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REVIEW ARTICLE

Hyperlipidaemia and cardioprotection: Animal models for translational studies

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Hyperlipidaemia is a well-established risk factor for cardiovascular diseases and therefore, many animal model have been developed to mimic the human abnormal elevation of blood lipid levels. In parallel, extensive research for the alleviation of ischaemia/reperfusion injury has revealed that hyperlipidaemia is a major co-morbidity that attenuates the cardioprotective effect of conditioning strategies (preconditioning, postconditioning and remote conditioning) and that of pharmacological interventions by interfering with cardioprotective signalling pathways. In the present review article, we summarize the existing data on animal models of hypercholesterolaemia (total, low density and HDL abnormalities) and hypertriglyceridaemia used in ischaemia/reperfusion injury and protection from it. We also

Abbreviations: ApoA-V, apolipoprotein A-V; APOC1, apolipoprotein C1 gene; APOE, apolipoprotein E gene; ApoE, apolipoprotein E; ApoE$^{-/-}$, deletion of apolipoprotein E gene; CETP, cholesteryl ester transfer protein; cp, corpulent; CRISPR, clustered regularly interspaced short palindromic repeats; CRISPR/Cas 9, CRISP associated protein 9; DHC, diet-induced hypercholesterolaemia; E3L, ApoE*3-Leiden transgenic mice; FHC, familial hypercholesterolaemia; HCD, high cholesterol diet; HDL-c, high density lipoprotein cholesterol; HFD, high-fat diet; I/R, ischaemia reperfusion; LDL-c, low density lipoprotein cholesterol; LDLr, LDL receptor; LDLr$^{-/-}$, deletion of LDL receptor; LpL, lipoprotein lipase; MI, myocardial infarction; NZW rabbits, New Zealand White rabbits; PHHC, Prague hereditary hypercholesterolaemic; PHT, post-prandial hypertriglyceridaemic rabbit model; S1P, sphingosine-1 phosphate; SR-BI, scavenger receptor BI; TC, total cholesterol; TGs, triglycerides; VLDLs, very low density lipoprotein; VLDL-c, very low density lipoprotein cholesterol; WD, Western diets; WHHL rabbits, Watanabe heritable hyperlipidaemic rabbits.

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provide recommendations on preclinical animal models to be used for translations of the cardioprotective strategies into clinical practice.

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1 | INTRODUCTION

Cardiovascular disease is the most common cause of mortality worldwide (Timmis et al., 2018). Hyperlipidaemia is the pathological state characterized by elevated levels of serum cholesterol and triglycerides (TGs) and it is considered as a major risk factor for cardiovascular disease. In fact, hyperlipidaemia is present in most patients with myocardial infarction (MI; Osipov, Bianchi, et al., 2009). Chronic elevation of blood cholesterol results in the development of atherosclerosis but also exerts a negative impact on the myocardium by increasing oxidative stress, mitochondrial dysfunction and apoptosis. Moreover, hypercholesterolaemia induces microvascular dysfunction through nitro-oxidative stress and induction of inflammation, mechanisms which may also account for increased susceptibility of the myocardium to infarction (see for a recent extensive review, Andreadou, Iliodromitis, et al., 2017).

Various animal species have been used to study the effects of diet on cholesterol homeostasis and atherosclerosis including mice (Temel & Rudel, 2007), hamsters (Dillard, Matthan, & Lichtenstein, 2010), guinea pigs (Fernandez & Volek, 2006), rats, rabbits (Badimon, Badimon, & Fuster, 1990; Aliev & Burnstock, 1998), minipigs (Shim, Al-Mashhadi, Sørensen, & Bentzon, 2016) and farm breed pigs (Badimon, Steele, Badimon, Bowie, & Fuster, 1985; Fuster et al., 1985; Palazón et al., 1998; Vilahur, Padro, & Badimon, 2011). Mice and rats are resistant to spontaneous development of atherosclerosis but both diet and genetic manipulations render these rodents more susceptible to atherosclerosis development, while genetically altered strains respond to cholesterol feeding to a greater extent. Some of these models, mainly mice and rats, have been employed for the investigation of hypelipidaemia's impact on myocardial ischaemia/reperfusion injury (I/R). However, a number of studies (including one in pigs) indicate that the effect of cardioprotective manoeuvres is blunted in these animals (Iliodromitis et al., 2006; Iliodromitis et al., 2010; reviewed in Ferdinandy, Hausenloy, Heusch, Baxter, & Schulz, 2014). In fact, high cholesterol diet (HCD)-induced hyperlipidaemia was the first co-morbidity where the loss of cardioprotection was observed in rabbits and rats (Szilvassy et al., 1995).

Several cardioprotective strategies aimed at the attenuation of myocardial I/R injury have been employed with prognostic benefit in some but not all patients (Hausenloy et al., 2017; Heusch, 2013), and therefore, it is of interest to consider whether hyperlipidaemia is one of the co-morbidities that interferes with cardioprotection (Andreadou, Iliodromitis, et al., 2017). Experimental and clinical studies have shown that hypercholesterolaemia may hamper the cardioprotective signalling of conditioning manoeuvres. Although the effect of hypelipidaemia on the mechanisms of myocardial I/R injury is not fully elucidated, hyperlipideamic animals exhibit deregulation of cardioprotective cascades such as inactivation of the reperfusion injury salvage kinase pathway, modulation of ATP sensitive potassium channels, impaired NO availability and a redistribution of the intracellular localization of connexin 43 in the cardiomyocytes (Görbe et al., 2011; Andreadou, Iliodromitis, et al., 2017). Nowadays, a pressing challenge is to define appropriate models of hyperlipidaemia to improve the translational potential of pharmacological and mechanical interventions related to cardioprotection and reveal the underlying mechanisms (Heusch, 2017).

In this review article, we summarize the current knowledge on the mice, rat and pig models of hyperlipidaemia placing emphasis on those that have been employed for preclinical studies on cardioprotection. We highlight the future perspectives of the use of each model for translational research in terms of infarct size reduction, strategies focusing on the lipid profile and the extent of atherosclerosis development.

2 | ANIMAL MODELS FOR HIGH TOTAL CHOLESTEROL AND HIGH LDL CHOLESTEROL

Cholesterol is a component of the cell membrane, and cholesterol metabolites, such as steroid hormones and vitamin D, serve important biological functions in vertebrates. Unbalanced diets containing high levels of fat and carbohydrates, the so-called Western diets (WD), frequently trigger hypercholesterolaemia. Also, genetic factors such as defects in the apolipoprotein genes or receptors (Fan & Watanabe, 2000) influence susceptibility to diet-induced hypercholesterolaemia (DHC). In humans, hyperlipidaemia includes hypercholesterolaemia and hypertriglyceridaemia and is classified as primary, also named as familial, and secondary. The manifestation of primary hyperlipidaemia is based on genetic defects of a single gene (monogenic) or of multiple genes (polygenic) and the respective phenotype is accompanied by well-characterized abnormal lipoprotein patterns. Secondary forms of hyperlipidaemia are acquired along life span following other disorders such as diabetes, nephrotic syndrome, hypothyroidism and prolonged use of drugs like corticosteroids and ß-adrenoceptor antagonists (beta-blockers). The main cause of hyperlipidaemia in Western

countries includes changes in lifestyle habits and the increased intake of saturated fat. The broad spectrum of lipid dysregulations found in human urges the need for the classification of the animal models of hyperlipidaemia according to their translational resemblance.

Increased circulating total cholesterol (TC) levels or increased cholesterol incorporated in low and very low-density lipoproteins (LDL and VLDL, respectively) are major risk factors for atherosclerosis. Therefore, most of the animal models that exhibit increased TC or LDL cholesterol (LDL-c) levels stand also as models of atherosclerosis (Emini Veseli et al., 2017). In contrast, high levels of HDLs are considered to be protective against atherosclerosis (Ference et al., 2017).

2.1 | Small animals (mice, rats and rabbits)

Small animals such as mice, rats and rabbits are often used due to ease of breeding, short gestation and life cycle, although they are naturally resistant to develop hypercholesterolaemia and atherosclerosis. While rodents show low expression/absence of cholesteryl ester transfer protein (CETP), rabbits have higher CETP activity, thereby higher LDL and low HDL levels representing a more useful animal model for hypercholesterolaemia research (Tsutsumi, Hagi, & Inoue, 2001).

2.1.1 | Diet-induced hypercholesterolaemia and high LDL cholesterol

Mice and rats

To induce hypercholesterolaemia, a long-term feeding (several weeks to months) with various diets supplemented with cholesterol (Csont et al., 2002; Giricz et al., 2017) are effectively used together with supportive substances causing lipid metabolism disturbances, for example, **cholate** (Giricz et al., 2017), coconut oil (Romain et al., 2018), corn starch and sucrose (Romain et al., 2018). Several studies have demonstrated that certain inbred strains of mice, such as C57BL/6, develop atherosclerotic lesions in response to high cholesterol diet (HCD) and fat that contain cholic acid to block cholesterol conversion to bile acids (Roberts & Thompson, 1976). Among the different diets, the typical rodent WD contains high levels of saturated fat (~35 kcal% fat and 21% w/w), such as cocoa butter, palm oil or dairy butter, cholesterol (~0.5 to 1% w/w) and cholic acid (~0.1% to 0.5% w/w). These diets when used for 12 weeks provoke TC and LDL-c elevation and signs of atherosclerosis (Dietschy, 1998; Zulet, Barber, Garcin, Higueret, & Martínez, 1999).

In contrast, outbreed rat strains (i.e. Sprague–Dawley or Wistar) fed with WD (~45 kcal% fat as hydrogenated coconut oil) or even low-fat diets (~12 kcal% fat as corn oil) that contain cholesterol (~1% w/w) and cholic acid (0.25–0.5% w/w) exhibit augmented levels of TC and LDL-c but are resistant to develop atherosclerosis under these conditions, unless a thyroid hormone inhibitor (2-thiouracil, ~0.5% w/w) is added. Indeed, the normal rat chow supplemented with 4% cholesterol, 1% cholic acid and 0.5% 2-thiouracil diet over 30 days increase plasma TC, TGs, LDL-c, VLDL cholesterol (VLDL-c) with a parallel decrease in HDL cholesterol (HDL-c; Raja, Saravanakumar, & Sathya, 2012), and 12 weeks of 4% cholesterol, 1% cholic acid and 0.5% 2-thiouracil induces atherosclerosis (Joris, Zand, Nunnari, Krolikowski, & Majno, 1983). Additionally, in rats, streptozotocin injection in addition to cholesterol and oil-containing diet induce simultaneous hypercholesterolaemia and hyperglycaemia within a short time period (Adameová et al., 2007). Besides high-fat diets (HFD), many studies have described dyslipidaemia in rats fed with carbohydrate-enriched diets and a combination of both (Wong, Chin, Suhaimi, Fairus, & Ima-Nirwana, 2016).

