликах.

Ключевые слова: гиперлипидемия, атеросклероз, экспериментальные модели

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INTRODUCTION

Hyperlipidemia is a pathological condition characterized by a significant increase in levels of blood cholesterol and triglycerides [1]. Chronically elevated blood cholesterol levels are a major risk factor for cardiovascular diseases, resulting in the development of atherosclerosis and exerting a negative effect on the myocardium, primarily due to increased oxidative stress, mitochondrial and endothelial dysfunction, as well as induction of inflammation and apoptosis [2, 3]. Hyperlipidemia is classified either as primary, also known as familial, developing due to genetic defects and having a characteristic abnormal lipid profile, or secondary, acquired as a result of cooccurring diseases (diabetes, nephrotic syndrome, hypothyroidism, liver disease, etc.), or following increased consumption of saturated fats [1]. Clinically, hyperlipidemia is characterized by increased levels of atherogenic lipoproteins in the blood: low-density lipoprotein (LDL) cholesterol, reflected in an increase in total cholesterol in the blood, and very low-density lipoprotein (VLDL) cholesterol, reflected in an increase in triglyceride levels in the blood. Another important factor contributing to atherogenesis is a decrease of anti-atherogenic high-density lipoproteins (HDL) in the blood [1, 4].

The action of hypolipidemic drugs is aimed at eliminating such disorders. Statins, known as HMG-CoA reductase inhibitors, are first-line drugs for reducing LDL cholesterol levels [5]. However, despite adequate statin therapy, patients remain at significant risk of atherosclerosis progression and, consequently, at risk of developing cardiovascular complications [6, 7]. Therefore, there is a need for new therapeutic agents to effectively reduce the level of atherogenic cholesterol.

An important role in studying the effectiveness of new lipid-lowering drugs is attributed to experimental modeling of hyperlipidemia and atherosclerosis in laboratory animals. The following species are used for this purpose: mice, rats, hamsters, guinea pigs, rabbits, monkeys, zebrafish, minipigs, and farm pigs [1, 8, 9]. Small animals, such as mice, rats, and rabbits, are often used due to the ease of breeding, low cost of maintenance, and a relatively short period of development of hypercholesterolemia and atherosclerosis [10]. However, none of the current models accurately simulates the human lipid profile or the progression of atherosclerosis, since each has its own advantages and disadvantages [4, 10, 11].

This review summarizes current knowledge about mouse, rat, and rabbit models of hyperlipidemia and atherosclerosis. The review is based on the analysis of experimental and review articles available in the PubMed, Google Scholar, and eLIBRARY.ru databases. Key search terms present in the title or abstract were: hyperlipidemia, hypercholesterolemia, cholesterol, atherosclerosis, experimental models, atherogenic diet, mice, rats, rabbits, ApoE, Ldlr, APOE*3-Leiden, APOE*3-Leiden.CETP, PCSK9, Fbn1, SR-B1, ApoB100, CETP, WHHL rabbits, and SMHL rabbits. The search resulted in 9,767 publications: 7,915 English-language and 1,852 Russian-language articles. When studying the abstracts, 65 English-language and 3 Russian-language publications containing data from experimental and

review articles available in full-text versions were selected and included in the review.

EXPERIMENTAL MODELS

Mice, rats, and rabbits are resistant to spontaneous development of hyperlipidemia, but atherogenic diet and genetic manipulations make these animals more susceptible to the development of hypercholesterolemia [1]. The serum lipid profile of experimental animals of different species differs – in mice and rats, a significant part of the total cholesterol is contained in antiatherogenic HDL, and in rabbits, total cholesterol is more evenly distributed between the lipoprotein fractions [4]. Additionally, rabbits are characterized by high activity of the Cholesteryl Ester Transfer Protein (CETP) in the plasma, while mice and rats lack it [12]. However, the advent of technologies for the creation of transgenic and knockout animals partially solves the problem of reproducing the main features of the human disease in animal models [10, 11]. In general, animal models of hyperlipidemia and atherosclerosis are based on a combination of an atherogenic diet and genetic manipulations [13].

