Abstract: Hyperlipidemia or dyslipidemia is a major risk factor for atherosclerotic diseases. Experimental animals play an important role in elucidating the molecular mechanisms of the pathophysiology of hyperlipidemia as well as in drug development. Rabbits are one of the most suitable models to study human hyperlipidemia because many features of the lipoprotein metabolism of rabbits are similar to those of humans such as LDL-rich lipoproteins in plasma, apolipoprotein B mRNA editing, and cholesteryl ester transfer protein. Currently, three types of rabbit models are commonly used for studying hyperlipidemia: (1) diet-induced hyperlipidemic rabbits, (2) spontaneous hyperlipidemic rabbits, and (3) gene-manipulated rabbits (transgenic and knockout rabbits). In this review, we give an overview of the features of hyperlipidemic rabbits and discuss the usefulness of rabbits for the development of anti-atherogenic drugs.

Keywords: rabbit; hyperlipidemia; lipoprotein; apolipoprotein; drug development

1. Introduction

Hyperlipidemia is one of the major risk factors for atherosclerosis, which has been the leading cause of mortality globally [1,2]. It is generally believed that an increase in plasma low-density lipoprotein (LDL), triglycerides (TG)-rich lipoproteins such as chylomicron (CM), and very-low-density lipoprotein (VLDL) and/or a decrease in high-density lipoprotein (HDL) are associated with or cause atherosclerosis [3]. For the study of human lipid disorders as well as for the development of therapeutic agents, it is essential to use an appropriate experimental animal. Ideal animal models for human hyperlipidemia should possess several important characteristics: (1) they should be easy to induce hyperlipidemia by diet intervention or genetic manipulation, (2) they should have similar lipoprotein profiles as humans, (3) they should be easy to handle and be of the proper size to allow for all anticipated experimental manipulations, and (4) they should be easy to acquire and maintain at a reasonable cost [4]. Until now, many animal models have been used for the study of hyperlipidemia, including mice, rats, hamsters, guinea pigs, rabbits, pigs, and nonhuman primates. Unfortunately, there is no single animal model that fulfills all the requirements. Although each animal model has its advantages and limitations with respect to plasma lipoprotein profiles, handling, reproducibility, and cost, rabbits possess several unique advantages for the study of lipid metabolism. Due to their high
susceptibility to a cholesterol diet, it is easy to induce hyperlipidemia and atherosclerosis in wild-type rabbits [5], which is different from most strains of wild-type mice. The hyperlipidemic models of mice have been generated by the targeting of genes, such as apolipoprotein (apo) E and LDL receptor (LDLR) [6,7]. Nevertheless, there are a number of features that make rabbits an appropriate model to study human hyperlipidemia. Unlike wild-type mice and rats (rodents) in which HDL is a major lipoprotein in plasma, ≈40% of plasma cholesterol in wild-type rabbits and >90% in cholesterol-fed rabbits are contained in the apo B-containing particles such as VLDL and LDL [8]. Humans and rabbits have abundant plasma cholesteryl ester transfer protein (CETP), an important regulator of HDL and cholesterol metabolism, whereas rodents do not have CETP [9]. Given that the restricted editing of apo B mRNA only occurs in the intestine in humans and rabbits, apo B-48 is only present in intestinally derived CM and CM remnants in humans and rabbits. However, in rodents, apo B mRNA editing occurs in both the intestine and liver [10]; therefore, apo B-48 is contained in both CM and VLDL particles. Furthermore, hepatic LDLR in both humans and rabbits is highly down-regulated according to the level of cholesterol uptake in the liver [8]. In addition, the appropriate size of rabbits enables researchers to obtain large amounts of plasma samples for both in vitro and in vivo studies.

2. Hyperlipidemic Rabbit Models

2.1. Diet-Induced Hyperlipidemic Rabbits

2.1.1. Cholesterol-Fed Rabbits

Rabbits are the first models for the study of lipoprotein metabolism and atherosclerosis. In 1913, a Russian experimental pathologist, Anitschow, described that feeding cholesterol dissolved in sunflower oil to rabbits elevated blood cholesterol levels, and within several weeks, rabbit arteries showed atherosclerotic lesions [11]. As herbivores, laboratory rabbits including New Zealand white (NZW) and Japanese white (JW) rabbits, on a normal standard diet, have relatively low plasma total cholesterol (TC) levels (30–90 mg/dL) at the age of 3–4 months compared with humans. When rabbits are fed a cholesterol diet, they rapidly develop hypercholesterolemia [12]. Kolodgie et al. tested low dietary cholesterol (0.05% to 0.25%) with 6% peanut oil for 30 weeks to explore a response of plasma TC levels in rabbits. Dietary cholesterol in the range of 0.05% to 0.15% resulted in a less than 2-fold stepwise increase in plasma TC, whereas rabbits receiving 0.20% and 0.25% dietary cholesterol showed significantly higher (4- to 5-fold) plasma TC compared to those rabbits fed a diet containing 0.05% to 0.15% cholesterol [13]. Cholesterol diets contain more than 1% cholesterol usually causes extraordinary elevation of plasma TC levels in rabbits, exceeding 2000 mg/dL. Such high level of plasma TC is never seen in human hypercholesterolemia. Therefore, it is generally recommended to use a 0.3–0.5% cholesterol diet, which results in hypercholesterolemia comparable to human familial hypercholesterolemia (FH) [8]. The major elevated lipoproteins in cholesterol-fed rabbits are those lipoproteins (called β-VLDL) derived from both the intestine and liver and they are quite atherogenic because they are rich in cholesteryl esters and can induce macrophages to transform into foam cells [14].

