REVIEW

Animal models used in the research of nanoparticles for cardiovascular diseases

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Abstract Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide. Tremendous progress has been made in the prevention and treatment of CVD; however, there are still lots of limitations and new technology is needed. Nanoparticles have been studied recently for CVD due to their nanoscale size and unique properties, and hold a potential to be a novel therapy for the treatment. To test the safety and effectiveness of drug-loaded nanoparticles for CVD prior to human studies, animal disease models are unavoidably needed. This review summarized the animal models used in the research of nanoparticles for CVD and provided a generic picture of current use of CVD animal models according to the different types of diseases which should be prioritized when considering the application of nanoparticles in treating CVD. This review would be useful resources not only for life science researchers and clinicians but also for those from chemistry and materials sciences background who may not have a systematic knowledge about CVD animal models.

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Introduction

Cardiovascular disease (CVD), including coronary artery disease, peripheral vascular disease, congestive heart failure, and atrial fibrillation, is the leading cause of mortality and morbidity worldwide (Joseph et al. 2017). Substantial improvements have been achieved in life expectancy and living quality due to better prevention and enhanced treatment for CVD, but there is still an urgent need for the drug innovation. Nanoparticles, defined as heterogeneous group of substances that vary in size (10–100 nm), have emerged as a potential candidate for drug delivery system. Nanoparticles possess several unique properties such as enhanced biocompatibility, reduced toxicity, and prolonged retention time (Dong et al. 2018). Besides, certain nanoparticles can serve as a drug due to their anti-inflammatory and antioxidant effects (Zhang et al. 2018). In this review, we summarized in vivo preclinical studies of nanoparticles for CVD using various animal models. These established animal models provided useful information to guide further experiments particularly when designing and choosing nanoparticles and would be useful resources not only for life science researchers and clinicians but also for those from chemistry and materials sciences background who may not have a

systematic knowledge about CVD animal models (Zaragoza et al. 2011).

Opportunities and challenges of nanoparticles for CVD treatment

The epidemiological transition in the twentieth century was marked by a significant decrease in deaths and disability from communicable diseases and an increase in non-communicable diseases (NCDs). Among NCDs, CVD is the leading cause of mortality and morbidity worldwide and accounts for approximately one-third of all deaths globally. According to a newly published data, prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990 to 18.6 million in 2019 (Roth et al. 2020). Both genetic and environmental factors are implicated in the development of CVD, which makes the treatment even more complicated.

Developing relevant CVD drugs is the common strategy for treatment. Aspirin, statins, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and other drugs have been validated in many large clinical trials to improve clinical outcomes in individuals with stable CVD (Leong et al. 2017). Further development on novel therapeutics such as using a delivery system to improve drug half-life and reduce side effects becomes a hot research topic. As the molecular processes underlying CVD become better defined, there are growing studies to intervene CVD using gene therapy. However, nuclear acid is easy to be identified and diminished and requires a carrier to protect them interacting with internal environment. Finding a delivery machine also seems a logical tool to bring gene therapy to fruition (Herrera et al. 2018).

Nanoparticles including inorganic nanoparticles, liposomes, and extracellular vesicles seem to be a good choice for this purpose. The nanoscale of nanoparticles enables themselves to cross natural barriers and enter into target cells more easily. Hence, drugs wrapped in nanoparticles could protect themselves from interactions with the surrounding environment and degradation, and further enhance the concentration in the targeted tissues. Additionally, nanoparticles can achieve controlled drug release by constructing a release system in response of internal stimuli such as pH, redox state, and the presence of biomolecules as well as external stimuli such as light

and magnetic field (Dong et al. 2018). For example, lipid nanoparticles are the carriers most used in clinical trials for therapeutics, due to their pronounced advantages over other delivery systems such as easy preparation, high biocompatibility, and biodegradability. Unfortunately, being synthetic and quite "unnatural," lipid nanoparticles can be toxic and induce immune response at high doses, particularly in the condition where the required dose is high or frequent application is required. However, these effects could be overcome by selecting proper lipid components (Zhang 2005; Xue et al. 2014). Up to now, several nano-formulations of lipid nanoparticles have been approved for human use. For example, BNT162b2, a kind of vaccine against COVID-19 and adopted lipid nanoparticles as vehicles, has been put into clinical use (No Author 2020). All these predict a promising application of using nanoparticles for the treatment of CVD.