The Prague hereditary hypercholesterolaemic (PHHC) rat (a strain crossbred from Wistar rats) is used as a model of hypercholesterolaemia induced by dietary cholesterol (Kovár, Tonar, Heczková, & Poledne, 2009). PHHC rats exhibit mild hypercholesterolaemia when fed with standard chow and develop remarkable hypercholesterolaemia (TC > 190 $mg \cdot dl^{-1}$ [5 mM]) on 2% cholesterol diet. In this strain, most of the cholesterol is found in VLDL particles. Concomitantly, both intermediate-density lipoprotein cholesterol and LDL-c concentrations rise without any increase in HDL-c. PHHC rats do not markedly differ from Wistar rats in the activities of enzymes involved in intravascular remodelling of lipoproteins, LDL catabolism, cholesterol turnover rate and absorption of dietary cholesterol (Kovár et al., 2009). Despite the presence of hypercholesterolaemia, PHHC rats do not develop atherosclerosis even after 6 months on 2% cholesterol diet. Importantly, the crossbreeding experiments documented that the hypercholesterolaemia of PHHC rats is polygenic (Kovár et al., 2009).

In the context of cardioprotection, HCD in mice have shown discrepant results on infarct size depending on the duration of the dietary intervention (Girod, Jones, Sieber, Aw, & Lefer, 1999). The use of WD in rodents mimics the human hyperlipidaemic profile and the increased saturated fat intake observed in humans of the Western countries. Recent developments in commercially available rodent diets have promoted reproducibility among experimental series. Therefore, the protocol of 14 weeks of WD in rodents (Andreadou, Efentakis, et al., 2017; Desmarchelier et al., 2012) is recommended to study the effect of cardioprotective interventions in the presence of DHC. Moreover, many of the above-discussed rat models of DHC have been used to investigate both non-pharmacological (ischaemic preconditioning, postconditioning and remote conditioning; Adameova et al., 2007; Kupai et al., 2009; Ma et al., 2012) and pharmacological cardioprotection (Csonka et al., 2014) in terms of reducing infarct size and improving post-ischaemic recovery of heart function. Most of these studies showed the abrogation of cardioprotection in hyperlipidaemia. However, as indicated above and because of some limitations in the use of small animals in hyperlipidaemia studies, more studies in large animal models would be preferable for cardioprotection studies.

Rabbits

Rabbits are herbivores and therefore do not tend to develop hypercholesterolaemia or atherosclerosis unless they undergo a dietary intervention. New Zealand White (NZW) rabbits are commonly used

to study hypercholesterolaemia and atherosclerosis. NZW rabbits under standard laboratory diet have low plasma TC levels and do not develop atherosclerosis. However, cholesterol-enriched diets (0.2–0.5% cholesterol) and HCD (1.0–1.5% cholesterol) greatly alter the lipid profile of NZW (Emini Veseli et al., 2017). Supplementation of standard diet with 0.2–0.5% cholesterol results in the early development of hypercholesterolaemia (within 6–8 weeks) and atherosclerosis and pronounced atherosclerosis—not affecting the abdominal aorta—is evident after 20–26 weeks.

Several studies have examined both mechanical and pharmacological cardioprotective interventions (Andreadou et al., 2012; Iliodromitis et al., 2006) in short-term-fed NZW rabbits and have provided possible explanations for the loss of postconditioning-induced cardioprotection with hypercholesterolaemia. Thus, this model stands as a well-characterized mild phenotype of hypercholesterolaemia for use in translational studies. On the other hand, HCDs lead to a massive increase in TC levels (1,500 and 3,000 mg·dl^{-1} [39 and 77 mM, respectively]; Fan & Watanabe, 2000) without significant translational potential.

Hypercholesterolaemia may exacerbate the I/R injury by altering signalling pathways on the myocardium (Andreadou, Iliodromitis, et al., 2017) and the lipid metabolism. The generation of ROS produces oxidized derivatives of cholesterol, the oxysteroles, which propagate lipid peroxidation and induce cell death and mitochondria dysfunction (Paradis, Leoni, Caccia, Berdeaux, & Morin, 2013). Particularly, oxysterols are involved in the development of atherosclerosis and in the genesis of chronic diseases (Lordan, Mackrill, & O'Brien, 2009).

2.1.2 | Genetic small animal models of high TC and high LDL

In various rodent strains, dietary cholesterol and fat have been reported to induce disturbances in cholesterol metabolism and aortic lipid accumulation (Dillard et al., 2010; Yin et al., 2012). However, there is a significant diversity of atherosclerotic lesions burden among different mice strains (Paigen, Morrow, Brandon, Mitchell, & Holmes, 1985). Therefore, genetic engineering tools, such as ablation of apolipoprotein E (ApoE; Getz & Reardon, 2006), LDL receptors (LDLr; Girod et al., 1999), or CETP gene mutations (Herrera et al., 1999), have been used to effectively generate animals with "human-like" cholesterol profile and a predisposition to develop atherosclerotic lesions when fed with a standard diet or exacerbated by HFD/HCD.

Mice

The mouse is characterized by high HDL but low concentrations of VLDL and LDL particles, and the genetic means for promoting hyperlipidaemia involve disturbing this balance. Genetic manipulations in mice disrupt the normal lipoprotein regulation and metabolism and are used for the induction of hypercholesterolaemia and atherosclerosis. Diets containing high levels of cholesterol and fat are frequently used to influence the genetic susceptibility of mouse models to bear hypercholesterolaemia. Most strains of mice are relatively resistant to the development of such phenotypes with changes in the lipoprotein profile, except for C57BL/6 mice.

Mice with deletion of the ApoE gene (ApoE^{-}/$^{-}$) are widely used due to their propensity to develop atherosclerotic lesions (Meir & Leitersdorf, 2004). This model presents a fivefold to sixfold increase in TC concentrations in comparison to parent C57BL/6 mice and fibrous plaques confined to the aortic root area are apparent after 20 weeks of age (Nakashima, Plump, Raines, Breslow, & Ross, 1994). When fed HFD of HCD, ApoE^{-}/$^{-}$ mice exhibit TC up to 1,160 mg·dl^{-1} (30 mM) and develop widely distributed atherosclerosis, similar to that seen in humans (Meyrelles, Peotta, Pereira, & Vasquez, 2011). Both models are useful for the investigation of I/R injury in preclinical studies as they reflect mild and severe hypercholesterolaemia/atherosclerosis respectively.

The deletion of LDL receptor (LDLr^{-}/$^{-}$) mouse is a model bearing a genetic mutation on LDLr and recapitulates the familial hypercholesterolaemia (FHC). When fed on a chow diet, these mice exhibit slightly elevated levels of TC in comparison to the wild types and mild atherosclerotic lesions (Getz & Reardon, 2006). Diet supplementation with cholesterol results in a massive increase of plasma TC and accelerated atherosclerosis. However, the use of this model of hyperlipidaemia is limited for investigation of cardioprotective strategies because infarct size was either increased or decreased upon diet supplementation (Ma et al., 2012). LDLr^{-}/$^{-}$ mice fed for 2 weeks HCD showed increased infarct size but long-term HCD (12 weeks) reduced infarct size when compared to wild-type and LDLr^{-}/$^{-}$ mice fed with normal chow (Girod et al., 1999).

Rats

With the establishment technologies for genetic manipulation and the rat genome sequencing, rats are increasingly used in biomedical research. Rats are preferable for the ease in blood collection and dissection of blood vessels over mice and they are lower cost than large animals.

ApoE^{-}/$^{-}$ Sprague–Dawley rats have been generated to effectively mimic hyperlipidaemia and atherosclerotic plaques as seen in humans with decreased HDL-c and markedly up-regulated TC and LDL-c (Zhao et al., 2018). However, there are only few publications using this model (Wei et al., 2015). LDLr^{-}/$^{-}$ rats have also been created by zinc-finger and clustered regularly interspaced short palindromic repeats associated protein 9 (CRISPR/Cas 9) technology. These rats on normal chow exhibit elevated TC, LDL-c, TGs and VLDL-c. Atherosclerotic plaques develop rapidly on WD (Sithu et al., 2017). The difference in lipid profiles between rodents and humans regarding the LDL-c and HDL-c distribution is due to the presence of CETP in humans which is responsible for transferring cholesterol ester from HDL particles to VLDL and LDL particles in exchange for TGs (Marotti et al., 1992). A rat which overexpresses the CETP protein has also been developed in a Dahl salt-sensitive hypertensive strain and this overexpression resulted in profound atherosclerosis. These rats also suffered from MI and decreased survival and thus presented a phenotype which differed from various mouse models (Herrera et al., 1999).

We must mention, however, that rats with genetic mutations have not been used so far for the investigation of I/R injury and further studies must be conducted to compare infarct size with that in wild-type littermates.

Rabbits

Watanabe heritable hyperlipidaemic (WHHL) rabbits bear a defect on the LDLr and as a result, they stand as an animal model of unprovoked hypercholesterolaemia, with increased levels of LDL-c and extended atherosclerotic lesions (Fan & Watanabe, 2000). This animal model resembles the FHC seen in humans (Aliev & Burnstock, 1998). Several types of atherosclerotic lesions have been observed in these animals, ranging from early fatty streaks to advanced lesions in the large vessels, including the abdominal aorta. WHHL rabbits are very useful in studying the biological processes of plaque destabilization and thrombogenesis (Shiomi, Koike, & Ito, 2013). However, they are not appropriate models for the investigation of chronic cardioprotective strategies because it is difficult for researchers to distinguish whether the cardioprotective effect is attributed to the attenuation of coronary atherosclerotic lesions development or to other direct effects on the myocardium (Hoshida et al., 1997). Moreover, increased plaque instability with risk of MI may produce high variability in the measurements of infarct size during I/R injury.

High-fructose and HFD-fed WHHL rabbits develop early insulin resistance and glucose tolerance and show aortic lesions with a lipid core and calcifications. This model has allowed researchers to investigate the effect of insulin resistance on atherosclerosis lesion formation (Ning et al., 2015). Recently, ApoE^{-}/$^{-}$ rabbits have been generated (Niimi et al., 2016). ApoE^{-}/$^{-}$ rabbits on regular laboratory diet exhibit mild hyperlipidaemia and diet enrichment with cholesterol leads to a drastic increase in TC. ApoE^{-}/$^{-}$ rabbits are more prone to develop atherosclerosis than wild-type rabbits when fed with a cholesterol diet for 10 weeks (Niimi et al., 2016). However, this rabbit model has not been tested yet in cardioprotection studies. The most recent genetic rabbit model of hypercholesterolaemia has been developed with the CRISPR/Cas9 system and involved the depletion of the LDLr. These LDLr^{-}/$^{-}$ animals 3 months old exhibit a 20-fold increased plasma TC and a 35-fold increase of LDL-c in comparison to wild-type rabbits. Importantly, they had also elevated TG and reduced HDL-c levels (Lu et al., 2018). Atherosclerotic lesions were observed in the coronary arteries, but further characterization of this model regarding atherosclerosis progression and MI is required.