MOUSE MODELS WITHOUT GENETIC MANIPULATION

One of the widely used methods for inducing hyperlipidemia in mice is long-term (3 weeks for the development of hypercholesterolemia and 12 weeks for the formation of an atherosclerotic plaque) use of a diet containing cholesterol (0.5–1.25%) with additional substances, such as cholic acid (0.1–0.5%), vegetable or coconut oil, as well as corn starch and sucrose [1, 4, 14, 15]. This model of hyperlipidemia varies in the ratio of ingredients in the diet [16]. Overfeeding mice exclusively with sucrose or fructose causes hypertriglyceridemia [1]. Among inbred mouse lines, C57BL/6 mice were more susceptible to hyperlipidemia and atherosclerosis [10, 17]. Regarding the sex of mice, it is recommended to include both sexes in studies on hyperlipidemia and atherosclerosis due to the influence of sex hormones on cholesterol levels [18]. However, in practice, most studies on atherosclerosis are conducted only on male mice aged 6–8 weeks [18].

GENETICALLY MODIFIED MOUSE MODELS

The rate of atherogenesis can be significantly accelerated in genetically modified mice when fed with a high-cholesterol diet, the variants of which are presented in Table 1 [10,16–18]. Most atherogenic diets contain varying percentages of saturated fat and cholesterol, with or without cholic acid. The most frequently used diets in research are the Western-type diet and its modified analogues with a high cholesterol content [16–18]. According to the literature, these diets increase the level of total cholesterol within 2–3 weeks and lead to the formation of atherosclerotic plaques in some species within 8 weeks [18]. As for the Paigen diet and a similar modified Western diet with cholic acid, they induce atherosclerosis, and severe pulmonary hypertension and inflammatory reactions often occur [16–18].

Table 1

Most Commonly Used Atherogenic Diets in Mouse Hyperlipidemia Studies

Diet name	Diet composition
Western-type diet	21% fat, 0.2% cholesterol, 34% sucrose [16]
Modified Western-type diet with high cholesterol	4.4% fat, 1.0% cholesterol [16]
Modified Western-type diet with high cholesterol	15.75% fat, 1.25% cholesterol [16]
Modified Western-type diet with high cholesterol	21% fat, 1.25% cholesterol, 34% sucrose [18]
Modified Western-type diet with high cholesterol	21% fat, 1.25% cholesterol [18]
Modified Western-type diet with high cholesterol	40% fat, 1.25% cholesterol [10]
Modified Western-type diet with high cholesterol	21% fat, 1.25% cholesterol, 0.5% cholic acid [18]
High-sucrose diet	20% fat, 65% sucrose [18]
Palm oil diet	10% palm oil, 0.1% cholesterol [16]
Semi-synthetic diets (low- and high-fat)	2–18 % fat, 0–1.25 % cholesterol [16]
Paigen diet	15% fat, 1.25% cholesterol, 0.5% cholic acid [17]

The most commonly used mouse models for studying hyperlipidemia and atherosclerosis are apolipoprotein E (*ApoE*$^{-/-}$) and LDL receptor (*Ldlr*$^{-/-}$) gene knockout mice. [19]. These two models, however, are not universal and have both advantages and disadvantages, depending on the objectives of the study, since they differ in lipid and glucose metabolism, as well as other mechanisms involved in atherogenesis [20]. ApoE is synthesized by hepatocytes and macrophages and has a number of important antiatherogenic functions: it is a ligand for LDL receptors and LDL-associated proteins, promoting the capture of atherogenic particles from the bloodstream [21]. Therefore, homozygous deletion of the *ApoE* gene in mice results in a pronounced increase in blood LDL and VLDL cholesterol levels [20, 21].

The main disadvantage of the complete absence of the ApoE protein is that the model is dominated by high blood cholesterol levels compared to *Ldlr*$^{-/-}$ mice and, as a result, they develop severe atherosclerotic lesions of the aorta within a few weeks [19]. Significantly reduced HDL cholesterol levels and altered HDL composition are observed in *ApoE*$^{-/-}$ mice compared to *Ldlr*$^{-/-}$ mice [10]. Another disadvantage of *ApoE*$^{-/-}$ mice is that most of the cholesterol in the plasma is VLDL cholesterol, compared to LDL cholesterol in humans [21].