Currently, we recommend a diet supplemented with 0.3–0.5% cholesterol and 3% soybean oil fed either ad libitum or restricted for most rabbit experiments. Representative hypercholesterolemia in cholesterol-fed rabbits is shown in Figure 1A. Plasma TC levels start to rise within one week and remain at high levels (≈800 mg/dL) thereafter. Hyperlipidemic rabbits can develop aortic lesions as early as four–six weeks after cholesterol diet feeding, but at 16 weeks, 20–40% of the aortic surface is covered by atherosclerosis which can be stained with Sudan IV (Figure 1B). The age of rabbits should be considered because young rabbits are more susceptible to aortic atherosclerosis than old rabbits even though there are no differences in plasma TC levels [15].
WHHL rabbits are genetically deficient in LDLR functions, therefore, even on a normal standard diet, the LDLR in WHHL rabbits results in a loss of the hepatic uptake of LDL and subsequent elevation of the plasma LDL levels similar to human FH [25–27]. Age-related changes in plasma lipids were observed in WHHL rabbits [22,28]. Compared with 3-month-old juvenile rabbits, 24-month-old rabbits showed a 45% decrease in TC (916 at 3 months to 508 mg/dL at 24 months) and a 42% decrease in LDL-C (680 at 3 months to 393 mg/dL at 24 months) [28]. Atkinson et al. compared plasma TC levels in heterozygous WHHL rabbits and NZW rabbits on a cholesterol diet for 24 weeks. On a 0.5% cholesterol diet, they showed hyperlipidemia (plasma TC, 385–518 mg/dL, and TG, 304–511 mg/dL), being 10-fold and 8-fold higher than normal wild-type rabbits [22]. Serum lipoproteins characterized by electrophoresis exhibited elevated β-lipoprotein with a broad β-pattern and diminished α-lipoprotein in WHHL rabbits. Yamamoto et al. demonstrated that WHHL rabbits have a dysfunctional LDLR with an in-frame deletion of 12 nucleotides that eliminate four amino acids from the ligand-binding domain of the LDLR. Mutant LDLRs cannot transport to the cell surface at a normal rate [24]. The dysfunction of the LDLR in WHHL rabbits results in a loss of the hepatic uptake of LDL and subsequent elevation of the plasma LDL levels similar to human FH [25–27]. Age-related changes in plasma lipids were observed in WHHL rabbits [22,28]. Compared with 3-month-old juvenile rabbits, 24-month-old rabbits showed a 45% decrease in TC (916 at 3 months to 508 mg/dL at 24 months) and a 42% decrease in LDL-C (680 at 3 months to 393 mg/dL at 24 months) [28]. Atkinson et al. compared plasma TC levels in heterozygous WHHL rabbits and NZW rabbits on a cholesterol diet for 24 weeks. On a 0.5% cholesterol diet, they showed hyperlipidemia (plasma TC, 385–518 mg/dL, and TG, 304–511 mg/dL), being 10-fold and 8-fold higher than normal wild-type rabbits [22]. Serum lipoproteins characterized by electrophoresis exhibited elevated β-lipoprotein with a broad β-pattern and diminished α-lipoprotein in WHHL rabbits. Yamamoto et al. demonstrated that WHHL rabbits have a dysfunctional LDLR with an in-frame deletion of 12 nucleotides that eliminate four amino acids from the ligand-binding domain of the LDLR. Mutant LDLRs cannot transport to the cell surface at a normal rate [24]. The dysfunction of the LDLR in WHHL rabbits results in a loss of the hepatic uptake of LDL and subsequent elevation of the plasma LDL levels similar to human FH [25–27].
diet, plasma TC levels in heterozygous WHHL rabbits were significantly higher than those in NZW rabbits (≈2000 in WHHL vs. ≈1000 mg/dL in NZW rabbits). However, on a 1% cholesterol diet, plasma TC levels reached a peak (≈3000 mg/dL) at eight weeks in both rabbits without significant differences between the two groups [29].

Besides spontaneous hypercholesterolemia and atherosclerosis, WHHL rabbits exhibited other metabolic abnormalities including insulin resistance [30] and visceral fat accumulation [31]. Some WHHL rabbits (also designated as myocardial infarction-prone Watanabe heritable hyperlipidemic, WHHLMI) developed coronary atherosclerosis and myocardial infarction [8,32,33]. To obtain a myocardial infarction-prone colony, WHHL rabbits with severe coronary atherosclerosis, myocardial infarction, and relatively higher plasma TC levels were selected and bred. Selective breeding was carried out for five to seven generations. WHHLMI rabbits exhibit 93% of coronary stenosis and 97% of myocardial infarction, whereas the corresponding values are 60% and 23% in original WHHL rabbits [32].

2.2.2. St. Thomas’ Mixed Hyperlipidemic (SMHL) Rabbits

The SMHL rabbit is a putative model of familial combined hyperlipidemia originally described as the St. Thomas’ Hospital rabbit in the 1980s. These rabbits showed spontaneously elevated plasma TC levels (394 mg/dL, 4- to 5-fold over normal rabbits) with moderately high or normal plasma TG levels (151 mg/dL, 2-fold over normal rabbits) and developed aortic atherosclerosis on a normal standard diet [34,35]. SMHL rabbits have normal LDLR function, and it is considered that elevated plasma VLDL and LDL levels are caused by overproduction of apoB-containing particles from the liver [34,36]. De Roos et al. compared plasma lipids of SMHL rabbits with WHHL rabbits on a low-cholesterol diet. With three months of feeding a 0.08% cholesterol diet, SMHL rabbits showed plasma TC of 264 ± 68 and TG of 290 ± 55 mg/dL compared with the TC of 791 ± 36 and TG of 232 ± 46 mg/dL in WHHL rabbits [37].

2.2.3. Postprandial Hypertriglyceridemic (PHT) Rabbits

The PHT rabbit was established through cross-breeding between WHHL rabbits with a hypertriglyceridemia phenotype and normal JW rabbits [38,39]. PHT rabbits showed high TG levels in both fasting (403 mg/dL, 11-fold over normal rabbits) and postprandial (1407 mg/dL, 22-fold over normal rabbits) states. In addition to hypertriglyceridemia, PHT rabbits exhibited insulin resistance along with obesity [39].