2.2 | Large animals (diet and genetic) of high TC and high LDL

The lipid profile of larger animals, such as pigs, dogs and nonhuman primates, is more similar to that of humans. However, their routine use in hyperlipidaemia experiments is limited by laboratory facilities, cost and ethical issues. Nevertheless, large animal models provide several key advantages over smaller animals: (a) their cardiovascular system including its neurohumoral regulation resemblances that of humans, (b) when fed with special diet they develop atherosclerosis similar to that in humans and (c) percutaneous interventions can be used in larger animals, providing the opportunity to assess cardioprotective strategies and evaluate pharmacological treatment (Amuzie et al., 2016; Hamamdzic & Wilensky, 2013).

Large animals such as dogs and pigs under normal chow exhibit a high HDL-c/low LDL-c profile during their life span, associated with a low cardiovascular risk (Tsutsumi et al., 2001; Yin et al., 2012). Spontaneous atherosclerosis in dog is rare, while it can be found in pigs depending on age and strain. Through dietary interventions (5–10% fat/0.5–1% cholesterol diets) and vascular lesion induction (usually balloon dilatation), the atherosclerotic process can be stimulated. Under a hypercholesterolaemic diet, pigs display TC levels similar to those observed in humans and they develop early-stage atherosclerotic lesions in the abdominal aorta and coronary arteries within a 50-day period (Badimon, 2001; Thim et al., 2010; Vilahur et al., 2011). Nonetheless, advanced complex and multiple atherosclerotic plaques development require longer time periods that are associated with increase in weight and size that make the model difficult to use for intervention procedures, surgery and laboratory handling. Consequently, minipig lines such as Göttingen, Yucatan or Ossabaw have been employed to overcome this situation (Kleinert et al., 2018). Ossabaw minipigs exert a metabolic syndrome with insulin resistance, obesity, hypertension and dyslipidaemia (Neeb et al., 2010), and they develop profound coronary atherosclerosis (Trask et al., 2012). DHC in Yucatan miniature pig was characterized by significantly elevated plasma TC, LDL, and VLDL levels, with a proportional reduction in HDL-c concentrations (Poledne & Jurčíková-Novotná, 2017). In comparison to DHC, spontaneous homozygous FHC pigs presented increased TC concentrations with a predominant shift to the LDL-c fraction, which displayed defective LDLr coupling and impaired LDL clearance with concomitantly decreased lecithin cholesterol acyltransferase activity. DHC exhibits a twofold higher TC/apolipoprotein B ratio, indicating less dense LDL particles than FHC. Recently, a minipig model with the same gene mutation, the Bretoncelles Meishan pig, became available (Thim et al., 2010). Likewise, the micro-minipig (the smallest pig line available for experimental purposes) has been employed as an atherosclerotic model, when fed an HFD/HCD (12–5%, respectively; Hasler-Rapacz, Nichols, Griggs, Bellinger, & Rapacz, 1994), but its use in I/R studies has not been established, probably due to the low weight of these animals.

Sex differences in humans are becoming increasingly essential for diagnostic and treatment strategies and, therefore, animal models should reflect such distinction. Göttingen minipigs were assessed for sex differences in metabolic parameters during a high cholesterol regimen, demonstrating more severe hypercholesterolaemia and atherosclerosis in female minipigs. Similar results regarding gender differences were later observed in Yucatan and Ossabaw pig lines (Christoffersen, Grand, Golozoubova, Svendsen, & Raun, 2007).

A Yucatan minipig model of FHC was constructed by DNA transposition of human D374Y-**proprotein convertase subtilisin/kexin type 9** gain-of-function mutation, displaying severe

hypercholesterolaemia due to decreased LDLr levels and LDL catabolism inhibition and, accordingly, associated with rapidly progressive atherosclerosis (Al-Mashhadi et al., 2013). Bama minipigs were modified by CRISPR/Cas9, targeting ApoE and LDLr and generating biallelic knockout pigs that presented moderately elevated TC, LDL-c and apoB levels, which were significantly increased after hypercholesterolaemic diet (Fang et al., 2018). To our knowledge, this model has not been tested in I/R injury.

The genetically engineered ExeGen™ consists of a Yucatan minipig model of LDLr deficiency to exert hyperlipidaemia and atherosclerosis. Different study protocols were applied, involving HFD administration and lipid-reduction pharmacotherapy with β-hydroxy β-methylglutaryl-CoA reductase inhibitor (**atorvastatin**) or ATP-citrate lyase inhibitor (**bempedoic acid**; Amuzie et al., 2016). These pigs displayed weight gain and increased concentrations of TC, LDL-c and HDL-c fractions, with the development of atherosclerotic plaques. Both atorvastatin and bempedoic acid attenuated these alterations and reduced Oil Red O lipid staining. In another LDLr knockout model, pigs on standard chow developed atherosclerotic lesions beginning at 6 months of age and atherosclerosis was intensified when a hyperlipidaemic diet was added. In this setting, treatment with **pitavastatin** failed to modify plasma TC concentration, but achieved a 52% reduction of plaque volume in intravascular ultrasound, that pathologically correlated with early-stage atherosclerotic lesions (Li et al., 2016). Overall, since pig models with single mutations do not resemble the human hyperlipidaemia,

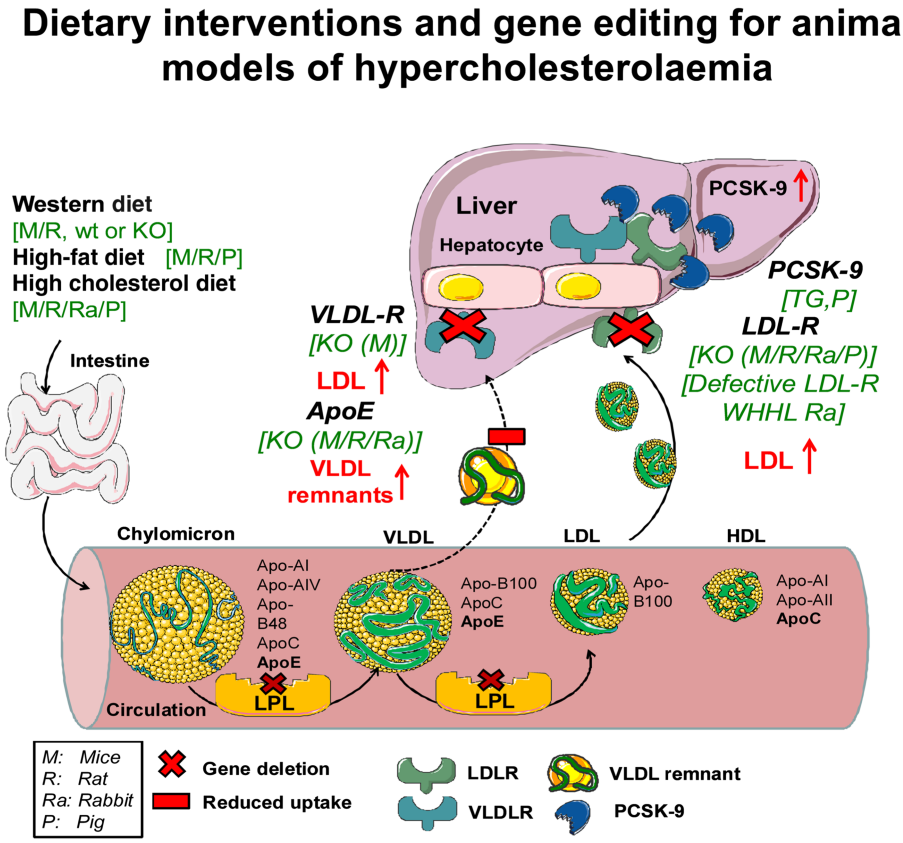

FIGURE 1 Schematic illustration of lipoprotein metabolism along with some dietary and genetic interventions that lead to hypercholesterolaemia. Dietary interventions include long-term feeding with various diets supplemented with cholesterol or fats together with supportive substances causing lipid metabolism disturbances. Western type diets are commonly used in rodents (mice and rats) in order to provoke mild hypercholesterolaemia through the increased uptake of fat while high-fat and high cholesterol diets are employed to produce more intense hypercholesterolaemic phenotypes. Genetic manipulations to provoke hypercholesterolaemia in animal models have been performed in various catabolic steps of lipoproteins. Lipoprotein lipase (LpL) hydrolyses triglycerides in lipoproteins, such as those found in chylomicrons and VLDL, into two free fatty acids and one monoacylglycerol molecule. LpL deletion leads to increased abundance of VLDL and LDL. LDL receptor (LDLR) mediates endocytosis of cholesterol from cholesterol-rich LDL by recognizing apolipoprotein apoB-100 and both LDLR and very LDL receptor (VLDLR) recognize lipoproteins baring the apolipoprotein E. The deletion of Ldlr, ApoE and VLDLR gene leads to impaired clearance of chylomicrons, VLDL and LDL. Therefore, these animals develop hypercholesterolaemia to a different degree depending on the animal model used. In parallel, PSCK-9 is a proprotein convertase involved in the degradation of LDLR from the membranes. Overexpression of PSCK-9 gene leads to increased binding of the PSCK-9 protein to the extracellular part of the LDL. In this way, LDLRs are internalized by the cells and degraded. Apo, apolipoprotein; KO; knockout; LDLR, LDL receptor; LPL, lipoprotein lipase; PHHC, Prague hereditary hypercholesterolaemic; PSCK-9, proprotein convertase subtilisin/kexin type 9; STH, St. Thomas Hospital; TG, transgenic; VLDL, very LDL; VLDLR, VLDL receptor; WHHL, Watanabe heritable hyperlipidaemic rabbits

they are discouraged for translational studies but are very helpful for mechanistic studies.

Dog models are less frequently employed due to their lack of atherosclerosis development and dyslipidaemia (Poledne & Jurčíková-Novotná, 2017). In this species, hypercholesterolaemia is induced through thyroid inhibition and dietary intervention, displaying after high-fat regimen increased TC, LDL-c and HDL-c concentrations, with an irregular atherosclerotic response. This model has been used to test lipid-lowering drugs (Yin et al., 2012).