Thus, a limitation of the use of *ApoE*$^{-/-}$ mice is that they do not have a lipid profile similar to that in humans, unlike *Ldlr*$^{-/-}$ mice [13]. *Ldlr*$^{-/-}$ is a model that reproduces familial hypercholesterolemia (in which there is a genetic mutation in the LDL receptors), however, its main drawback is a milder degree of hyperlipidemia [1, 21]. First- and second-generation statin therapy had no hypocholesterolemic effect on *ApoE*$^{-/-}$ and *Ldlr*$^{-/-}$ mice, in contrast to third-generation statins, which, in turn, were effective only in the context of a diet containing a relatively low amount of cholesterol (0.15%) [21].

Third-generation statins were shown to suppress atheromatous plaque development in *ApoE*$^{-/-}$ mice [18]. Administration of ezetimibe, which selectively inhibits intestinal cholesterol absorption, effectively reduced cholesterol levels in the VLDL and LDL fractions and increased HDL cholesterol levels, resulting in reduction of aortic atherosclerotic lesions in *ApoE*$^{-/-}$ mice fed with a diet containing 0.15% cholesterol [20, 21]. These results were consistent with clinical observations in humans. Acyl-coenzyme A:cholesterol acyltransferases inhibitor (avasimibe) reduced blood cholesterol levels and prevented atherosclerosis in *ApoE*$^{-/-}$ mice [20].

ApoE$^{-/-}$ and *Ldlr*$^{-/-}$ models are considered to be unsuitable for evaluation of some drugs (e.g. proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors), which can be explained by the fact that human PCSK9 stimulates liver lipogenesis and aggravates the progression of atherosclerosis through mechanisms dependent on ApoE and LDL receptors [10, 18]. It is also known that monoclonal antibodies to PCSK9 did not affect the level of total cholesterol and the degree of atherosclerotic lesions in *ApoE*$^{-/-}$ mice. However, such treatment reduced the level of total cholesterol and triglycerides and weakened the severity of atherosclerosis in another mouse model – *APOE*-3Leiden.CETP* [10].

The next model was the *ApoE*$^{-/-}$/ *Ldlr*$^{-/-}$ double knockout mouse, which is a model with more severe hyperlipidemia and atherosclerosis [13]. This mouse model is considered to be suitable for studying the effect of lipid-lowering drugs without the use of an atherogenic diet [13, 21]. As for the therapeutic effect, it is known that in these mice, the acyl-coenzyme A:cholesterol acyltransferase inhibitor did not reduce the level of cholesterol in the blood, but it did reduce the degree of atherosclerotic damage to the aorta [21].

Transgenic *APOE*3-Leiden* (*E3L*) mice were generated by introducing a construct containing the human *APOE*3-Leiden* gene sequence into C57Bl/6 mice [21]. This apolipoprotein is associated with a familial form of hyperlipidemia [13]. Compared to *ApoE*$^{-/-}$ and *Ldlr*$^{-/-}$ mice, *APOE*3-Leiden* mice develop moderate hyperlipidemia (*ApoE*$^{-/-}$ mice have severe hyperlipidemia, while *Ldlr*$^{-/-}$ mice have mild hyperlipidemia) [21]. The advantage of this model over *ApoE*$^{-/-}$ mice is the absence of an inflammatory reaction [13]. Statin therapy was found to have hypolipidemic and antiatherosclerotic effects in *APOE*3-Leiden* mice [10, 21]. Avasimibe also reduced cholesterol levels and the extent of atherosclerotic lesions [23].

Transgenic *APOE*3-Leiden.CETP* mice were generated by crossing *APOE*3-Leiden* mice with mice expressing CETP [21, 23]. This model exhibits elevated basal cholesterol levels and a human-like lipoprotein profile characterized by a shift from HDL to an increased VLDL/LDL fraction [22]. Thus, *APOE*-3Leiden.CETP* mice are a preferred model for studying lipid metabolism compared to *ApoE*$^{-/-}$, *Ldlr*$^{-/-}$, *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$, and *APOE*3-Leiden* mice [23]. In addition, this model has well proven itself for assessing the hypolipidemic and antiatherosclerotic effects of drugs. In addition to statins, fibrates – PPARα (peroxisome proliferator-activated receptor alpha) agonists, PCSK9 inhibitors also demonstrated their efficacy [10, 24–29]. *APOE*-3Leiden.CETP* mice were a model of choice for evaluating the efficacy of PCSK9 monoclonal antibodies (alirocumab and evinacumab) in preclinical trials [26–29].