2.3. Gene-Manipulated Rabbits

2.3.1. Transgenic (Tg) Rabbits

Hyperlipidemic rabbits were also generated by the overexpression of human apo B-100, E, and C-III genes in the liver. Human apo B-100 Tg rabbits resulted in a 3-fold increase in plasma TC and TG levels compared with those in non-Tg rabbits, and the majority of the plasma TC was distributed in the LDL, with striking enrichment of TG content [40]. Ding et al. generated Tg rabbits overexpressing the human apo C-III gene. Apo C-III Tg rabbits showed 3-fold higher plasma TG levels than non-Tg rabbits (191 in Tg vs. 59 mg/dL in non-Tg), although TC and HDL-C levels were not changed. Lipoprotein analysis revealed that increased TG in apo C-III Tg rabbits was distributed in CM and VLDL [41]. Tg rabbits expressing human apo E3, the most common isoform in humans, and apo E2, a variant associated with type III hyperlipoproteinemia, were also reported. Tg rabbits expressing higher levels of human apo E3 (≈20 mg/dL) showed marked combined hyperlipidemia characterized by an increase in both LDL and VLDL [42,43]. Overexpression of human apo E2 in rabbits exhibited 8-fold increases in plasma TC and 15-fold increases in plasma TG compared with non-Tg rabbits [44].
2.3.2. Knockout (KO) Rabbits

For a long time, it had been impossible to generate KO rabbits; however, the emergence of recent gene-editing technologies has dramatically changed the field of KO rabbits. Recently, apo E and LDLR KO rabbits were generated and have been used for the study of hyperlipidemia [45–47]. ApoE-KO rabbits exhibited mild hyperlipidemia, with TC levels at ≈200 mg/dL on a normal standard diet [46,48]. When challenged with a cholesterol diet, apo E KO rabbits showed greater susceptibility to hyperlipidemia than did the wild-type rabbits, and their plasma TC and TG levels were remarkably increased, with a 6.3-fold increase in TC and a 5.7-fold increase in TG compared with those of wild-type rabbits [48]. Hyperlipidemia in apo E KO rabbits was caused by elevated remnant lipoproteins predominated by apo B-48 and rich in both apo A-I and apo A-IV contents. Lu et al. generated LDLR KO rabbits and found that, similar to WHHL rabbits, LDLR deficiency markedly increased plasma TC levels (272–1013 in LDLR-KO rabbits vs. 51 mg/dL in the wild-type rabbits) on a normal standard diet. Increased plasma TC levels were mainly caused by elevated LDL-C (124–730 in LDLR-KO rabbits vs. 21 mg/dL in the wild-type rabbits) [47]. Apo E and LDLR double-KO rabbits were also generated by the same group and exhibited remarkable hyperlipidemia on a normal standard diet [49]. These KO rabbits may be useful for anti-atherosclerotic drug development in the future.

3. Hyperlipidemic Rabbit Models for the Development of Drugs

As mentioned above, rabbits are also useful in the research of lipid-lowering drugs due to their similarity with human lipid metabolism. In this respect, the most important contribution made by hypercholesterolemic rabbits is the discovery of a potent lipid-lowering drug, statin, the best prescribed drug for hyperlipidemic patients in the world [50]. In the 1970s, Endo discovered the first statin, named compactin (also called ML-236B or mevastatin) [51]. However, at first, he found that compactin could not reduce plasma cholesterol in mice and rats [52], so his company almost terminated the study. Later, Endo continued to conduct his research using different animals such as rabbits, monkeys, and dogs and finally disclosed that compactin indeed exhibited lipid-lowering effects [53–56].

Now, we know that rodents are basically different from humans and rabbits in terms of cholesterol metabolism, and the majority of cholesterol in rodents is derived from food, whereas in humans and rabbits, cholesterol is mainly synthesized in the liver [8]. Therefore, using hypercholesterolemic rabbits, one can not only test a new drug but can also examine new functions of existing drugs.

3.1. Statins

Statins, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, have been widely used by hyperlipidemic patients. Statins have a similar structure to HMG-CoA, a precursor of cholesterol, and inhibit HMG-CoA reductase, the rate-limiting enzyme of cholesterol biosynthesis, which is the major pathway for its lipid-lowering functions [57]. In addition, statins indirectly up-regulate LDLR activity and reduce the secretion of VLDL into circulation [57]. The lipid-lowering and atheroprotective effects of statins have been verified by many studies using different hypercholesterolemic rabbits (Table 1).

Regardless of different types of statins, doses, and durations, all studies showed that statins can reduce plasma TC levels in hypercholesterolemic rabbits, while some studies failed to demonstrate anti-atherogenic effects. Bocan et al. reported that atorvastatin showed anti-atherogenic effects in an iliac–femoral artery microscopic lesion but did not reach a significant difference in the thoracic aorta gross lesion [58]. Pravastatin significantly reduced plasma TC levels and coronary atherosclerotic lesions in WHHL rabbits but had no effects on aortic atherosclerotic lesions [59]. These studies indicate that the efficacy of statins on atherosclerosis is more complicated than their lipid-lowering effect, possibly due to the pluripotent effect of statins.
Table 1. Lipid-lowering and anti-atherosclerotic effects of statins in rabbit models.