A hallmark of vascular disease and early atherosclerosis plaque formation in humans is endothelial dysfunction. This condition, which seems to have important effects in cardiac injury, can be studied in the porcine model of hypercholesterolaemia. As in humans, pigs fed an HFD for a relatively short period of time (10 days) develop endothelial dysfunction amenable for the study of different interventions (Vilahur, Gutiérrez, et al., 2015; Vilahur, Padró, et al., 2015).

A summary of dietary interventions and gene editing for animal models of hypercholesterolaemia and high LDLc is illustrated in Figure 1.

3 | ANIMAL MODELS FOR HYPERTRIGLYCERIDAEMIA

Hypertriglyceridaemia is an independent risk factor for coronary artery disease and several clinical studies have suggested that it is also an independent risk factor for early development of atherosclerosis (Boquist et al., 1999). Dietary TGs are packaged together with cholesterol and lipoproteins (mainly apolipoprotein-B48) in enterocytes to form chylomicrons. Chylomicrons are carried from lymphatic vessels into the circulation where they are hydrolysed to remnants which are cleared from the circulation via hepatic LDLr (Figure 2). Once in the liver, TGs are released in the form of apolipoprotein B-100 containing VLDL particles. Lipoprotein lipase (LpL) through lipolysis plays an essential role in the formation of remnant particles from TG-rich lipoproteins (chylomicrons and VLDL) which have been proposed to have a pro-atherogenic role. TG-rich lipoproteins–lipolysis leads to the release of potentially toxic oxidized fatty acids that induce vascular inflammation, and, in parallel, remnants per se transform macrophages into foam cells (Miller et al., 2011). TG levels are inversely related to HDL-cholesterol levels.

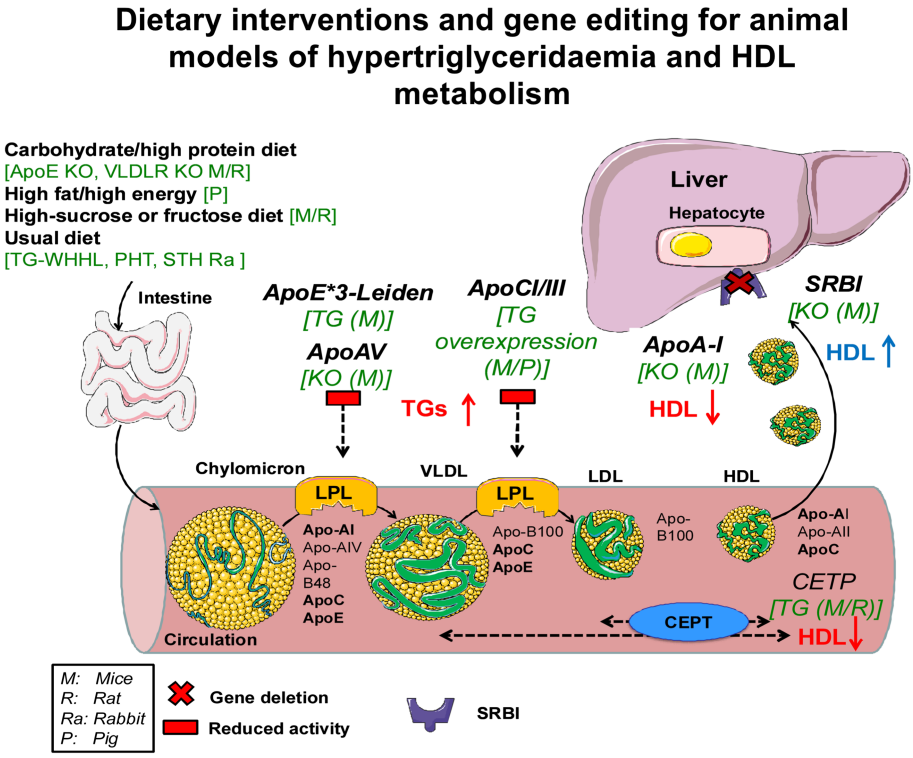

FIGURE 2 Schematic illustration of lipoprotein metabolism together with some dietary and genetic interventions that lead to hypertriglyceridaemia and disturbed HDL metabolism. Similar to the induction of hypercholesterolaemia, different types of diets are used to introduce mice to hypertriglyceridaemia and they mostly contain carbohydrates and sucrose instead of fat content. ApoE*3-Leiden mice regulate the expression of APOE and APOC1 apolipoproteins, present a moderate hyperlipidaemia uptake, and lead to a significant increase of plasma TG levels. Apolipoprotein A-V (ApoA-V) and apolipoprotein C-III (APOCIII) have opposing effects on plasma TG metabolism and they act as exchangeable constituents of VLDL and HDL and they are activating LpL. Therefore, ApoA-V knockout mice and mice with overexpression of APOCIII, APOCI have decreased LpL enzyme activity and up-regulated triglycerides. Regarding HDL metabolism, ApoA-I null mice and the CETP transgenic mice bearing the human or cynomologus monkey CETP protein have reduced plasma HDL-c levels, while deletion of the scavenger receptor BI (SR-BI) results in an increase in plasma HDL-c. ApoE-3*L, ApolipoproteinE*3-Leiden mice, apolipoprotein; CETP, cholesteryl ester transfer protein; KO, knockout; LPL, lipoprotein lipase; PHHC, Prague hereditary hypercholesterolaemic; SR-BI, scavenger receptor BI; STH, St. Thomas Hospital; TG, transgenic; TGs, triglycerides; WHHL, Watanabe heritable hyperlipidaemic rabbits

3.1 | Small animals

As in humans, rabbit apoB-48 is only present in dietary-derived chylomicrons but not in liver-derived VLDLs whereas, in the mouse, apoB-48 is also produced in the liver. Hence, mouse VLDLs contain both apoB-48 and apoB-100. Furthermore, rodents have a soluble form of hepatic lipase while humans have the membrane-bound type to perform the clearance of remnant lipoproteins (de Silva, Más-Oliva, Taylor, & Mahley, 1994).

3.1.1 | Diet-induced hypertriglyceridaemia

Mice

ApoE/LDLr$^{-/-}$ mice fed a low carbohydrate/high protein diet have doubled TG levels and marginally increased TC after 10 weeks displaying higher plaque burden than ApoE/LDLr$^{-/-}$ mice fed regular chow (Kostogrys et al., 2012). Likewise, fructose supplemented LDLr$^{-/-}$ or C57Bl/6 mice fed standard or WD increased TG levels twofold as compared to matched controls (Mastrocola et al., 2016). Interestingly, infarct size was 50% larger in C57Bl/6 mice exposed to a high-fructose diet as compared to the standard diet (Mastrocola et al., 2016).

Rats

Overfeeding rats with sucrose or fructose induces hypertriglyceridaemia. Whereas sucrose favours hepatic fatty acid esterification and VLDL synthesis, fructose deteriorates VLDL–TGs catabolism (Hirano, Mamo, Poapst, Kuksis, & Steiner, 1989). Wistar rats fed a high-sucrose (68%) or fructose (60%) diets have a fourfold increase in TG levels after 3 and 8 weeks respectively (Hirano et al., 1989; Kawashima et al., 2018). The protective effects of ischaemic preconditioning were abrogated in fructose fed-hypertriglyceridaemic rats (Babbar, Mahadevan, & Balakumar, 2013).

Rabbits

Homozygous inbreeding of WHHL rabbits provided hypercholesterolaemic rabbit colonies presenting TG levels between 150 and 1,500 mg·dl^{-1} (1.69 to 16.9 mM; TG–WHHL; Zhang, Jin, Liu, Liu, & Ito, 2009). Crossbreed between TG–WHHL rabbits and Japanese White rabbits resulted in a post-prandial hypertriglyceridaemic rabbit model (PHT) that exhibits remarkably high levels of serum TGs after feeding a standard diet (Kawai et al., 2006). However, both TG–WHHL and PHT rabbits develop insulin resistance and obesity and therefore also serve as a model of metabolic syndrome. Long-term treatment with **probucol** significantly ameliorates myocardial injury in TG–WHHL rabbits (Hoshida et al., 1997). The PHT rabbits have not been tested in I/R studies so far.

3.1.2 | Genetic animal models of hypertriglyceridaemia

Mice

APOE*3-Leiden transgenic (E3L) mice are generated by introducing into C57Bl/6 mice a human APOE*3-Leiden gene construct, consisting of APOE*3-Leiden and apolipoprotein C1 (APOC1) genes and a promoter element that regulates the expression of APOE and APOC1 genes. As compared with ApoE$^{-/-}$ and LDLr$^{-/-}$ mice, E3L mice present a mouse model of moderate hyperlipidaemia (cholesterol levels on chow are about 77 mg·dl^{-1} [2 mM] and do not exceed 970 mg·dl^{-1} [25 mM] on an HFD; Zadelaar et al., 2007). Yet the presence of the APOC1 gene lowers lipolysis and VLDL uptake through both the LDLr and LDL receptor-related protein, leading to a significant increase of plasma TG levels on a regular chow diet and a prominent increase under an HFD. E3L mice develop atherosclerotic lesions with all the characteristics of human vascular pathology, varying from fatty streaks to mild, moderate and severe plaques.

Apolipoprotein A-V (ApoA-V) and apolipoprotein C-III have opposing effects on plasma TG metabolism since they act as exchangeable constituents of VLDL and HDL (Qu et al., 2007). ApoA-V accelerates TG-rich lipoprotein catabolism by activating LpL. ApoA-V knockout mice display four times higher TG levels than their wild-type littermates, whereas mice overexpressing human ApoA-V gene display plasma TG levels one third of those of the control littermates (Pennacchio et al., 2001). In contrast, APOCI or APOCIII overexpressing mice have elevated plasma TG levels because of low LpL catalytic activity (Jong et al., 1997). Indeed, transgenic APOCIII production results in hypertriglyceridaemia due to the delayed catabolism of VLDL and chylomicrons (Ito, Azrolan, O'Connell, Walsh, & Breslow, 1990). ApoB-100 overexpressing mice show hypertriglyceridaemia, however if these mice are fed an HCD they show both hypercholesterolaemic and hypertriglyceridaemic phenotype (Csont et al., 2007).

VLDLr$^{-/-}$ mice present twofold higher TG levels than their wild type (316 mg·dl^{-1} [3.6 mM] vs. 141 mg·dl^{-1} [1.6 mM]) and the increase in TG is exacerbated (544 mg·dl^{-1} [6 mM)]) when VLDLr$^{-/-}$ mice are crossed with heterozygous LpL-deficient and human apoB transgenic mice (Yagyu et al., 2002). VLDLr$^{-/-}$ mice have smaller infarct size probably due to protection from cardiac lipotoxicity (Perman et al., 2011) and therefore are not suitable to study cardioprotective interventions in I/R injury.