Various mouse models have been developed to study the effects of PCSK9 on lipid metabolism and atherosclerosis. PCSK9 plays an important regulatory role in cholesterol metabolism, due to the degradation of the LDL receptor [30]. Decreased LDL receptor levels de-intensify LDL metabolism, which can lead to hypercholesterolemia [30, 31]. Liver tissue is characterized by the highest level of PCSK9 expression in mice. However, it is also highly expressed in the intestine, and lower expression is observed in the kidneys, spleen, and aorta [31]. All plasma PCSK9 is secreted by the liver [31]. PCSK9 is known to be

involved in the development of atherosclerosis, and its inhibitors are now being used as new drugs to lower cholesterol levels [26–29, 31].

Therefore, some of the most popular models are those without germline editing that overexpress the human protein PCSK9 [10]. Overexpression of PCSK9, mediated by adeno-associated virus (*PCSK9-AAV*) induced hyperlipidemia (after 3 weeks) and atherosclerosis (after 12 weeks) in mice, when combined with an atherogenic diet (21% fat and 1.25% cholesterol) [30, 32, 33]. Phenotypically, this mouse model mimics *Ldlr*$^{-/-}$ mice [34]. Also, a transgenic mouse model (*hPCSK9tg)* expressing the human *PCSK9* gene was developed [35]. A study comparing the extent of aortic atherosclerosis in *hPCSK9tg/Ldlr*$^{-/-}$ and *hPCSK9tg/ApoE*$^{-/-}$ mice found that the latter had a larger area of aortic atherosclerosis and higher levels of total cholesterol and triglycerides in the blood [36]. Studies show that *hPCSK9tg* mice are well suited for screening various PCSK9 inhibitors (PKF8-mFc and evolocumab) [37]. In *PCSK9* knockout mice (*Pcsk9*$^{-/-}$), a 2–3-fold increase in the number of LDL receptors in the liver and very low levels of LDL cholesterol in the blood were reported [38, 39]. In these mice, plasma PCSK9 levels are undetectable, but LDL cholesterol levels are reduced by only 60%, suggesting a role of extrahepatic PCSK9 in their regulation [31, 37].

Mice with a mutation in the glycoprotein fibrillin-1 gene and knockout gene for the apolipoprotein E (*ApoE*$^{-/-}$*/Fbn1*$^{C1039G+/-}$) were also created [13]. Mutations in the *Fbn1* gene lead to Marfan syndrome, a genetic disorder characterized by fragmentation of elastic fibers [40]. This model was developed primarily to study unstable atheromatous plaques, with their subsequent rupture and associated complications. [13, 40]. It turned out that the area of atherosclerotic lesions in the aorta in *ApoE*$^{-/-}$*/Fbn1*$^{C1039G+/-}$ mice was 3 times larger than in *ApoE*$^{-/-}$ mice [40]. A limitation of this model is premature mortality of mice due to aortic aneurysm rupture. [13].

Another model for studying atherosclerotic plaque rupture is scavenger receptor class B type 1 (SR-B1) and apolipoprotein E (*SR-B1*$^{-/-}$*/ApoE*$^{-/-}$) knockout mice [10]. *SR-B1*$^{-/-}$*/ApoE*$^{-/-}$ mice developed severe coronary artery disease and obliterating coronary atherosclerosis even when fed with a standard diet [41]. The main limitation of this model is early mortality at 5–8 weeks of age [10, 41].

Transgenic mice expressing ApoB100 and lacking LDL receptor (*APOB100/Ldlr*$^{-/-}$) were developed to study hyperlipidemia and atherosclerosis. ApoB-100 is a component of VLDL and LDL which affects the uptake and subsequent degradation of LDL by the liver [42]. These mice, without the use of an atherogenic diet, showed a lipid profile very similar to that in humans, but their use is limited due to accompanying locomotor disorders, which makes these mice useful as a model of Alzheimer's disease [42].