| Rabbit     | Diet             | Drug                        | Plasma TC | Atherosclerosis | Reference |
|------------|------------------|-----------------------------|-----------|-----------------|-----------|
|            |                  | Compactin (5 mg/kg)         | 16% ↓     | -               | Watanabe  |
|            |                  | Compactin (25 mg/kg)        | 41% ↓     | (2 weeks)       | [54]      |
|            |                  | for 2 weeks                |           |                 |           |
|            |                  | Lovastatin (2 mg/kg)       | 37% ↓ *   | -               | Kroon     |
|            |                  | for 39 days                |           | (39 days)       | [60]      |
|            |                  | Lovastatin (6 mg/kg)       | 48% ↓ *   | -               |           |
|            | 27% casein       | for 39 days                |           |                 |           |
|            | semi-purified    | Compactin (5 mg/kg)         | 16% ↓     | -               | Kritchevsky|
|            |                  | for 2 weeks                |           |                 | [61]      |
|            |                  | Lovastatin (5 mg/kg)       | 54% ↓ *   | 43% ↓ *         |           |
|            | 2% cholesterol   | for 8 weeks                |           | (Aortic arch, scale graded gross lesion) |           |
|            | 6% corn oil      |                             |           |                 |           |
|            |                  | Lovastatin (5 mg/kg)       | 50% ↓ *   | 74% ↓ *         | Kobayashi |
|            |                  | for 12 weeks               |           | (Aorta, gross lesion) |           |
|            |                  | Simvastatin (5 mg/kg)      | 80% ↓ *   | 81% ↓ *         |           |
|            |                  | for 12 weeks               |           |                 |           |
|            |                  | Lovastatin (3 mg/kg)       | 20% ↓ *   | -               | Auerbach  |
|            |                  | for 6 weeks                |           |                 | [63]      |
|            |                  | Atorvastatin (3 mg/kg)     | 57% ↓ *   | -               |           |
|            |                  | for 6 weeks                |           |                 |           |
|            |                  | Lovastatin (2.5 mg/kg)     | 40% ↓ *   | 39% ↓           | Bocan     |
|            |                  | Simvastatin (2.5 mg/kg)    | 43% ↓ *   | 41% ↓           | [58]      |
|            |                  | for 8 weeks                |           |                 |           |
|            |                  | Pravastatin (2.5 mg/kg)    | 37% ↓ *   | 13% ↓           |           |
|            |                  | for 8 weeks                |           |                 |           |
|            |                  | Atorvastatin (2.5 mg/kg)   | 32% ↓ *   | 69% ↓ *         |           |
|            |                  | for 8 weeks (AUC)          | 62% ↓ *   |                 |           |
|            |                  | (Iliac–femoral artery, microscopic lesion) |           |                 |           |
|            |                  | Lovastatin (0.1 mg/kg)     | 27% ↓ *   | 64% ↓ *         | Hayashi   |
|            |                  | for 12 weeks               |           | (Aortic arch, microscopic lesion) |           |
|            | 0.5% cholesterol | Simvastatin (2.5 mg/kg)    | 40% ↓     | 39% ↓           | Rikitake  |
|            |                  | for 12 weeks               |           |                 | [64]      |
|            |                  | Pravastatin (50 mg/kg)     | 33% ↓ *   | -               | Tsutjita  |
|            |                  | for 8 weeks (12 weeks)     | 62% ↓ *   |                 | [67]      |
|            |                  | Lovastatin (0.03% diet)    | 40% ↓     | -               | Ma        |
|            |                  | for 10 days                |           |                 | [66]      |
|            |                  | Pravastatin (50 mg/kg)     | 33% ↓ *   | -               |           |
|            |                  | for 8 weeks (24 weeks)     | 54% ↓ *   |                 |           |
|            |                  | Lovastatin (0.6 mg/kg, subcutaneously) | 39% ↓ * |                 | Watanabe  |
|            |                  | for 32 weeks (32 weeks)    | 37% ↓ *   | (Thoracic aorta, microscopic lesion) |           |
|            |                  | Pitavastatin (0.5 mg/kg)   | 29% ↓ *   | 39% ↓ *         | Shiomi    |
|            |                  | for 16 weeks (16 weeks)    | 64% ↓     |                 | [68]      |
|            |                  | (Aorta, gross lesion)       |           |                 |           |

3.2. Fibrates

Fibrate is an agonist of the peroxisome proliferator-activated receptor α, which up-regulates the expression of the lipoprotein lipase, apo A-I, and apo A-II genes in the liver [70]. Fibrates are known as potent TG-lowering drugs for humans because they can reduce TG-rich lipoproteins such as CM, VLDL, and their remnants. In both humans and rodents, fibrates significantly decrease plasma TG, but this effect is either absent or only slight in rabbits [71,72]. In spite of this, Saitoh et al. reported that fibrate can exert an anti-atherosclerotic effect in cholesterol-fed NZW rabbits [73]. Corti et al. evaluated the effects of fenofibrate on atherosclerotic plaque regression using magnetic resonance imaging (MRI). Atherosclerosis was induced by balloon injury and nine-month 0.2% cholesterol diet feeding in NZW rabbits. The baseline established
atherosclerotic burden was assessed by MRI, and then the rabbits were treated with fenofibrate for six months. Fenofibrate treatment did not change plasma LDL-C levels but increased plasma HDL-C levels. MRI analysis showed that fenofibrate treatment led to an 11% reduction in the aortic lesions compared to the pre-treatment baseline area [74]. Jeanpierre et al. examined the effect of fenofibrate on plaque thrombogenicity and plaque stability in cholesterol-fed NZW rabbits with balloon injury. Fenofibrate significantly decreased tissue factor expression (42% reduction) and plaque cholesterol content (45% reduction) in the iliac artery of rabbits [75].