Rats

The rats that are homozygous for the corpulent gene (cp/cp) become obese, insulin resistant and hypertriglyceridaemic. Hyperlipidaemia in the cp/cp rat is primarily due to hepatic hypersecretion of VLDL. Thus, with a regular diet, hyperlipidaemia is essentially confined to TG-rich fractions, and elevations of cholesterol are generally marginal. Among the different cp strains, the JCR:LA-cp rats display hyperlipidaemia associated with apoB-48-containing particles after oral fat loading (60% fat), particularly in the early post-prandial phase. This pattern likely contributes to atherogenesis by facilitating or exacerbating the saturation of LpL activity (Mangat et al., 2007). Hypertension (140–150 mm Hg) in Prague hereditary hypertriglyceridaemic rats (Vrána & Kazdová, 1990) develops in parallel with the increase of plasma TGs.

So far, severe myocardial I/R injury has been reported in hypertriglyceridaemic rats (Babbar et al., 2013). Moreover,

ischaemic postconditioning was markedly impaired in hypertriglyceridaemic rat hearts as compared to matched controls. However, pharmacological reduction of TGs using 8-week treatment with fenofibrate restored the ischaemic postconditioning effect (Babbar et al., 2013).

Rabbits

The St. Thomas Hospital rabbit displays a Mendelian form of hypertriglyceridaemia accompanied by accelerated atherosclerosis (Beaty et al., 1992).

3.2 | Large animal models for hypertriglyceridaemia

Göttingen minipigs under a dietary intervention consisting of HFD/high energy diet or low-fat/low energy diet (i.e. energy derived from fat was equivalent to 55% and 13%, respectively) evidenced that TG levels were significantly elevated in the HFD/high energy diet group, without influence on TC, glucose and insulin concentrations (Johansen, Hansen, Richelsen, & Malmlöf, 2001). In this model, the increased TG levels were associated with an increase in the HDL-c fraction,however the LDL-c and the VLDL-c cholesterol fractions were not reported (Johansen et al., 2001). In Yucatan minipigs, hypercholesterolaemic chow induced an increase of TC levels as well as of LDL-c and HDL-c. The levels of TG, however, remained unchanged (Osipov, Robich, et al., 2009).

Transgenic miniature pig with human APOCIII overexpression had a significant 2.5-fold increase in plasma TG concentration, associated with impaired TG catabolism and a reduced LpL activity (Wei et al., 2012).

So far, severe myocardial I/R injury has been reported in hypertriglyceridaemic Yucatan minipigs hearts as compared to the hearts of the respective control animals (Osipov, Robich, et al., 2009). In line with the rat data, ischaemic postconditioning significantly improved endothelial function and decreased area of no reflow and necrosis in minipigs fed a regular chow, whereas in those fed a hypercholesterolaemic-enriched diet (2% cholesterol and 15% lard by weight) for 4 weeks did not improve endothelial function or reduced area of no reflow and necrosis (Zhao, Yang, You, Cui, & Gao, 2007).

4 | ANIMAL MODELS FOR HDL METABOLISM

HDL-c exerts cardio/vascular-protective properties by taking part in reverse cholesterol transport, from cholesterol efflux (Vaidya et al., 2019), lipoprotein remodelling to hepatic lipid uptake and clearance (Favari et al., 2015). Accordingly, HDL levels have been inversely related to cardiovascular risk and atherosclerosis development. The HDL fraction exerts direct cardioprotective effects, reduces infarct size, and improves cardiac performance (Theilmeier et al., 2006; Vilahur, Gutiérrez, et al., 2015). However, this relationship seems to be more complex than originally thought due to, at least in part, the complexity of HDL particles with changes in composition that may result in a shift in HDL functions in the presence of different cardiovascular risk factors (Padró et al., 2017; Woudberg et al., 2017). Therefore, multiple experimental models have been developed to study HDL, most of them targeting different steps of the metabolism of HDL particles.

4.1 | Small animals (mice, rats and rabbits)

Multiple *ex vivo* and *in vivo* studies conducted in small animals have proven that the cardiovascular benefit of HDL goes beyond its role on the reverse cholesterol transport. Indeed, HDL presents multiple benefits including antioxidant, anti-inflammatory and anti-thrombotic properties (Keul et al., 2019; Woudberg et al., 2017). Genetic animal models, diet-induced animal models and native or reconstituted HDL-c have been used to explore the cardioprotective effect of HDL (see Table 3).

4.1.1 | Non-genetic animal models for HDL

Following on the seminal work from Badimon et al., in the early 90s where plasma HDL isolated from healthy rabbits and injected into rabbits with a cholesterol-enriched diet resulted in the inhibition of atherosclerosis progression and the induction of regression of existing atherosclerosis (Badimon, Badimon, Galvez, Dische, & Fuster, 1989; Badimon et al., 1990), several preclinical studies exploring the role of HDL in cardioprotection have been conducted in mice and rats. The cardioprotective effect of HDL has been tested following the administration of different types of HDL. First, human plasma HDL, isolated from healthy individuals, reduced ventricular arrhythmias and infarct size in a dose-dependent manner when given prior to or after an ischaemic insult to an isolated rat or mouse heart model (Calabresi et al., 2003; Frias et al., 2013; Mochizuki et al., 1991) or in vivo (Theilmeier et al., 2006). On the contrary, plasma HDL isolated from patients with MI failed to reduce the infarct size in isolated rat hearts (Soares et al., 2019). The species origin of the isolated HDL to be used for cardioprotective studies in rats and mice does not seem to affect its cardioprotective effect as both mice and human HDL seem to activate the cardioprotective signalling pathways in a similar manner (Pedretti et al., 2019). The use of synthetic or reconstituted HDL particles has been developed with the aim to facilitate its clinical translation compared to native HDL. Originally made of purified or recombinant ApoA-I and phospholipids (usually phosphatidylcholine), their protective effect against I/R has been shown in both rats and mice, although it is less pronounced than that of native HDL (Calabresi et al., 2003; Frias et al., 2013; Imaizumi et al., 2008). If the concentration of ApoA-I is critical for cardioprotection (Gu, Shi, & Wu, 2007), the addition of sphingosine-1 phosphate (S1P) to the composition of reconstituted HDL improves the cardioprotective effect of

TABLE 1 Animal models of hypercholesterolaemia, values of lipid levels and a brief description of the phenotype

Animal model	Protocol	TC mg dl^{-1} (mM)	LDL-c mg dl^{-1} (mM)	HDL-c mg dl^{-1} (mM)
Mice				
C57BL/6J	Normal chow	75–110 (1.9–2.9)	10 (0.26)	50 (1.3)
C57BL/6 N	Adult mice 9 weeks on WD	181 ± 5 (4.7 ± 0.1)	N/A	123 ± 3 (3.2 ± 0.07)
C57BL/6J	Adult mice 14 weeks on WD (TD88137)	233 ± 43 (6.0 ± 1.1)	N/A	N/A
C57BL/6J	Adult mice 2 weeks on HCD	144 ± 9 (3.7 ± 0.2)	N/A	N/A
C57BL/6J	Adult mice 12 weeks on HCD	295 ± 18 (7.6 ± 0.5)	N/A	N/A
$ApoE^{-/-}$	Normal chow 4–6 months old	400–600 (10.3–15.5) 460 ± 50 (11.9 ± 1.3)	140 (3.6)	50 (1.3)
$APOE^{-/-}$	4–6 months old 2 weeks on HCD 10 weeks old on WD for 20 weeks	1,048 ± 46 (27.1 ± 1.2) 567 ± 265 (14.7 ± 6.8)	N/A N/A	224 ± 12 (5.8 ± 0.3) 54.1 ± 25.4 (1.4 ± 0.7)
$LDLR^{-/-}$	Female phenotype at 16 weeks on standard chow Male phenotype at late stages on standard chow	250 ± 8 (6.5 ± 0.2) 358 ± 13 (9.3 ± 0.3)	168 ± 5 (4.3 ± 0.1) N/A	69 ± 3 mg·dl^{-1} (1.7 ± 0.07) N/A
$LDLR^{-/-}$	Female mice 16 weeks old on WD (TD88137)	1.677 ± 98 (43.4 ± 2.5)	761 ± 57 (19.7 ± 1.5)	12 ± 2 mg·dl^{-1} (0.3 ± 0.05)
$LDLR^{-/-}$	Adult mice 2 weeks on HCD Adult mice 12 weeks on HCD	2,479 ± 213 (64.1 ± 5.5) 3,180 ± 70 (82.2 ± 1.8)	N/A N/A	N/A N/A
$ApoA\text{-}V^{-/-}$	Adult mice on standard chow	Unchanged compared to wild-type-mixed 129Sv/C57BL6 strain controls littermates	N/A	Similar to wild-type littermates
APO-Leiden 3	Adult male on chow diet Adult female on chow diet	128 ± 4 (3.3 ± 0.1) 120 ± 8 (3.1 ± 0.2)	N/A	N/A
APO-Leiden 3	2 months old mice atherogenic diet (containing 40.5% sucrose, 15% cocoa butter, 1% cholesterol, and 0.5% sodium cholate) for 2 or 4 months	93 ± 23 (2.4 ± 0.6)	N/A	N/A
Rats				
Wistar	Male on standard diet	70 ± 3.9 (1.8 ± 0.1) 65 ± 8 (1.7 ± 0.2) 83.6 ± 7.4 (2.2 ± 0.2)	9.3 ± 3.9 (0.24 ± 0.10) N/A 13.2 ± 2.6 (0.34 ± 0.06)	28 ± 4.2 (0.7 ± 0.1) N/A 49.8 ± 5.8 (1.3 ± 0.2)
Wistar	Male adult rats HFD (5% palm oil) for 3 weeks	77 ± 10 (1.98 ± 0.26)	N/A	N/A
Wistar	Male adult rats High-fat–high cholesterol diet (5% palm oil, 1% cholesterol) for 3 weeks	90.5 ± 16 (2.4 ± 0.4)	N/A	N/A
Wistar	Male with insulin resistance High-fat–high cholesterol diet for 5 days	116 ± 23 (3.0 ± 0.6)	53.4 ± 15.1 (1.38 ± 0.39)	33 ± 6 (0.86 ± 0.15)
Wistar	Male 7 weeks old supplemented with CCT diet (4% cholesterol, 1% cholic acid, and 0.5% 2-thiouracil) for 30 days	198 ± 11 (5.1 ± 0.3)	34.2 ± 4.6 (0.9 ± 0.1)	26 ± 3 (0.7 ± 0.07)
James C Russell corpulent (JCR:LA-cp) rat	Adult rats on normal chow	159 ± 12 (4.12 ± 0.31)	17.8 ± 7 (0.46 ± 0.18)	84 ± 7.3 (2.16 ± 0.19)