Animal models for studying nanoparticles as a treatment for CVD

Animal models remain the best tool to investigate the novel pharmacological treatment of nanoparticles for CVD. The complicated nature of CVD presents challenges to test the application of nanoparticles in treating CVD. Better understanding of all animal models used is therefore the key in the study. In this paper, the most commonly used CVD animal models and their usages in testing nanoparticle applications for the treatment of CVD are reviewed. We focused on the animal models according to the type of CVDs and explained the complexity of choosing proper animal models to best mimic the pathological conditions of CVDs. We did not exam and compare which nanoparticle should be chosen and their potentially complicated properties when interacting with animals due to very random data in the limited applications. However, the properties of nanoparticles, especially when interacting with physiological system is the important aspects to be investigated in each individual study. Interdisciplinary collaboration with experts in chemistry and materials would greatly improve our understanding of how to best use nanoparticles to treat CVDs in this aspect.

The common animal models are mainly created based on cardiovascular pathological conditions, such as hypertension, atherosclerosis, myocardial infarction, and myocardial ischemia-reperfusion (Table 1), and the

availability and feasibility of choice of animals for these cardiovascular pathological conditions.

Both small animals such as mice and rats and large animals such as rabbits, canines, swine, sheep, and non-human primates are used in the study and they have their own advantages and disadvantages. For example, small animals are easier to handle and house, have a shorter gestation time, and have lower maintenance cost than larger animal models (Zaragoza et al. 2011). These features make small animals the most used model for cardiac physiology and pathology, genetics, pharmacology, and long-term survival studies. In addition, the availability of transgenic and knockout strains and little difficulty in creating new genetic modifications make the mouse one of the most attractive models for research. Nevertheless, large animals have similar cardiovascular system to human at both the organ and cellular levels, thus transitions from the researches in those large animals to human researches are more likely to repeat and the results obtained are also ready to use. In the following sections, we summarize all those animal models according to the type of CVD and how they have been used to test the applications of nanoparticles in treating CVD.

Hypertension animal models

Hypertension is known for persistently elevated blood pressure in the arteries. High blood pressure is a major risk factor for many diseases such as coronary artery diseases and stroke which usually does not cause obvious symptoms. Hypertension is classified into essential hypertension and secondary hypertension. Human essential hypertension is a complicated disease that involved both genetic and environmental factors. It has been demonstrated that genetic predisposition, excessive salt intake, over-stress, and hyperactivation of renin-angiotensin-aldosterone system are involved in the development of hypertension. Therefore, hypertension animal models are established mainly based on the above etiology.

There are four major hypertension models produced so far. Spontaneously Hypertensive Rat (SHR) is the internationally recognized animal model which is closest to human essential hypertension and has been widely used in basic research on essential hypertension and antihypertensive drug screening (Doris 2017). Fructose-(Klein and Kiat 2015), dexamethasone-(Beg et al. 2015), and DOCA-(Chadha et al. 2012) induced