3.3. Ezetimibe

Ezetimibe is an inhibitor of cholesterol absorption through the targeting of Nieman Pick C1 like 1 protein at the brush border of intestinal epithelial cells. Ezetimibe is often prescribed for patients with elevated plasma TC, LDL-C, and apo B, either as monotherapy or in combination with statins [76]. The pharmacological functions of ezetimibe on atherosclerosis, thrombosis, and fatty liver disease have been investigated in rabbits (Table 2). Gómez-Garre et al. examined the effect of ezetimibe combined with simvastatin on cholesterol-fed rabbits with femoral artery injury. Although ezetimibe did not significantly change plasma TC levels, the intima/media ratio of the femoral artery was reduced by 13% (ezetimibe), 27% (simvastatin), and 28% (ezetimibe plus simvastatin) compared with that of control rabbits [77]. Patel et al. evaluated the effect of ezetimibe on atherothrombosis [78]. Atherosclerosis was induced by cholesterol diet feeding and balloon injury, and then plaque disruption and thrombosis were triggered by Russell’s viper venom and histamine. Ezetimibe treatment reduced plasma TC levels and decreased plaque size and thrombus area [78]. Honda et al. recently showed that ezetimibe treatment significantly decreased thrombus occlusion in the femoral artery in angiotensin II-perfused rabbits [79]. In addition, Ogawa et al. examined the effect of ezetimibe on rabbits with nonalcoholic steatohepatitis, which was induced by feeding a diet containing 1.25% cholesterol and 20% corn oil. Ezetimibe therapy lowered plasma TC levels and suppressed hepatic fat depositions and fibrosis [80].

| Target Disease        | Rabbit and Manipulation | Drug                        | Plasma TC | Outcome                  | Reference  |
|-----------------------|-------------------------|-----------------------------|-----------|--------------------------|------------|
| Atherosclerosis       |                         | Ezetimibe (0.6 mg/kg)       | 8\% ↓     | 13% ↓*                  | Gómez-Garre [77] |
|                       |                         | Combination (Eze + Sim)     | 37\% ↓    | 28% ↓*                  |            |
|                       |                         |                             | (6 weeks) | (Femoral artery, intima/media ratio) |            |
| Atherothrombosis      |                         | Ezetimibe (1 mg/kg)         | 86\% ↓*   | Plaque area: 38% ↓*     | Patel [78] |
|                       |                         |                             | (6 months) |                          |            |
|                       |                         | Ezetimibe (0.6 mg/kg)       | 18\% ↓*   | 51% ↓*                  | Honda [79] |
|                       |                         | Rosvastatin (1 mg/kg)       | 23\% ↓*   | 12% ↓                   |            |
|                       |                         |                             | (4 weeks) | (Thrombotic occlusion)   |            |
| NASH                  |                         | Ezetimibe (0.6 mg/kg)       | ≈ 40% ↓*  | Lipid droplet: ≈ 15% ↓* | Ogawa [80] |
|                       |                         |                             | (8 weeks) |                          |            |

NZW, New Zealand white; JW, Japanese white; Chol, cholesterol; NASH, nonalcoholic steatohepatitis; TC, total cholesterol; TG, triglycerides. Plasma TC and outcomes are expressed as % compared with those of control rabbits (* p < 0.05).
3.4. Probucol

Probucol was originally synthesized in the 1970s as an anti-oxidant and was subsequently found to have lipid-lowering effects [81]. Although the lipid-lowering effect is relatively mild compared to statins, probucol possesses strong anti-oxidative activity along with HDL-lowering and anti-atherosclerotic effects [82]. Probucol was prescribed in the 1980s before the birth of statin. Since probucol is notorious for its HDL-lowering effect, probucol is now used only in Asian countries such as Japan, Korea, and China. The anti-atherosclerotic effect of probucol has been well characterized in cholesterol-fed and WHHL rabbits. Pharmacological effects of probucol on the lipoprotein profiles and atherosclerosis are summarized in Table 3. Naruszewicz et al. reported that probucol reduced LDL-C and HDL-C in WHHL rabbits [83]. Kita et al. and Carew et al. demonstrated an anti-atherosclerotic effect of probucol in WHHL rabbits [84,85]. Although the reduction in plasma TC levels was quite mild, probucol-treated WHHL rabbits showed a significant reduction in aortic atherosclerosis [84,85]. Daugherty et al. tested the anti-atherosclerotic effect of probucol on a cholesterol-fed rabbit model and showed that probucol treatment protected against lesion progression without affecting plasma TC levels [86]. Oshima et al. reported that probucol treatment led to the regression of the established aortic atherosclerosis in WHHL rabbits [87]; however, others failed to reproduce the results [88]. We have shown that probucol can also inhibit the initiation of atherosclerosis by reducing monocyte adherence and infiltration into the subintima [89]. Furthermore, probucol reduces coronary atherosclerosis and stabilizes plaques in WHHL rabbits [90]. The anti-atherosclerotic effect of probucol occurs mainly through its anti-oxidative activity on LDL [91]. In fact, 69% of probucol in plasma was distributed on the LDL particles in WHHL rabbits [84].

| Rabbit | Drug | Panel Lipids | Atherosclerosis | Findings | Reference |
|--------|------|--------------|-----------------|----------|-----------|
| WHHL rabbits (Normal standard diet) | 1% probucol in diet (4 weeks) | TC: 24%↓ VLDL-C: 4%↓ IDL-C: 2%↓ LDL-C: 36%↓ HDL-C: 53%↓ (4 weeks vs. pre-treatment) | - | up-regulation of LDL fractional catabolic rate | Naruszewicz [83] |
| (Male and female) | 1% probucol in diet (6 months) | TC: 17%↓ (6 months) | 87%↓* (Thoracic aorta, gross lesion) | protective effect of LDL oxidation | Kita [84] |
| (Male and female) | 1% probucol in diet (≈ 33 weeks) | TC: 12%↓ (during treatment) | 65%↓* (Aorta, gross lesion) | protective effect of lesional LDL degradation | Carew [85] |
| (Male) | 1% probucol in diet (5 months) | TC: 35%↓* VLDL-C: 51%↓* IDL-C: 19%↓ LDL-C: 33%↓* HDL-C: 45%↓* (5 months) | ≈39%↓* (Aorta, gross lesion) | regression of atherosclerosis (≈34%↓* vs. baseline lesion) | Oshima [87] |
| (Male) | 0.3% probucol in diet (16 weeks) | TC: 12%↓* HDL-C: 12%↓ (16 weeks) | 41%↓* (Coronary artery, stenosis) | protective effect of coronary atherosclerosis | Li [90] |
### Table 3. Cont.