TABLE 1 (Continued)

Animal model	Protocol	TC mg dl^{-1} (mM)	LDL-c mg dl^{-1} (mM)	HDL-c mg dl^{-1} (mM)
Prague hereditary hypercholesterolaemic (PHHC) rat	Male adult rats fed on chow diet	97 ± 8 (2.5 ± 0.2)	N/A	N/A
PHHC rat	Male adult rats HFD (5% palm oil) for 3 weeks	104 ± 12 (2.7 ± 0.3)	N/A	N/A
PHHC rat	Male adult rats High-fat–high cholesterol diet (5% palm oil,1% cholesterol) for 3 weeks	164 ± 9 (4.2 ± 0.2)	N/A	N/A
Sprague–Dawley	Adult rats 64 weeks old	Liver: 5.39 ± 0.14 mg·g^{-1} tissue	94 ± 16 (2.4 ± 0.4)	N/A
Sprague–Dawley ApoE$^{-/-}$	On normal chow 24 weeks old	Up-regulation compared to wild-type littermates	Up-regulation compared to wild-type littermates	Decreased
Sprague–Dawley ApoE$^{-/-}$	On WD 24 weeks old	Up-regulation compared to wild-type littermates	Up-regulation compared to wild-type littermates	Decreased
Sprague–Dawley LDLR$^{-/-}$	64 weeks old rats on normal chow 64 weeks old WD for 52 weeks (from the 12th week of age)	Liver: 10.38 ± 2.17 mg·g^{-1} tissue Liver: 21.11 ± 3.40 mg·g^{-1} tissue	168 ± 8 (4.3 ± 0.2) 139 ± 12 (3.6 ± 0.3)	N/A N/A
Sprague–Dawley LDLR$^{-/-}$	WD 24 weeks old	Up-regulation compared to wild-type littermates	Up-regulation compared to wild-type littermates	Unaltered compared to wild type
Rabbits				
New Zealand White rabbit	Standard diet	29 ± 1 (0.7 ± 0.03)	8 ± 0.4 (0.2 ± 0.01)	18 ± 1 (0.5 ± 0.02)
New Zealand White rabbit	Male 0.5% Cholesterol for unspecified period of time	811 ± 48 (21.0 ± 1.2)	317 ± 24 ± 0.6)	44 ± 4 (1.1 ± 0.1)
New Zealand White rabbit	Adult male rabbits 8 weeks with cholesterol enriched diet*	1,402 ± 125 (36.3 ± 3.2)	N/A	N/A
New Zealand White rabbit	Adult male rabbits 6 weeks with cholesterol enriched diet*	912 ± 90 (23.6 ± 2.3)	N/A	N/A
Watanabe hereditary hypercholesterolaemic (WHHL) rabbit	Young male rabbits Adults male rabbits	698 ± 31 (18.1 ± 0.8) 650–950 (16.8 ± 24.6)	N/A N/A	N/A
ApoE$^{-/-}$ rabbit	Rabbits were fed the standard chow	156 ± 59 (4.0 ± 1.5)	N/A	17 ± 6 (0.4 ± 0.15)
ApoE$^{-/-}$ rabbit	0.3% cholesterol for 2 weeks	1,070 ± 61 (27.7 ± 1.6)	N/A	15 ± 1 (0.4 ± 0.02)
Pigs				
Ossabaw pig	High-fat/cholesterol diet for 43 weeks	338 ± 28 (8.7 ± 0.7)	255 ± 29 (6.6 ± 0.7)	75 ± 9 (1.9 ± 0.2)
Yucatan pig	High-fat/cholesterol diet for 43 weeks	420 ± 72 (10.9 ± 1.9)	351 ± 76 (9.0 ± 1.9)	60 ± 10 (1.6 ± 0.3)
Pigs	Female, fixed crossbreeding, Cholesterol-rich diet (2% cholesterol; 1% cholic acid; 20% beef tallow) for 100 days	Increased	Increased	Increased
Yucatan minipigs with transposition of human D374Y-PCSK9 gene expression	Phenotype had developed after 8 weeks	Increased ~770 (~20)	Increased	Decreased compared to wild type

TABLE 1 (Continued)

Animal model	Protocol	TC mg dl^{-1} (mM)	LDL-c mg dl^{-1} (mM)	HDL-c mg dl^{-1} (mM)
ApoE$^{-/-}$ Bama miniature pigs	8 weeks old	99.4 ± 21.3 (2.57 ± 0.55)	Increased compared to wild type	Increased compared to wild type
ApoE$^{-/-}$ Bama miniature pigs	3-month-old pigs High-fat/cholesterol diet for 3 months	~1,550 (~40)	Increased compared to wild type	Increased compared to wild type
Göttingen minipigs	Female 9–10 months old 5 weeks on HFD (55% in fat)	79 ± 6.6 (2.03 ± 0.17) Unchanged compared to low-fat diet	N/A	39.9 ± 2.7 (1.03 ± 0.07)
APOCIII transgenic miniature pig	Standard diet	Similar to wild type	Similar to wild type	Similar to wild type
Farm pigs	HCD for 8 or 16 weeks	10-fold increase compared to normal fed	10-fold increase compared to normal fed	20–80 (0.5–2)

reconstituted HDL to the equivalent of native HDL (Brulhart-Meynet et al., 2015). In fact, S1P is important for the cardioprotection by HDL. HDL bound-S1P predicts the severity of coronary atherosclerosis in humans (Sattler et al., 2014) and HDL reduces the risk of periprocedural infarction in patients undergoing percutaneous coronary intervention (Sattler et al., 2009). S1P is known to be cardioprotective by triggering preconditioning mechanisms (reviewed in Karliner, 2013) and S1P$^{-/-}$ mice exhibit no reduction of infarct size when undergoing an ischaemic preconditioning protocol (Keul et al., 2016). Other alternatives in the composition of reconstituted HDL consider the substitution of ApoA-I by ApoA-I Milano (Marchesi et al., 2008) or other ApoA-I variants such as 37pA (Gomaraschi et al., 2008).

4.1.2 | Genetic animal models for HDL

Multiple genetically modified animal models have been developed with the aim to enlighten the physiology of HDL particles. These models all target different steps of the HDL particle homeostasis.

Mice with genetic deletion of ApoA-I, phospholipid transfer protein, ATP binding cassette transporter A1, or lecithin cholesterol acyltransferase have a decrease in plasma HDL-c. The deletion of scavenger receptor BI (SR-BI) results in an increase in plasma HDL-c. Other plasma lipoproteins levels such as LDL-c and VLDL-c are also affected in these models (also reviewed by Hoekstra & Van Eck, 2015).

ApoA-I null and heterozygous mice have plasma HDL-c levels reduced by approximately 80% and 50%, respectively, compared to wild-type mice. When subjected to in vivo ischaemia, these mice have a 52% and 125% increase in infarct size compared to wild type (Dadabayev et al., 2014). In a SR-BI/ApoE double knockout mouse model, spontaneous MI and early death occur under a standard chow diet (Braun et al., 2002). Similarly, SRB-I/LDL receptor double knockout mice fed with a WD containing 0.5% cholesterol develop atherosclerosis, ischaemic heart disease, and early death (Liao et al., 2017). Although the generation of these genetically modified mice greatly contributes to the understanding of the metabolism and function of HDL, they may not represent an ideal model to mimic the clinical setting for cardioprotective studies due to the complexity of HDL metabolism that these models may fail to reproduce.

A model that exhibits decreased HDL-c and a variable degree of atherosclerosis along with a small increase in VLDL-c and LDL-c on the basal (chow) diet is the CETP transgenic mice bearing the human or cynomologus monkey CETP protein (Jiang et al., 1993). The increase in VLDL-c and LDL-c is exacerbated upon an HFD regimen, reaching values of TC of 250 mg·dl^{-1} versus 163 mg·dl^{-1} of non-transgenic mice. With the use of these transgenic mice, CETP activity was found inversely associated with ApoA-I and positively associated with apoB (Marotti et al., 1992).

4.2 | Large animal models for HDL

Pig models have been used to investigate HDL effects on lipid profile and atherosclerosis. Farm pigs were fed an HCD for 8 weeks, 16 weeks or standard diet (control). Eight- and 16-week HCD induced 10-fold higher TC and LDL values than in control animals. The resulting HDL-c concentration between 20 and 80 mg·dl^{-1} (0.5 to 2 mM) correlated inversely with the number and degree of atherosclerotic lesions (Pelosi et al., 2014). The cardioprotection associated with the administration of native HDL particles against I/R disappears when infused HDL particles are formed under hypercholesterolaemic conditions highlighting the negative impact of hypercholesterolaemia on HDL-related cardioprotective effects (Vilahur, Gutiérrez, et al., 2015). Again, S1P is important here, since S1P loading of HDL restores the vascular protective effects of HDL from patients with coronary artery disease (Sattler et al., 2015).

A summary of dietary interventions and gene editing for animal models of hypertriglyceridaemia and HDL metabolism is illustrated in Figure 2.