Table 1 Common animal models for CVDs

Cardiovascular disease or pathological conditions	Intervention	Typical features
Hypertension	Spontaneous; fructose; dexamethasone; DOCA	Elevated blood pressure
Atherosclerosis	High cholesterol; continuous intimal injury through catheter, balloon angioplasty, or nitrogen exposure	Lipid abnormality with elevated triglyceride and other liver enzymes; atherosclerotic plaques on the wall of arteries featured by foam cells
Myocardial infarction	Permanent LAD ligation; ISO	Elevated myocardial enzymes and inflammatory cytokines; reduced ejection fraction; macroscopic appearance of scar; obvious histological alterations such as fibrosis and left ventricular remodeling.
Myocardial ischemia--reperfusion	Partial LAD ligation and blood reperfusion	Similar to MI model
Pulmonary arterial hypertension	Monocrotaline; hypoxia	Thick wall of the pulmonary peripheral arteries; right ventricular remodeling
Arrhythmia	Calcium chloride; barium chloride	Disorders of heart rhythm
Abdominal aortic aneurysm	Chronic infusion of angiotensin II into low-density lipoprotein receptor–deficient (LDLr$^{-/-}$) mice in combination with a high-fat diet; elastase infusion of the aorta	Macroscopic appearance of the abdominal aorta; macrophage activation within the aortic media

Abbreviations: *DOCA*, deoxycorticosterone acetate salt; *LAD*, anterior descending coronary artery; *ISO*, isoproterenol

hypertension models are all secondary hypertension models, which can mimic hypertension combined with insulin resistance, hypertension caused by activation of the mineralocorticoid receptor and elevated aldosterone, respectively. The hypertension animal model is characterized with elevated blood pressure.

As mentioned above, human essential hypertension is a complex disease associated with both genetic and environmental factors. Therefore, one single animal model may not be able to fully mimic the hypertensive responses and is therefore not sufficient to explain the antihypertensive effects of drugs when using nanoparticle as its delivery system. Therefore, various hypertension animal models are needed and results from these different models need to be compared before any conclusion can be drawn.

The current hypertension animal models used in the study of nanoparticles for the treatment of hypertension are summarized in Table 2. The nanoparticles combined with antihypertensive drugs such as nifedipine and lercanidipine hydrochloride enhanced the drug efficacy by prolonging the retention time in vivo. But those effects have not been tested for a long period of time and this is the same to their toxicity and side effect. Generally, antihypertensive drugs need to be continuously used and even for the rest of life. The animal models used at the moment normally last for couple of months as its maximum. Therefore, conclusion obtained should be further tested and verified. Nevertheless, these applications suggested that it was feasible to using drug-loaded nanoparticles for the treatment of hypertension.

Atherosclerosis animal models

Atherosclerosis, characterized by sub-endothelial accumulation of fatty substances called plaques, is the main underlying cause of myocardial infarction and stroke (Sluimer and Daemen 2009). It usually takes decades to form plaques with various inflammatory cytokines and immune cells contributing to the process. Rats and mice were inherently resistant to atherosclerosis. Therefore, transgenic models such as $LDLR^{-/-}$ mouse (Ishibashi et al. 1993) and $apoE^{-/-}$ mouse were established to develop atherosclerosis through gene knockout technology. However, gene knockout animals are rather expensive and may impose a substantial financial pressure to any research as well as limit the number of samples obtained. The rabbit is used as the ideal alternate animal for experimental atherosclerosis

by high-cholesterol diet or repeated or continuous intimal injury through catheter, balloon angioplasty, or nitrogen exposure (Zaragoza et al. 2011). The rabbit atherosclerosis model is a no plaque rupture model while porcine atherosclerosis models are valid to investigate the plaque rupture and restenosis. The high-cholesterol diet–induced atherosclerosis models present lipid abnormality with elevated triglyceride and other liver enzymes, and atherosclerotic plaques on the wall of arteries featured by foam cells. The external injury-induced atherosclerosis models exhibit atherosclerotic plaques without abnormal lipid profiles.