| Rabbit            | Drug Plasma Lipids | Atherosclerosis | Findings                  | Reference     |
|-------------------|--------------------|-----------------|---------------------------|---------------|
| Wild-type rabbits (Cholesterol diet) |                    |                 |                           |               |
| NZW               | 1% probucol in diet (60 days) | TC: 16% ↓ (60 days) | Thoracic: 79% ↓ * Abdominal: 85% ↓ * (Aorta, gross lesion) | anti-atherosclerotic effect without plasma lipid lowering Daugherty [86] |
| NZW (male)        | 0.3% probucol in diet (4 weeks) | TC: 4% ↓ HDL-C: 49% ↓ * (Aorta, gross lesion) | 65% ↓ * (Aorta, gross lesion) | protective effect of initial atherosclerosis Nii [89] |

WHHL, Watanabe heritable hyperlipidemic; NZW, New Zealand white; Chol, cholesterol; TC, total cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; IDL-C, intermediate-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Plasma lipids and atherosclerosis are expressed as % compared with those of control rabbits (*p < 0.05).

#### 3.5. CETP Inhibitors

Epidemiological studies have demonstrated that lower plasma HDL-C is associated with increased coronary heart disease (CHD) risk [92]. Therefore, for a long time, it has been hypothesized that elevated plasma HDL-C levels may be beneficial to cardiovascular functions. CETP is a plasma protein that facilitates the transport of cholesteryl ester and triglycerides between the lipoproteins. It collects triglycerides from VLDL or LDL and exchanges them for cholesteryl ester from HDL, and vice versa. CETP inhibitors prevent the transfer of cholesteryl ester and increases plasma HDL-C levels; therefore, their use is intended to reduce the risk of atherosclerosis by improving blood lipid levels [93]. Until now, several CETP inhibitors have been developed. Interestingly, CETP only exists in humans and a few laboratory animals, such as rabbits, guinea pigs, and hamsters, whereas mice and rats do not have CETP [9]. To study the functions of CETP and its inhibitors, rabbits are often used. The effects of CETP inhibitors in rabbits are summarized in Table 4. Many studies showed that administration with these CETP inhibitors effectively increased plasma HDL-C in rabbit models [94–99]. Dalcetrapib administration mildly reduced plasma TC levels in cholesterol-fed rabbits [96,97]. Furthermore, dalcetrapib, torcetrapib, and K-312 showed an atheroprotective effect in cholesterol-fed rabbits [96,98,99]. Our laboratory also demonstrated that genetic ablation of the CETP gene in rabbits led to increased plasma HDL-C and lowered plasma TC levels, and it protected against diet-induced atherosclerosis [100]. In the early clinical trials, four CETP inhibitors, namely torcetrapib, dalcetrapib, anacetrapib, and evacetrapib, could significantly elevate plasma HDL-C levels. Although clinical trials with three other inhibitors failed to show any beneficial effect for CHD, anacetrapib decreased the incidence of CHD [101].

### Table 4. Effects of cholesteryl ester transfer protein (CETP) inhibitors in rabbit models.

| Rabbit         | Drug Plasma Lipids | Atherosclerosis | Reference  |
|----------------|--------------------|-----------------|------------|
| Normal standard diet |                    |                 |            |
| JW (male)      | Dalcetrapib (300 mg/kg) for 7 days | 2.1-fold ↑ * (7 days) | 4% ↑ (7 days) | 73% ↑ * (7 days) | - Kobayashi [94] |
| NZW (male)     | Dalcetrapib (300 mg/kg) for 2 weeks | 3.3-fold ↑ * (2 weeks) | 7% ↑ (2 weeks) | 86% ↑ * (2 weeks) | - Brodeur [95] |
| High-cholesterol diet |                |                 |            |
| JW (male)      | Dalcetrapib (%225 mg/kg) for 6 months | 2.0-fold ↑ * (6 months) | - (6 months) | 24% ↓ * (Aortic arch, gross lesion) | 70% ↓ * Okamoto [96] |
| NZW (male)     | Dalcetrapib (300 mg/kg) for 2 weeks | 2.7-fold ↑ * (2 weeks) | 21% ↑ (2 weeks) | 72% ↑ * (2 weeks) | - Brodeur [95] |
Table 4. Cont.

| Rabbit                  | Drug                        | Plasma Lipids | Atherosclerosis | Reference |
|------------------------|-----------------------------|---------------|-----------------|-----------|
| JW (male) 0.25% Chol diet for 12 weeks | Dalcetrapib (100 mg/kg)     | 1.3-fold †    | 6% ↓            | Huang [97] |
|                        | Dalcetrapib (300 mg/kg)     | 1.9-fold †*   | 21% ↓           | (Aorta, gross lesion) |
|                        |                             |               | 12% ↑           |           |
|                        |                             |               | 3% ↑            |           |
| NZW (male) 0.2% Chol, 10% coconut oil diet for 16 weeks | Torcetrapib (60–90 mg/kg)  | 3.6-fold †    | 28% ↑          | Morehouse [98] |
|                        |                             |               | 59% ↑           |           |
|                        |                             |               | 3% ↓            |           |
|                        | K-312 (10 mg/kg)            | ≈4.7-fold †*  | ≈33% ↑          | Miyosawa [99] |
|                        |                             |               | ≈54% ↓*         |           |
|                        | K-312 (30 mg/kg)            | ≈5.1-fold †*  | ≈18% ↑          |           |
|                        |                             |               | ≈55% ↓*         |           |
|                        | (18 weeks)                  | (18 weeks)    | (18 weeks)      |           |
|                        |                             | (6 weeks)     | (16 weeks)      |           |
| JW, Japanese white; NZW, New Zealand white; Chol, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. Plasma lipids and atherosclerosis are expressed as % or fold-change compared with those of control rabbits (* p < 0.05).