Currently, the optimal models for studying the hypolipidemic and antiatherosclerotic effects of drugs are transgenic *APOE*3-Leiden.CETP* mice. To study different PCSK9 inhibitors, the *PCSK9-AAV*, *hPCSK9tg*, *hPCSK9tg/Ldlr*$^{-/-}$, and *hPCSK9tg/ApoE*$^{-/-}$ models are also common.

LIMITATIONS OF THE USE OF MICE IN HYPERLIPIDEMIA AND ATHEROSCLEROSIS STUDIES

Despite various genetic modifications and atherogenic diets, mouse models still have a number of shortcomings, primarily related to the distribution of the atheromatous plaque and the structure of the vascular wall [10]. Thus, the main site of atherosclerotic lesions in mice is the aortic sinus and the innominate artery, while in humans, it is the coronary and carotid arteries, as well as peripheral vessels [10, 43]. In mice, unlike humans, the arterial wall consists only of endothelium, without a layer of elastic connective tissue (subendothelium). In addition, the middle layer (tunica media) is less thick, and vasa vasorum is absent [44, 45]. Moreover, thrombotic lesions in the lumen of the vessel may not persist in mice, since the fibrinolytic balance is shifted towards lysis [43].

RAT MODELS WITHOUT GENETIC MANIPULATION

Currently, a number of diets have been proposed for the development of hyperlipidemia in Wistar and Sprague Dawley rats. They are presented in Table 2 [4, 10, 46–49]. Notably, the most commonly used protocol for inducing hypercholesterolemia, as in mice, was the addition of 1.25% cholesterol, 21% fat, and 34% sucrose to the animals' diet for 2–3 weeks to develop hyperlipidemia and for 8–12 weeks to develop mild atherosclerotic lesions in the aorta [46–49]. Also, for the induction of hyperlipidemia, intraperitoneal administration of Tween-80 or poloxamer 407 is possible, which leads to a rapid increase in the level of lipids in the blood, especially triglycerides. However, after a single administration, lipid levels decrease on day 5 [4, 50]. With regard to the development of an atheromatous plaque, it has long been believed that

rats are immune to the development of atherosclerosis if they are fed with an atherogenic diet exclusively [10]. For this purpose, vitamin D2, promoting aortic lipidosis, was sometimes added to the diet [4].

A disadvantage of this model for studying the therapeutic effect is the abnormal response to some drugs, such as statins. Instead of decreasing the activity of hepatic HMG-CoA reductase, reductase, statins significantly increase it, resulting in the lack of hypolipidemic effects [51]. Overall, there is currently no compelling evidence that rat models may have advantages over mouse ones [10].