Table 3 summarizes the studies using nanoparticles for the treatment of atherosclerosis. Some modified nanoparticles like oligonucleotide functionalized nanoparticles could be specifically recognized by foam cells, which may serve as a potential delivery vehicle and therefore is worth for future study (Sharma et al. 2010). Superparamagnetic iron oxide nanoparticles for example could reach the target region under external magnetic gradient. This opens up the opportunity for further investigations aiming both to improve targeting efficacy and to develop the potential "magnetic drug targeting"–based approaches to therapy of arterial injuries and/or atherosclerotic plaques (Matuszak et al. 2018). In most of the study, drug-loaded with nanoparticles showed reduced lesion size and inflammatory responses than free drug in atherosclerosis animal model, suggesting that nanoparticles may be a promising strategy to prevent atherosclerosis. However, there are also some studies which did not show any anti-atherogenic effects with administration of nano-formulated drugs while enhanced accumulation of drugs in the desired regions were observed (Matuszak et al. 2018). Therefore, selecting optimal drugs turns to be crucial and important.

Myocardial Infarction animal models

Myocardial infarction (MI) occurs when blood flow decreases or stops at certain part of the heart, causing damage to cardiomyocytes. MI is a life-threatening disease and can cause sudden death. Victims survived from MI often suffer from adverse ventricular remodeling, which is also known as heart failure. Therefore, it is essential to explore new therapy strategies to rescue the ischemic cardiomyocytes and attenuate ventricular remodeling. It has been revealed that myocardial hypertrophy, fibrosis, inflammation, mitochondrial

Table 2 Hypertension animal models used in the study of nanoparticles for the treatment of hypertension

Type	Animal	Nano-delivery system	Carried drugs	Administration route	Measurement	Results	Refs
Spontaneously Hypertension Model	Male, adult rats	Polymeric nanoparticle (PCL, PLAGA, Eudragit RL/RS)	Nifedipine	Oral	Systolic arterial blood pressure by tail-cuff method	BP within normal range after 10h of dosing with all three NPs while PEG solution failed to achieve such sustained effect	(Kim et al. 1997)
	Male rats	PLA nanoparticles	Aliskiren	By gavage		BP was lower in both powdered and nanoparticle-loaded aliskiren groups with a more pronounced effect in the latter case. Only nanoparticle-loaded aliskiren increased the expression of nNOS along with increased NOS activity in the heart (by 30%).	(Pechanova et al. 2019)
Fructose-Induced Hypertension Model	Wistar rats	SLN	Isradipine	Oral		Isradipine nanoparticles showed a decrease in systolic blood pressure for 36h, while suspension showed a decrease in systolic blood pressure for only 2h.	(Thirupathi et al. 2017)
	Male SD rats	NLC	Lercanidipine hydrochloride	Oral		NLCs released lercanidipine hydrochloride for a longer period of time in a controlled manner than plain drug.	(Rampise et al. 2014)
Dexamethasone-Induced Hypertension Model	Unisex Wistar rats	SNEDDS (SNEOF and CSNEOF)	Olmesartan medoxomil	Intravenous injection		After 48h, rats were found normotensive (BP<130mm Hg) with SNEOF and CSNEOF, while rats with marketed formulation didn't show such lasting effect. .	(Beg et al. 2015)
DOCA-Induced Hypertension Model	Rats	lecithin/chitosan nanoparticles	HCT and HCT-β-CD	Oral		HCT and HCT-β-CD loaded nanoparticles demonstrate 1.5--fold percentage decrease in systolic blood pressure and a prolonged duration of action.	(Chadha et al. 2012)

SLN: solid lipid nanoparticles; *DOCA*, deoxycorticosterone acetate-salt; *NLC*: Nano-structured lipid carriers; *HCT*: Hydrochlorothiazide; *HCT-β-CD*: hydro-chlorothi-azide complexed with β-cyclodextrin

dysfunction, and autophagy/apoptosis are all involved in the progression of post-infarct ventricular remodeling. Using drug delivery system of nanoparticles carrying with cardioprotective agents to target any of the mechanisms above will benefit the dying cardiomyocytes. To examine their effectiveness, appropriate animal models need to be chosen to imitate human myocardial infarction as much as possible. Surgical ligation MI model and isoproterenol-induced MI model are current well-received models.