3.6. HDL, Apo A-I, Apo A-I\textsubscript{Milano}, and Apo A-I Mimetic Peptides

HDL, especially its compositional protein apo A-I, possesses a number of physiological functions to protect against atherosclerosis, including reverse cholesterol transport, anti-inflammation, anti-oxidization, mediation of vascular tone, and anti-thrombosis [102–104]. The concept of elevation of plasma HDL or apo A-I to reduce cardiovascular risk has been suggested by both clinical and experimental studies. Many of these experiments were performed in hypercholesterolemic rabbits, using either HDL or apo A-I (including apo A-I variants and apo A-I mimetic peptides), as summarized in Table 5.

Badimon et al. first examined the effect of HDL administration in cholesterol-fed rabbits. A plasma HDL–VHDL (d = 1.063–1.21 g/mL and d = 1.21–1.25 g/mL) fraction was isolated from normal rabbits. HDL–VHDL was administrated intravenously to 0.5% cholesterol-fed rabbits for eight weeks. HDL–VHDL treatment led to a 61% reduction in aortic atherosclerosis over the control [105]. Badimon et al. also demonstrated that such treatment can result in the regression of aortic atherosclerosis (48% reduction) [106]. Most recently, Ben-Aicha et al. compared the atheroprotective properties of HDLs isolated from normolipidemic and hyperlipidemic rabbits. Atherosclerosis was induced by a combination of cholesterol diet feeding and balloon injury. Administration of HDL from normolipidemic rabbits regressed aortic lesions by 4.3% compared with the baseline, whereas HDL from hyperlipidemia increased the lesions by 6.5% [107].

Direct injection of apo A-I into rabbits to test the atheroprotective effects has been attempted. For example, Miyazaki et al. showed that injection with purified rabbit apo A-I significantly reduced atherosclerosis by 48% over the control rabbits [108]. Soma et al. generated carotid atherosclerosis by an extra-arterial collar placement in 1% cholesterol-fed rabbits, and administration of the apo A-I\textsubscript{Milano}–phosphatidylcholine (PC) complex inhibited neointimal formation without affecting plasma TC levels [109]. Chiesa et al. evaluated whether apo A-I\textsubscript{Milano} mobilizes lipids from carotid artery fatty streaks. Lipid-rich plaques were generated at common carotid arteries by a perivascular electrical injury, followed by 1.5% cholesterol diet for 90 days. The effect of apo A-I\textsubscript{Milano}–phospholipid complex administration was assessed by intravascular ultrasound. A single administration of the apo A-I\textsubscript{Milano}–phospholipid complex decreased the plaque area (29% reduction with 1000 mg dose) by the end of the 90-min infusion compared with the pre-infusion [110]. Ibanez et al. reported a plaque regression effect of apo A-I\textsubscript{Milano} using MRI. Abdominal aortic atherosclerosis was induced by a combination of nine-month 0.2% cholesterol-rich diet and twice aortic balloon injury. After lesions were established, recombinant apo A-I\textsubscript{Milano}–phospholipid was administered for four days. Apo A-I\textsubscript{Milano}–phospholipid administration reduced the lesions by 6.1% over the vehicle control and 5.1% compared with baseline [111]. In addition, transgenic expression of human apo A-I and apo A-II also protects against diet-induced atherosclerosis [112,113].
The apo A-I mimetic peptide, 18-amino acid peptide (18A), was originally designed as a model peptide of the class A amphipathic helix by Anantharamaiah in the 1980s [114]. 18A with PC formed a discoidal complex, which was structurally similar to apo A-I. The 18A–PC complex showed similar functions to apo A-I such as cellular cholesterol efflux, activation of lecithin–cholesterol acyltransferase activity, and anti-inflammatory effects. The structure of 18A was refined and derivative peptides were synthesized, including Ac-18A-NH₂, 4F, 5F, and Ac-hE18A-NH₂ [115]. To evaluate the effects of lipid metabolism and atherosclerosis, mimetic peptides were tested in rabbits [116–118]. Van Lenten et al. and Iwata et al. showed anti-atherosclerotic effects of the apo A-I mimetic peptide in cholesterol-fed [117] and WHHL rabbits [118].