Table 2

Most Commonly Used Atherogenic Diets in Rat Hyperlipidemia Studies

Diet name	Diet composition
Western-type diet	21% fat, 0.2% cholesterol, 34% sucrose [47]
Modified Western-type diet with high cholesterol	2% cholesterol, 0.2% cholic acid [46]
Modified Western-type diet with high cholesterol	21% fat, 1.25% cholesterol, 34% sucrose [47]
Modified Western-type diet with high cholesterol	21% fat, 1.25% cholesterol [48]
Modified Western-type diet with sucrose, cholic acid, and propylthiouracil	0.5% cholesterol, 0.2% cholic acid, 5% sucrose, 0.05% propylthiouracil [46]
High-cholesterol diet	1% cholesterol [46]
Modified Western-type diet with high cholesterol	3% cholesterol, 0.5% cholic acid, 1.5% vegetable oil [49]
High-cholesterol and cholic acid diet	2.43% cholesterol, 0.49% cholic acid [46]
Modified Western-type diet with high cholesterol, cholic acid, and propylthiouracil	3% cholesterol, 0.2% cholic acid, 0.5% propylthiouracil, 10% fat [46]
High-fat diet	33.5% fat, 1.5% soybean oil [46]
Modified Western-type diet with high cholesterol	1% cholesterol, 2% coconut oil [46]
High-cholesterol and cholic acid diet	2% cholesterol, 0.25% cholic acid [46]
High-cholesterol diet with cholic acid and propylthiouracil	4% cholesterol, 1% cholic acid, 0.5% propylthiouracil [46]
Modified Western-type diet with high cholesterol	12.5% palm oil, 12.5% fat, 5% cholesterol, 2% cholic acid [46]
High-cholesterol diet	2% cholesterol [49]
High-fat diet	60% fat [46]
High-fat diet	42% fat [46]
High-fat diet	33.5% fat, 1.5% soybean oil [46]
Modified Western-type diet with fat and sucrose	10% fat, 20% sucrose, 2% cholesterol, 1% cholic acid [46]
High-cholesterol diet	6% cholesterol [46]
High-cholesterol and cholic acid diet	2% cholesterol, 0.5% cholic acid [46]
Thomas-Hartroft diet	40% oil, 5% cholesterol, and 5% sodium cholate [10]
Paigen diet	15% fat, 1.25% cholesterol, 0.5% cholic acid [46]
High-fat, vitamin D, and nicotine diet	20% fat, vitamin D3 300 000 IU/kg/day, nicotine 25 mg/kg/day [4]
High-sucrose diet	20% fat, 65% sucrose [47]

The Prague hereditary hypercholesterolemic (PHHC) rat is a rat line obtained by crossing with Wistar rats. It models hypercholesterolemia on an atherogenic diet [1]. In this line, most of the cholesterol is VLDL cholesterol [1, 52]. However, despite the presence of hypercholesterolemia, PHHC rats do not develop atherosclerosis even after receiving a 2% cholesterol diet for 6 months [51].

GENETICALLY MODIFIED RAT MODELS

In order to study hyperlipidemia and atherosclerosis in rats, similar methods to mouse models were employed, i.e. knockout of the apolipoprotein E gene (*ApoE*$^{-/-}$) and LDL receptors (*Ldlr*$^{-/-}$), as well as double knockout of the *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$ genes [10]. For the formation of the atheromatous plaque, *ApoE*$^{-/-}$ и *Ldlr*$^{-/-}$ rats needed a diet with a high fat content (42%), but even under these conditions, aortic damage was insignificant [10, 53, 54]. *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$ rats showed significant atherosclerotic lesions in the aorta only after a long time (48 weeks) [10, 54]. Additionally, a more pronounced degree of hypercholesterolemia was observed in models with double knockouts [55].

Thus, it turned out that the formation of atherosclerotic lesions in *ApoE*$^{-/-}$, *Ldlr*$^{-/-}$, and *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$ rats requires a much longer period of time and a diet with a higher fat content, compared to mice [10]. A less common model of hypercholesterolemia is the rat overexpressing CETP protein (*hCETPtg*), which develops severe atherosclerotic lesions in the aorta but shows significantly high mortality [1].

LIMITATIONS OF USING RATS IN HYPERLIPIDEMIA AND ATHEROSCLEROSIS STUDIES

Rats, even genetically modified, were found to be more resistant to the development of the atheromatous plaque due to their low susceptibility to endothelial inflammation caused by hyperlipidemia [56].

RABBIT MODELS WITHOUT GENETIC MANIPULATION

Rabbits are often used as an experimental animal model to study the atherosclerotic process because their lipid metabolism is more similar to that of humans than of mouse and rat [4, 12, 57]. Also, rabbits are highly sensitive to a cholesterol diet, due to which they quickly develop severe hypercholesterolemia, leading to severe aortic atherosclerosis [12]. However, recently there has been a trend towards a decrease in the use of this animal model, probably due to the availability of genetically modified mice [13, 58].

Currently, the following types of rabbit models are used: rabbits on an atherogenic diet; rabbits with Watanabe hereditary hyperlipidemia and St. Thomas mixed hyperlipidemia; and genetically modified rabbits [59]. In rabbits fed with an atherogenic diet, more than 90% of cholesterol is VLDL and LDL cholesterol [12]. Since female rabbits have higher blood cholesterol levels than male rabbits, these characteristics make males much more commonly used for studies of hyperlipidemia and atherosclerosis [12, 51].