The surgical ligation MI model is made by ligating the left anterior descending coronary artery (LAD). Rat is dominantly used in the respect of heart damage because, while rats share many of the advantages with mice, their larger size greatly facilitates surgical operations. The mortality in surgical ligation MI models is higher than other non-traumatic MI models because the animals receiving thoracotomy often die from complications such as pneumothorax. However, after training and practice, the ligation method has higher stability than other methods. The myocardial infarction is more thorough, and the size of the infarct size is positively correlated with the height of the ligation site.

Isoproterenol (ISO)–induced MI model mimics sympathetic activation in the pathogenesis of myocardial infarction. ISO-induced MI model is widely adopted in promoting chronic myocardial infarction due to the lower mortality rate and less complexed procedure compared to the surgical ligation MI model. However, the infarct area caused by this method occasionally shows non-necrotic myocardium. Besides, the infarct area mainly distributes on the left ventricular wall and septum, especially near the apex. This method is also used for establishing the heart failure model and hyperthyroid heart disease model (Zhang et al. 2018).

The preferred large animal model of heart damage is the pig, because the collateral coronary circulation and arterial anatomy of pigs and humans are very similar and infarct size can be accurately predicted. These MI animal models present elevated myocardial enzymes, reduced ejection fraction, and obvious histological alterations such as fibrosis and left ventricular remodeling.

Table 4 briefly summarizes the MI animal models used in the study of nanoparticles for the treatment of acute myocardial infarction or post-infarct heart failure. Improved cardiac function and decreased infarct size were noticed in the MI animal model treated with empty nanoparticles or drug-loaded nanoparticles. Nucleic acid nanotherapies were investigated in MI animal model as

well. Nox2-siRNA nanoparticles were observed to prevent upregulation of Nox2 and significantly recover cardiac function in mice receiving LAD ligation. In the past few years, several cardiac gene therapy clinical trials were conducted with aim at inducing therapeutic angiogenesis in the ischemic heart. However, the efficiency of cardiac gene delivery remains a major hurdle preventing success (Cannata et al. 2020). Nanoparticles could address a breakthrough in delivery efficiency and hold a great promise for cardiac gene therapy.

Myocardial ischemia-reperfusion animal models

Myocardial ischemia-reperfusion (I/R) injury occurs when blood supply returns to the heart after a period of ischemia (Lejay et al. 2016). The possible mechanisms of myocardial I/R injury are as follows: (1) the outbreak of oxygen free radicals; (2) Ca^{2+} ovedoad; (3) mitochondrial dysfunction; (4) inflammation; (5) energy metabolism disorders. Myocardial I/R injury is a vital negative factor influencing the therapeutic efficacy for the MI victims who accept revascularization such as percutaneous transluminal coronary intervention (PCI) and coronary artery bypass grafting (CABG). The I/R animal model used is normally based on surgical ligation MI model. The difference is that left anterior descending coronary artery is partially ligated to achieve reperfusion in I/R model, while in MI model, it is completed ligated. The myocardial I/R animal model established by this method can better simulate human myocardial ischemia-reperfusion. Besides, isolated Langendorf I/R heart is often used for the ex vivo study of myocardial I/R injury. Since the isolated heart is detached from nerve innervation and systemic humoral factors, the heart rate, pre-and post-load, perfusion pressure, and other factors can be controlled. It is therefore especially suitable to study the effects of some single factors on cardiac function and metabolism without interference effects of related factors. However, the conclusions from isolated I/R heart are worthy of consideration when extending to humans because this model is isolated from inner environment. Small animals such as mice and rats are admired by researchers to build myocardial I/R animal model and the reasons are similar to MI animal model. At present, there is no agreeable conclusion on the exposure time of ischemia and reperfusion because they are affected by the size of the animal and the tolerance of the organ or tissue to ischemia and hypoxia.