### Table 5. HDL or apo A-I therapeutics tested in rabbit models.

| Agent | Rabbit, Manipulation, and Treatment | Outcome | Reference |
|-------|-----------------------------------|---------|-----------|
| **HDL** | | | |
| HDL + VHDL (d = 1.063–1.25 g/mL) | ● NZW rabbit (male and female)  
● Atherosclerosis induction 0.5% cholesterol diet for 8 weeks  
Treatment: 50 mg/week (once a week for 8 weeks), IV |  
● Plasma lipids  
TC: →, HDL-C: →  
● Aortic gross lesion 61% ↓  
| Badimon [105] |
| HDL + VHDL (d = 1.063–1.25 g/mL) | ● NZW rabbit  
● Atherosclerosis induction 0.5% cholesterol diet for 60 days  
Treatment: 50 mg/week (once a week for 30 days), IV |  
● Plasma lipids  
TC: →, HDL-C: →, TG: →  
● Aortic gross lesion 54% ↓ *  
| Badimon [106] |
| HDL (isolated from HC and NC rabbits) | ● NZW rabbit  
● Atherosclerosis induction Hypercholesterolemic diet for 90 days + balloon aortic denudation  
Treatment: 75 mg/week (once a week for 30 days), IV |  
● Aortic lesion assessed by MRI  
NC-HDL: 4.3% ↓ * vs. baseline  
HC-HDL: 6.5% ↑ * vs. baseline  
| Ben-Aicha [107] |
| **Apo A-I and apo A-I\textsubscript{Milano}** | | | |
| Apo A-I | ● NZW rabbit (male)  
● Atherosclerosis induction 0.5% cholesterol diet for 60 days  
Treatment: 40 mg protein/injection for 30 days, IV |  
● Plasma lipids  
TC: →, HDL-C: →  
● Aortic gross lesion 48% ↓ *  
| Miyazaki [108] |
| Apo A-I\textsubscript{Milano} + PC | ● NZW rabbit (male)  
● Atherosclerosis induction 1% cholesterol diet for 21 days + carotid arterial collar placement  
Treatment: 40 mg protein/injection for 10 days, 5 times IV |  
● Plasma TC: →  
● Carotid artery intima/media ratio 59% ↓ *  
| Soma [109] |
| Apo A-I\textsubscript{Milano} + DPPC | ● NZW rabbit (male)  
● Atherosclerosis induction 1.5% cholesterol diet for 90 days + carotid arterial electric injury  
Treatment: 250–1000 mg protein/injection for 90 min, single IV |  
● Plasma lipids  
VLDL-C: ↑, HDL-C: ↑  
● Carotid artery lesion assessed by IVUS  
250 mg: 3% ↓ (vs. pre-treatment)  
500 mg: 12% ↓ (vs. pre-treatment)  
1000 mg: 29% ↓ (vs. pre-treatment)  | Chiesa [110] |
| Apo A-I\textsubscript{Milano} + POPC (ETC-216) | ● NZW rabbit (male)  
● Atherosclerosis induction 0.2% cholesterol diet for 9 months + balloon aortic denudation  
Treatment: 75 mg protein/injection for 4 days (2 times), IV |  
● Abdominal aortic plaque size assessed by MRI  
6.1% ↓ *  
(5.1% ↓ * vs. pre-treatment)  | Ibanez [111] |
Table 5. Cont.

| Agent | Rabbit, Manipulation, and Treatment | Outcome | Reference |
|-------|-----------------------------------|---------|-----------|
| Ac-hE18A-NH₂ | WHHL rabbit (male) | Plasma TC 49% ↓ (* vs. pre-treatment) | Gupta [116] |
|       | Treatment: 15 mg/kg for 18 h, single IV |         |           |
|       | NZW (female) | Plasma lipids (2 months) TC: 19% ↓ (D-4F), 28% ↓ * (L-4F) HDL-C: + (D-4F, L-4F) | Van Lenten [117] |
|       | Atherosclerosis induction 1% cholesterol diet for 1 month | Aortic gross lesion 58% ↓ * (D-4F), 46% ↓ * (L-4F) | |
|       | Treatment: 10 mg/kg/day (daily for 1 month), SC |         |           |
| D-4F  |                        |         |           |
| L-4F  |                        |         |           |
| EPS24218 + DPPC + SM (ETC-462) | WHHL rabbit (male and female) | Plasma lipids (12 weeks) TC: 22% ↑ * LDL-C: 30% ↓ * HDL-C: 30% ↑ * | Iwata [118] |
|       | Treatment: 50 mg/kg (twice a week for 12 weeks), IV | Aortic lesion volume assessed by IVUS 25% ↓ * (7% ↓ vs. pre-treatment) | |

HDL, high-density lipoprotein; VHDL, very-high-density lipoprotein; apo, apolipoprotein; HC, hypercholesterolemic; NC, normocholesterolemic; PC, phosphatidylcholine; DPPC, dipalmitoyl phosphatidylcholine; POPC, palmitoyl-2-oleoyl phosphatidylcholine; SM, sphingomyelin; NZW, New Zealand white; WHHL, Watanabe heritable hyperlipidemic; IV, intravenous injection; SC, subcutaneous injection; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; IVUS, intravascular ultrasound. Outcomes are expressed as % compared with those of vehicle control rabbits or baseline pre-treatment (*p < 0.05).

4. Limitation of Rabbit Models

Rabbits have a number of advantages to study hyperlipidemia and for drug development. However, some limitations should be considered when using rabbit models. Unlike mice, laboratory rabbits are generally outbred. Thus, commercial rabbits may show variations in responses to a cholesterol diet and plasma lipid levels [119,120]. Such variations in lipids will certainly affect the extent of atherosclerosis and interfere with the evaluation of drug effects. To minimize the variation, rabbits can be prescreened by feeding them a cholesterol diet for a short term in advance, and then only those rabbits with high plasma lipid levels can be selected [89,121]. Hepatic lipase (HL) activity in the post-heparin plasma of rabbits is naturally lower than that in humans and rodents [122,123]. A recently developed automated assay for measuring HL activity revealed that HL activities in the post-heparin plasma of rats and humans are 10-fold and 4-fold higher than those of rabbits [124].

5. Conclusions

Rabbits are still an important model for the study of lipid metabolism and atherosclerosis. Rabbits have a number of unique features that make them useful for hypolipidemic drug development. The emergence of genome editing technology will enable us to generate more KO/knock-in rabbits for the study of hyperlipidemia and atherosclerosis. These gene-manipulated rabbits will certainly provide novel insights not only into molecular mechanisms of hyperlipidemia but also into the development of therapeutic strategies.

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Abbreviations

Apo  apolipoprotein
CETP  cholesteryl ester transfer protein
CHD  coronary heart disease
CM  chylomicron
FH  familiy hypercholesterolemia
HDL  high-density lipoprotein
HDL-C  high-density lipoprotein cholesterol
HL  hepatic lipase
JW  Japanese white
KO  knockout
LDL  low-density lipoprotein
LDL-C  low-density lipoprotein cholesterol
LDLR  low-density lipoprotein receptor
MRI  magnetic resonance imaging
NZW  New Zealand white
PC  phosphatidylcholine
TC  total cholesterol
TG  triglycerides
Tg  transgenic
VHDL  very-high-density lipoprotein
VLDL  very-low-density lipoprotein
VLDL-C  very-low-density lipoprotein cholesterol
WHHL  Watanabe heritable hyperlipidemic
WHHLMI  myocardial infarction-prone Watanabe heritable hyperlipidemic

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