New Zealand White rabbits are often used to study hyperlipidemia and atherosclerosis [13, 58]. For this purpose, various variants of the atherogenic diet have been developed, presented in Table 3 [4, 13, 58]. However, when fed with a diet containing more than 1% cholesterol for a long time (more than 4 weeks), rabbits develop high hypercholesterolemia and severe atherosclerotic lesions exceeding those seen in humans, so a diet with cholesterol in the range of 0.3–0.5% is recommended [58]. Also, it is recommended to use vegetable oils (3–8% soybean, coconut, or corn oil) for 8 weeks to form hyperlipidemia and for 16 weeks to form the atheromatous plaque [58, 59]. A cholesterol-free diet enriched with casein may also cause hypercholesterolemia and atherosclerosis in rabbits [60]. It is believed that a possible mechanism of hypercholesterolemia in this case is associated with a decrease in the synthesis of bile acids and the excretion of fecal sterols, which leads to an increase in the level of total cholesterol and LDL [60]. It is worth noting that rabbits fed with casein developed less severe aortic atherosclerosis than rabbits receiving a cholesterol diet [58, 60].

Table 3

Most Commonly Used Atherogenic Diets in Hyperlipidemia Studies in Rabbits

Diet name	Diet composition
Atherogenic diet for rabbits	3–8% soybean or corn oil, 0.3–0.5% cholesterol [13]
Atherogenic diet for rabbits	3–8% soybean or corn oil, 1.0–1.5% cholesterol [58]
Cholesterol-free diet containing casein	27% casein [60]

Compared with hypercholesterolemia and atherosclerosis in humans, rabbits fed with an atherogenic diet show a number of differences. For example, the main lipoproteins are not LDL but VLDL, and there are large differences in blood lipid levels and the extent of atherosclerotic lesions due to individual differences in response to the cholesterol diet [61–63].

Watanabe heritable hyperlipidemic (WHHL) rabbits have a genetic mutation in the gene encoding the LDL receptor, leading to high blood cholesterol levels when fed with a normal diet, resembling human familial hypercholesterolemia [63]. In experimental studies of hyperlipidemia and atherosclerosis, the advantages of using WHHL rabbits compared to rabbits fed with an atherogenic diet include:

1) the lipid profile of WHHL rabbits is characterized by high LDL and low HDL levels, whereas the major lipoproteins in rabbits fed with an atherogenic diet are VLDL and LDL, while HDL levels usually do not change;

2) hypercholesterolemia is constantly present in all homozygous WHHL rabbits on a normal diet, and variations in plasma total cholesterol levels and lipoprotein ratios are small compared to rabbits fed with a special atherogenic diet;

3) in WHHL rabbits, atherosclerotic lesions have a pattern similar to the same stage of atherosclerosis in humans;

4) in WHHL rabbits, coronary atherosclerosis and myocardial infarction are often observed, which corresponds to clinical manifestations in humans [61, 62].

Thus, the WHHL rabbits are particularly suitable for studies aimed at developing lipid-lowering drugs.

St. Thomas mixed hyperlipidemic (SMHL) rabbits receiving a normal diet have elevated total

cholesterol levels, normal LDL levels, and normal or elevated blood triglyceride levels [59, 60]. When fed with a low-cholesterol diet, SMHL rabbits develop hyperlipidemia associated with excess hepatic apoB production and characterized by high levels of LDL and VLDL [60]. This rabbit model is rarely used in research [59].

When evaluating the effects of lipid-lowering drugs in New Zealand rabbits receiving an atherogenic diet and WHHL rabbits, such drugs as statins, ezetimibe, and evolocumab were effective [50, 59, 64–66]. Fibrates (PPARα agonists) significantly reduced plasma triglyceride levels in both humans and rodents, but this effect was absent or weakly pronounced in rabbits [60]. CETP inhibitors (torcetrapib, dalcetrapib, anacetrapib, and evacetrapib) in rabbits on an atherogenic diet showed a strong atheroprotective effect and significantly increased HDL levels [60].