Table 3 Atherosclerosis animal models used in the study of nanoparticles for the treatment of atherosclerosis

Type of atherosclerosis model	Animal	Nano-delivery system	Carried drugs	Administration route	Measurement	Results	Refs
Gene knockout mice	ApoE null C57-Bl/6 mice	Oligonucleotide functionalized nanoparticles	None	Intravenous injection	1) Lipid analysis 2) Immunohistochemistry	Oligonucleotide functionalized nanoparticles were specifically recognized by the scavenger receptors on lipid-laden foam cells, providing a strategy for targeting atherosclerotic lesions	(Sharma et al. 2010)
	Ldlr$^{-/-}$ mice	(PLGA-b-PEG) copolymer	LXR agonist GW3965	Retro-orbital injection		NP-LXR was more effective than free GW3965 at inducing LXR target gene expression and suppressing inflammatory factors in macrophages. Treatment with NP-LXR over two weeks markedly reduced the CD68-positive cell (macrophage) content of plaques (by 50%) without increasing total cholesterol or triglycerides in the liver and plasma.	(Zhang et al. 2015)
	ApoE$^{-/-}$ mice	Lipid nanoparticles	siCCR2	Intravenous injection		Lipid nanoparticles encapsulated siCCR2 showed a marked reduction of inflammatory Ly-6C^{high} monocytes, 46% reduced presence of myeloid cells, and a 38% reduction of lesion size in the aortic root.	(Leuschner et al. 2011)
Atherosclerosis model induced by balloon injury, high-cholesterol diet or their combination	Rabbit	Lipid nanoparticles	DTX	Intravenous injection		LDE-DTX treated group showed reduced atheroma area and lowered expression of pro-inflammatory markers compared to controls, without hematological, hepatic, or renal toxicity consequent to LDE-DTX treatment.	(Meneghini et al. 2019)
	Rabbit	Superparamagnetic iron oxide nanoparticles	Dexamethasone	Intra-arterial infusion		Enhanced inflammatory burden in the plaques, increased macrophage content, and larger intima-media thickness was observed in animals treated with SPION-DEXA compared with controls.	(Matuszak et al. 2018)

PLGA-b-PEG, poly(lactide-co-glycolide)-b-poly (ethylene glycol); *LXR*, liver X receptor; *DTX*, docetaxel

Table 4 MI models used in the study of nanoparticles for the treatment of acute myocardial infarction or post-infarct heart failure

Type of MI model	Animal	Nano-delivery system	Carried drugs	Administration route/dose	Measurement	Results	Refs
Surgical Ligation MI Model	Adult male C57B-L/6 mice	Polyketal nanoparticles	Nox2-NADPH oxidase siRNA	Intramyocardial injection	1) Electrocardiogram 2) Echocardiography 3) Cardiac MRI 3) Serum parameters measurement 4) Histological analysis	Nox2-siRNA particles prevent upregulation of Nox2 and significantly recovered cardiac function.	(Somasuntharam et al. 2013)
	Male FVB mice	PLGA nanoparticles	Insulin-like growth factor	Intramyocardial injection		PLGA-IGF-1 NPs was sufficient to prevent cardiomyocyte apoptosis, reduce infarct size, and improve left ventricle ejection fraction 21 days after experimental MI in mice.	(Chang et al. 2013)
	Male C57B-L/6 mice	PLGA nanoparticles	Pitavastatin	Intravenous injection		Treatment with Pitavastatin-NPs attenuated post-infarct left ventricular remodeling accompanied by a reduction of monocytes/macrophages in the heart, whereas pitavastatin solution treatment did not.	(Mao et al. 2017)
	Wistar rats	LDE	MTX	Intravenous injection		LDE-MTX treatment achieved a 40% improvement in left ventricular systolic function and reduced the infarction size, myocyte hypertrophy and necrosis, number of inflammatory cells, and myocardial fibrosis.	(Maranhao et al. 2017)
	Sprague Dawley rats	PEG-modified SLNs	Sch B	Intravenous injection		Treatment with Sch B loaded SLNs exhibited higher heart drug concentration and longer blood circulation time than the drug solution. MMP-Sch B SLNs also showed the best therapeutic efficacy by reducing the infarction size to the greatest extent	(Shao et al. 2017)
	Female York-shire swine	PLGA nanoparticles	FGF1 and CHIR99021	Intramyocardial injection		PLGA nanoparticles formulated with CHIR99021 and FGF1 provided an effective slow-release system for up to 4 weeks. Intramyocardial injection of CHIR + FGF1-NPs reduced infarct size by 20–30% and preserved cardiac contractile function in I/R pig models.	(Fan et al. 2020)
Isoproterenol-Induced MI Model	Wistar albino rats	Copper nanoparticles	None	Oral		Low-dose copper nanoparticles and exercise training significantly prevented ISO-induced MI through preconditioning and GSK-3b inhibition.	(Sharma et al. 2018)
	Adult male Wistar albino rats	Gold nanoparticles	None	Intravenous injection		Gold nanoparticles of 50nm diameter improved myocardial injury after ISO-induced myocardial infarction in rats.	(Ahmed et al. 2017)
			None				