TABLE 1 Animal models of hypercholesterolaemia, values of lipid levels and a brief description of the phenotype

Animal model	VLDL mg dl^{-1} (mM)	TGs mg dl^{-1} (mM)	Brief description of phenotype	Reference
Mice				
C57BL/6J	20 (0.5)	65 (0.8)	Normal lipidaemic profile	Jang et al., 2012; Andreadou, Efentakis, et al., 2017
C57BL/6 N	N/A	78 ± 4 (0.9 ± 0.04)	Mild hypercholesterolaemia *Increased body weight, hyperglycαemia, and hyperinsulinαemia*	Desmarchelier et al., 2012
C57BL/6J	N/A	37 ± 9 (0.4 ± 0.1)	Mild hypercholesterolaemia Model of metabolic syndrome *Increased body weight and hyperglycαemia*	Andreadou, Efentakis, et al., 2017
C57BL/6J	N/A	25 ± 17 (0.3 ± 0.2)	Hypercholesterolaemia with unstable triglyceride levels *Body weight changes and glucose tolerance were not reported*	Girod et al., 1999
C57BL/6J	N/A	284 ± 105 (3.2 ± 1.2)	Hypercholesterolaemia and hypertriglyceridaemia *Body weight changes and glucose tolerance were not reported*	Girod et al., 1999
$ApoE^{-/-}$	200 (5.2)	110 (1.2) 115 ± 35 (1.3 ± 0.4)	Mild hypercholesterolaemia and atherosclerotic lesions on the aortic sinus *Moderate increase in body weight* *Glucose levels were not reported*	Meyrelles et al., 2011 Jiang, Jones, Husband, & Dusting, 2003
$APOE^{-/-}$	822.4 ± 38.6 (21.3 ± 1.0) N/A	824 ± 35 (3.9 ± 0.4) 96.4 ± 29.6 (1.1 ± 0.3)	Severe hypercholesterolaemia and extended atherosclerosis *Increased body weight and glucose intolerance*	Meyrelles et al., 2011 Jiang et al., 2003; Doumouchtsis et al., 2017
$LDLR^{-/-}$	13 ± 1 (0.34 ± 0.03) N/A	124 ± 8 (1.4 ± 0.09) 495 ± 17 (5.6 ± 0.2)	Moderate elevation of TC *Body weight and glucose levels are similar to $Ldlr^{+/+}$ animals* (Ngai et al., 2010) *At late adulthood, this model presents with hypertriglyceridaemia*	Yin et al., 2012 Girod et al., 1999
$LDLR^{-/-}$	904 ± 47 (23.4 ± 1.2)	404 ± 35 (4.6 ± 0.4)	Extreme elevation in TC, LDL-c, VLDL. Increased TGs and decreased HDL levels *Body weight changes and glucose tolerance were not reported*	Yin et al., 2012
$LDLR^{-/-}$	N/A N/A	5,397 ± 784 (60.9 ± 8.9) 4,964 ± 735 (56.0 ± 8.3)	Severe hypercholesterolaemia and hypertriglyceridaemia *Body weight and glucose levels are similar to $Ldlr^{+/+}$ animals* (Ngai et al., 2010)	Girod et al., 1999
$ApoA\text{-}V^{-/-}$	Increased in compared to wild-type littermates	153 ± 77 (1.7 ± 0.9)	Four times higher TG levels than their wild-type littermates. **This is a mouse model of hypertriglyceridaemia** *No changes in body weight and glucose levels*	Qu et al., 2007; Pennacchio et al., 2001

TABLE 1 (Continued)

Animal model	VLDL mg dl^{-1} (mM)	TGs mg dl^{-1} (mM)	Brief description of phenotype	Reference
APO-Leiden 3	N/A	213 ± 8.9 (2.4 ± 0.1) 230 ± 27 (2.6 ± 0.3)	Moderate hyperlipidaemia **Significant raise of plasma TG levels** on a regular chow diet and a prominent raise under an HFD. *No changes in body weight and glucose levels*	Bijland et al., 2009
APO-Leiden 3	N/A	N/A	Increase in VLDL and LDL fractions while **HDL is very low when compared to the non-transgenic control.** After 4 months, lesions had developed which were advanced at the aortic arch *Increased body weight and glucose intolerance*	Leppänen, Luoma, Hofker, Havekes, & Ylä-Herttuala, 1998
Rats				
Wistar	10.8 ± (0.28 ± 0.05) N/A 22.4 ± 3.11 (0.58 ± 0.08)	125 ± 10 (1.4 ± 0.1) 106 ± 18 (1.2 ± 0.2) 59.6 ± 5.36 (0.7 ± 0.06)	Normal lipidaemic profile	Ferko et al., 2018 Kovár et al., 2009 Raja et al., 2012
Wistar	N/A	109.8 ± 37 (1.24 ± 0.42)	Marginally elevated TC *Changes in body weight or glucose tolerance were not reported*	Kovár et al., 2009
Wistar	N/A	159 ± 35 (1.79 ± 0.39)	Elevated TC *Changes in body weight or glucose tolerance were not reported*	Kovár et al., 2009
Wistar	24.3 ± 5.2 (0.63 ± 0.13)	490 ± 42 (5.5 ± 0.5)	Hypercholesterolaemia *Hyperinsulinaemia and hyperglycaemia*	Adameová et al., 2007; Ferko et al., 2018
Wistar	125.7 ± 5.0 (3.26 ± 0.13)	169 ± 4 (1.9 ± 0.04)	Increased plasma TC, TG, LDL-C, VLDL-C, decreased HDL. Marked atherosclerosis *Increased body weight and blood pressure. Glucose tolerance was not reported*	Raja et al., 2012
James C Russell corpulent (JCR:LA-cp) rat	N/A	337 ± 42 (3.80 ± 0.47)	Male cp/cp rats are characterized by hyperleptinaemia, hyperinsulinaemia and hyperphagia along with the marked hypertriglyceridaemia *Increased body weight Glucose tolerance was not reported*	Reimer & Russell, 2008
Prague hereditary hypercholesterolaemic (PHHC) rat	N/A	81.5 ± 18.6 (0.92 ± 0.21)	Relatively higher HDL-c *Glucose levels similar to Wistar rats*	Kovár et al., 2009
PHHC rat	N/A	84 ± 34 (0.95 ± 0.38)	Slight exacerbation of the normal fed phenotype *Changes in body weight or glucose tolerance were not reported*	Kovár et al., 2009

TABLE 1 (Continued)

Animal model	VLDL mg dl^{-1} (mM)	TGs mg dl^{-1} (mM)	Brief description of phenotype	Reference
PHHC rat	N/A	125.8 ± 42 (1.42 ± 0.47)	Most of the cholesterol in PHHC rats on cholesterol diet is carried out inVLDL and IDL. **Similar to the dys-betalipoproteinaemia (hyperlipoproteinaemia type III) in humans.** *Changes in body weight or glucose tolerance were not reported*	Kovár et al., 2009
Sprague–Dawley	10 ± 1 (0.26 ± 0.03)	Liver: 13.12 ± 1.35 mg·g^{-1} tissue	Normal lipidaemic profile	Sithu et al., 2017
Sprague–Dawley ApoE^{-}/$^{-}$	Elevated	Not significantly elevated	Females and males are resistant to developing hyperlipidaemia *Body weight is slightly increased. Glucose tolerance* Severe hyperlipidaemia and redistribution of cholesterol. The diet exacerbates the phenotype and accelerates atherosclerosis development.	Zhao et al., 2018
Sprague–Dawley ApoE^{-}/$^{-}$	Elevated	Not significantly elevated		Zhao et al., 2018
Sprague–Dawley LDLR^{-}/$^{-}$	178 ± 26 (4.61 ± 0.67) 29 ± 6 (0.75 ± 0.16)	Liver: 25.76 ± 5.72 mg·g^{-1} tissue Liver: 7. 76 ± 0.72 mg·g^{-1} tissue	Moderate increase in LDL. Atherosclerotic lesions developed only on HCD *Increased body weight and glucose intolerance.* Model of atherogenesis, particularly in the context of diabetes and obesity	Sithu et al., 2017
Sprague–Dawley LDLR^{-}/$^{-}$	Elevated compared to wild type	Dramatic elevation of TGs	Severe hypelipidaemia. **The only model of genetic manipulation in rats that shows a predisposition for elevated TGs.** *No changes in body weight and glucose tolerance* The diet exacerbates the phenotype and accelerates atherosclerosis development.	Zhao et al., 2018
Rabbits				
New Zealand White rabbit	4 ± 0.3 (0.1 ± 0.01)	47 ± 5 (0.53 ± 0.06)	Normal lipidaemic profile	Yin et al., 2012
New Zealand White rabbit	439 ± 26 (11.4 ± 0.7)	48 ± 4 (0.54 ± 0.05)	Hyperlipidaemia that is mainly attributed to a redistribution of cholesterol in favour of VLDL particles *Body weight and glucose tolerance were not reported*	Yin et al., 2012
New Zealand White rabbit	N/A	N/A	Hypercholesterolaemia with atherosclerosis evident in the ascending aorta, the ostia of the coronaries, and the epicardial vessels *Increased body weight Glucose tolerance was not reported*	Kremastinos et al., 2000

TABLE 1 (Continued)

Animal model	VLDL mg dl^{-1} (mM)	TGs mg dl^{-1} (mM)	Brief description of phenotype	Reference
New Zealand White rabbit	N/A	N/A	Hypercholesterolaemia and early signs of atherogenesis *Increased body weight glucose tolerance was not reported* A suitable model for prevention strategies from atherosclerosis	Iliodromitis et al., 2006
Watanabe hereditary hypercholesterolaemic (WHHL) rabbit	N/A	189 ± 24 (2.1 ± 0.3) 652.2 ± 138.1 (7.4 ± 1.6)	Pronounced hypercholesterolaemia Hypertriglyceridaemia/severe coronary atherosclerosis *No change in body weight and glucose tolerance*	Hoshida et al., 1997; Aliev & Burnstock, 1998
ApoE$^{-/-}$ rabbit	N/A	Increased but with marked variations.	Model of hyperlipidaemia due to a sixfold increase in TC. HDL-c was not remarkably changed *No changes in body weight and increased serum glucose levels* (Beierfuß et al., 2017)	Niimi et al., 2016
ApoE$^{-/-}$ rabbit	N/A	132 ± 58 (1.5 ± 0.7)	Suitable model of mixed hypertriglyceridaemia and severe hypercholesterolaemia HDL-c was not remarkably changed *Body weight changes and glucose tolerance were not reported*	Niimi et al., 2016
Pigs				
Ossabaw pig	N/A	41 ± 7 (0.46 ± 0.08)	Hyperlipidaemia with a minor increase in triglycerides, native atheroma, and greater elevations in metabolic features of metabolic syndrome compared to Yucatan pig *Increased body weight and glucose intolerance*	Neeb et al., 2010 Trask et al., 2012
Yucatan pig	N/A	41 ± 6 (0.46 ± 0.07)	Hyperlipidaemia without increase in triglycerides, less native atheroma than the Ossabaw pig *Increased body weight and normal glucose tolerance*	Neeb et al., 2010
Pigs	Increased	Unaltered	Diet-induced hyperlipidaemia in smaller period of time *Body weight changes and glucose tolerance were not reported*	Casani, Sanchez-Gomez, Vilahur, & Badimon, 2005
Yucatan minipigs with transposition of human D374Y-PCSK9 gene expression	N/A	Unaltered on standard diet Increased on HFD	Hypercholesterolaemia and spontaneous development of progressive atherosclerotic lesions *No change in body weight and glucose tolerance*	Al-Mashhadi et al., 2013
ApoE$^{-/-}$ Bama miniature pigs	N/A	Similar to the wild type	Moderate, yet consistently, elevated serum cholesterol levels *Body weight changes and glucose tolerance were not reported*	Fang et al., 2018

TABLE 1 (Continued)

Animal model	VLDL mg dl^{-1} (mM)	TGs mg dl^{-1} (mM)	Brief description of phenotype	Reference
ApoE$^{-/-}$ Bama miniature pigs	N/A	~133 (~1.5)	Severe hypercholesterolaemia and progressive atherosclerotic lesions *Body weight changes and glucose tolerance were not reported*	Fang et al., 2018
Göttingen minipigs	N/A	21.3 ± 2.7 (0.24 ± 0.03) Increased in comparison to low-fat diet	These pigs mimic the metabolic syndrome in humans. They exhibit hypertriglyceridaemia. *Increased body weight and glucose levels*	Johansen et al., 2001
APOCIII transgenic miniature pig	Similar to wild type	94.9 ± 10.4 (1.1 ± 0.1)	Model of hypertriglyceridaemia without any other abnormality in lipids. *Body weight changes and glucose tolerance were not reported* Low survival rates of the pigs may hamper their use	Wei et al., 2012
Farm pigs	N/A	N/A	HDL-c levels were inversely associated with the development of atherosclerotic lesions *Body weight changes and glucose tolerance were not reported*	Pelosi et al., 2014

Note. Mice consume a low-fat diet and this forms the basis for the formulation of the standard mouse or rodent chow containing 4% to 6% fat (fat weight per weight of diet) and a cholesterol content <0.02% (w/w). Western diet (WD) for mice consists of 21% milk fat and 0.2% cholesterol (0.15% added, 0.05% from milk fat). High cholesterol diet (HCD) for mice contains 1.25% cholesterol and 15.8% fat. Cholesterol-enriched diet in rabbits consists of 1 g–2 g·kg^{-1} (0.1–0.2%) of normal chow and 6% corn oil.