Thus, although WHHL rabbits are advantageous for assessing the lipid profile and the extent of atherosclerotic lesions, rabbits on an atherogenic diet can also be used to assess the lipid-lowering and anti-atherosclerotic activity of drugs.

GENETICALLY MODIFIED RABBIT MODELS

Advances in genetic engineering have made it possible to create genetically modified rabbits to study the pathophysiological features of the atherosclerotic process, which may be useful in studying the effectiveness of new lipid-lowering drugs [41]. Thus, transgenic rabbits have been used to study cardiovascular diseases and lipoprotein metabolism over the past two decades [67, 68]. However, after the creation of rabbits with knockout genes, they began to be used as models of hyperlipidemia and atherosclerosis [68].

Transgenes expressed in rabbits can be broadly divided into three categories: 1) proteins that directly bind to lipoproteins, such as apo: apoAI, apoAII, apoB-100, apoCIII, apoE; 2) enzymes that participate in lipid metabolism: hepatic lipase, lipoprotein lipase, phospholipid transfer protein (PLTP), catalytic polypeptide, lecithin-cholesterol acyltransferase (LCAT); 3) proteins that may participate in the pathogenesis of atherosclerosis: matrix metalloproteinase-12 (MMP-12), 15-lipoxygenase (ALOX15), C-reactive protein, and vascular endothelial growth factor (VEGF). [58, 67].

Currently, the most widely used models for studying hyperlipidemia and atherosclerosis are rabbits with knockout of the apolipoprotein E gene (*ApoE*$^{-/-}$) and LDL receptors (*Ldlr*$^{-/-}$), as well as models with double knockout of the *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$ genes [40, 68]. Thus, *ApoE*$^{-/-}$ rabbits demonstrated a mild degree of hyperlipidemia on a standard diet, and when fed with an atherogenic diet (0.3% cholesterol and 3% soybean oil), they developed severe hyperlipidemia (within 2 weeks) and atherosclerotic aortic lesions (within 10 weeks) [13, 68]. Compared to WHHL rabbits, *ApoE*$^{-/-}$ rabbits did not show changes in HDL cholesterol levels, which is a drawback of this model [69]. *Ldlr*$^{-/-}$ rabbits at 3 months of age had a 20-fold increase in total blood cholesterol and a 35-fold increase in LDL cholesterol compared to rabbits receiving an atherogenic diet [68]. They also had elevated triglyceride levels and reduced HDL cholesterol levels [68]. *ApoE*$^{-/-}$/*Ldlr*$^{-/-}$ double knockout rabbits do not require an atherogenic diet to develop severe hyperlipidemia [68, 69].

LIMITATIONS OF USING RABBITS IN HYPERLIPIDEMIA AND ATHEROSCLEROSIS STUDIES

Limitations of using rabbits are related to the anatomical and physiological features of atheromatous plaque formation. Thus, atherosclerosis develops predominantly in the arch and thoracic part of the aorta, with minimal lesions in the abdominal part, and coronary atherosclerosis is usually limited to the left coronary arteries [13]. In addition, rabbits, especially non-pedigreed ones, can respond differently to an atherogenic diet and not develop pronounced hyperlipidemia even on a high-cholesterol diet [58]. To minimize differences, rabbits can be pre-examined by feeding them with a cholesterol diet for a short period of time, and then only the rabbits that showed high levels of lipoproteins in the blood can be selected [60].

CONCLUSION

Taking into account the constant increase in life expectancy and the spread of the Western-type diet in the population, the treatment of hyperlipidemia and the prevention of atherosclerotic lesions are an urgent tasks. Currently, many models of experimental animals and variants of atherogenic diets have been proposed for the induction of hypercholesterolemia.

The most common animals for creating hyperlipidemia and atherosclerosis are mice, rats, and rabbits. Rodent models are characterized by a short life cycle, high reproduction rate, and ease of research manipulations, which makes them a convenient model for studying hypercholesterolemia. It is worth noting that various genetic manipulations with

rodents made it possible to overcome the significant difference in the lipid profiles of humans and rodents. In terms of lipoprotein metabolism, rabbits are superior to mice and rats due to their similarity in the development of pathology to humans, but rabbit hyperlipidemia and atherosclerosis models also have their limitations.

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