TABLE 2 Animal models of hypercholesterolaemia used in cardioprotection

Animal model	Ischaemia/reperfusion protocol	Key findings	Reference
Mice			
C57BL/6J WD for 14 weeks	30 min ischaemia/2 hr reperfusion	Infarct size comparable to the mice fed on normal chow	Andreadou, Efentakis, et al., 2017
C57BL/6J short-(2 weeks) and long-term (12 weeks) HCD	30 min ischaemia/2 hr reperfusion	Short-term HCD leads to similar infarct size in comparison to normal fed mice while 12 weeks diet decreases infarct size	Girod et al., 1999
ApoE$^{-/-}$ on normal chow	30 min ischaemia/2 hr reperfusion	Infarct size comparable to wild-type littermates	Efentakis et al., 2017
ApoE$^{-/-}$ HCD (2 weeks)	30 min ischaemia/24 hr reperfusion	Increased myocardial infarct size in comparison to normal fed ApoE$^{-/-}$	Scalia et al., 2001
LDLR$^{-/-}$ on normal chow	30 min ischaemia/2 hr reperfusion	This genetic mutation reduces infarct size in comparison with WT littermates	Girod et al., 1999
LDLR$^{-/-}$ short-(2 weeks) and long-term (12 weeks) HCD	30 min ischaemia/2 hr reperfusion	Short-term diet increases infarct size while long-term HCD attenuates myocardial necrosis	Girod et al., 1999

(Continues)

TABLE 2 (Continued)

Animal model	Ischaemia/reperfusion protocol	Key findings	Reference
Rats			
Wistar rats HCD for 12 weeks	30 min ischaemia/2 hr reperfusion	Infarct size comparable to normal healthy rats. Preconditioning and postconditioning-mediated cardioprotection was abolished	Kupai et al., 2009
Wistar rats with insulin resistance High-fat/cholesterol diet for 5 days	30 min ischaemia/2 hr reperfusion	High-fat/cholesterol diet did not affect infarct size	Adameová et al., 2007 Ferko et al., 2018
Rabbits			
New Zealand White rabbits cholesterol-enriched diet for 6–8 weeks	30 min ischaemia/3 hr reperfusion	Similar or slightly elevated infarct size compared to normal fed New Zealand White rabbits	Iliodromitis et al., 2006; Kremastinos et al., 2000; Andreadou et al., 2012
Watanabe hereditary hypercholesterolaemic (WHHL) rabbit on standard laboratory diet	30 min ischaemia/24 hr reperfusion	Infarct size in WHHL rabbit is greater than age-matched New Zealand White rabbits	Hoshida et al., 1997
Pigs			
Yucatan minipig 20 weeks old High-fat/cholesterol diet for 1 month	60 min ischaemia/2 hr reperfusion	Infarct size was higher in comparison to non-hypecholesterolaemic animals	Osipov, Robich, et al., 2009
Young healthy pigs HCD (20% beef tallow, 2% cholesterol, and 1% cholic acid) during 10 days	90 min of ischaemia followed by 21 days of reperfusion	Infarct size was ~44% larger in comparison to non-hypercholesterolaemic animals	Vilahur, Casani, Juan-Babot, Guerra, & Badimon, 2012

Note. Infarct size has been measured by triphenyl tetrazolium chloride (TTC) staining.

TABLE 3 Experimental models used to define the role of HDL metabolism on cardioprotection

Animal model	Ischaemia/reperfusion protocol	Treatment	Key findings	Reference
Mice				
C57BL/6 mice on normal and HFD	30 min ischaemia/1 hr reperfusion	rHDL (25-mg ApoA1/ml) delivered during reperfusion	Reduction in infarct size in mice on normal and HFD	Heywood et al., 2017
C57Bl6/N mice	30 min ischaemia/24 hr reperfusion	HDL administered intravenously for 21 days prior to ischaemia	Reduction in infarct size	Theilmeier et al., 2006
C57BL/6 mice	35 min ischaemia/45 min reperfusion	rHDL (100, 200, and 400 $\mu g \cdot ml^{-1}$) perfused for 7 min at onset of reperfusion	Dose-dependent reduction in infarct size	Frias et al., 2013
C57BL/6 mice	45 min ischaemia/24 hr reperfusion	rHDL enriched with S1P infused 1 min before reperfusion	Reduction in infarct size	Brulhart-Meynet et al., 2015
ApoA1$^{-/-}$ C57BL/6 mice	30 min ischaemia/3 hr reperfusion	—	Increase in infarct size in ApoA1$^{-/-}$ mice	Dadabayev et al., 2014
Rats				
Healthy male Sprague–Dawley rats	15 min ischaemia/20 min reperfusion	Physiological concentrations of HDL infused during I/R	Reduction in the incidence of arrhythmias	Mochizuki et al., 1991
Healthy male Sprague–Dawley rats	20 min ischaemia/30 min reperfusion	HDL (0.5 and 1.0 $mg \cdot ml^{-1}$) perfused 10 min prior to ischaemia	Improved post-ischaemic left ventricular functional recovery at reperfusion	Calabresi et al., 2003

(Continues)

TABLE 3 (Continued)

Animal model	Ischaemia/reperfusion protocol	Treatment	Key findings	Reference
Healthy male Sprague–Dawley rats	20 min ischaemia/30 min reperfusion	Synthetic HDL (0.5, 1.0, and 2.0 mg·ml^{-1}) perfused 10 min prior to ischaemia	Dose-dependent improved left ventricular functional recovery	Rossoni et al., 2004
Healthy male Sprague–Dawley rats	20 min ischaemia/30 min reperfusion	Synthetic HDL (1.0 mg·ml^{-1}) perfused 10 min prior to ischaemia	Improvement in post-ischaemic left ventricular developed pressure recovery and attenuation of coronary perfusion pressure elevation	Gomaraschi et al., 2008
Healthy male Wistar rats	Rat coronary artery ligation	rHDL was infused 10 min before permanent ligation	Reduction of fibrosis in ligated hearts	Kiya et al., 2009
Healthy male Sprague–Dawley rats	30 min ischaemia/3 hr reperfusion	Synthetic HDL infused 10 min before reperfusion	Reduction in creatine kinase, TNF-α, and IL-6 in cardiac tissue	Gu et al., 2007
Healthy male Wistar rats	5 min ischaemia/3 min reperfusion	rHDL was infused 10 min before occlusion	Suppression of reperfusion-induced arrhythmias	Imaizumi et al., 2008
Healthy male Wistar rats	35 min ischaemia/90 min reperfusion	HDL from healthy and MI patients infused during first 7 min of reperfusion	HDL isolated from MI patients failed to reduce the infarct size	Soares et al., 2019
Rabbits				
Healthy Male New Zealand White rabbits	30 min ischaemia/1 hr reperfusion ApoA1-Milano	Hearts were treated during the 10-min pretreatment and the 60 min of reperfusion with ApoA1-Milano	Reduction of tissue lipid hydroperoxides in hearts subjected to global ischaemia	Marchesi et al., 2008
Healthy Male New Zealand White rabbits	30 min ischaemia/4 hr reperfusion	100 mg·kg^{-1} synthetic ApoA1-Milano (ETC-216) 1 day before and at the time of the surgical procedure	Reduction in infarct size	Marchesi et al., 2004 Marchesi et al., 2008
Pigs				
Young healthy pigs	60-min closed-chest coronary balloon occlusion followed by reperfusion for 3 days when cardiac magnetic resonance was performed	Isolation of HDL particles from hypercholesterolaemic and non-hypercholesterolaemic pigs. 4 days and 1 day before the induction of ischaemia, two intravenous infusions of 15 mg·kg^{-1} HDL particles were performed	HDL particles from hypercholesterolaemic pigs are not cardioprotective	Vilahur, Gutiérrez, et al., 2015

5 | CONCLUSIONS AND RECOMMENDATIONS

Despite the fact that various animal models of different types of hyperlipidaemia exist, only some of them have been employed for studying myocardial I/R injury and cardioprotection. An ideal animal model for studying hyperlipidaemia and cardioprotection would be affordable and mimic adequately the human phenotype including the gradual development of atherosclerosis and the direct effect of hyperlipidaemia on the myocardium and other tissues. However, several limitations regarding the lipidaemic profile of different animal species in comparison to that measured in humans should be taken into consideration. The animal models of hypercholesterolaemia with a brief description of their phenotypes are illustrated in Table 1. Models with HFD/HCDs and genetic modifications have been suggested for cardioprotection (Table 2) and exogenous supplementation with lipoprotein particles in I/R injury has proven to be very useful for mechanistic studies (Table 3). We must mention, however, that due to reproducibility issues of lipid levels especially in the diet-induced hyperlipidaemia models, appropriate time and age-matched controls are needed. Moreover, in most of the hyperlipidaemic models, confounding effect of obesity and insulin resistance should be taken into account (see Table 1). Only a few animal species (mainly the large animals) possess the lipid profile similar to humans but studies on myocardial I/R injury are scarce. Therefore, further studies in these animal models are required to gather more data on the effect of hyperlipidaemia on I/R injury and cardioprotection for discovery and validation of effective cardioprotective drug targets and translating these findings into the clinical arena.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

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CONFLICT OF INTEREST

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