Table 4 (continued)

Type of MI model	Animal	Nano-delivery system	Carried drugs	Administration route/dose	Measurement	Results	Refs
	Male Wistar rats	Cerium oxide nanoparticles		Intraperitonial administration		Nano-ceria showed a promising ameliorative and prophylactic effect against cardiac toxicity compared to Captopril reference drug.	(El Shaer et al. 2017)
	Male BAL-B/c mice	Nanoliposome	SMV	Intragastric (i.g.) and intraperitoneal administration		By i.p. administration, the SMV-Lipo at an equal SMV dose exhibited more noticeable inhibitory effects than the crude SMV on cardiac remodeling. In addition, SMV-Lipo administrated by either i.p. or i.g. more significantly improved the plasma SMV concentration than the crude SMV.	(Tuerdi et al. 2016)
	Adult male guinea pigs	Poly-lactic acid nanoparticle	Curcumin and nisin	Subcutaneous injection		Curcumin-nisin-based nanoparticle showed significant cardioprotection in the guinea pig and was nontoxic.	(Nabofa et al. 2018)

PLGA, poly D; L, lactide-co-glycolide; PEG, polyethylene glycol; LDE, lipid core nanoparticles; SLN, solid lipid nanoparticles; MTX, methotrexate; Sch B, schisandrin B; SMV, simvastatin

Table 5 briefly reviewed the I/R animal models used in the study of nanoparticles for the treatment of myocardial I/R injury. PLGA nanoparticles and other inorganic nanoparticles were tested either as empty or loaded with most used clinical drugs on these animal models. For majority of the study, reduced inflammatory responses, apoptosis, and lesion size were observed in myocardial I/R animal models treated with nanoformulated drugs, indicating the potential of nano-drug delivery system for the treatment of I/R injury. For example, silver nanoparticles increased the level of cytokines and aggravated I/R injury. For the concern of safety, silver nanoparticles are not proper nanoparticles for the treatment of I/R injury.

Other animal models

There are some other animal models adopted to study the effect of nanoparticles for CVD, such as pulmonary arterial hypertension model, arrhythmia model, and abdominal aortic aneurysm model. These animal models are more specific targeted for individual CVD conditions. Overall, drug-loaded nanoparticles showed cardioprotective effects in these animal models. Prostaglandin I2 and its analogues (such as beraprost sodium, BPS) are beneficial for the treatment of PAH. Intravenous administration of BPS nanoparticles (once per week, 20 μg/kg) protected against monocrotaline-induced and hypoxia-induced pulmonary arterial remodeling and right ventricular hypertrophy. The extent of this protection was similar to that observed with oral administration (once per day, 100 μg/kg) of BPS alone (Ishihara et al. 2015). The beneficial effects of BPS-NP on PAH animal models seem to be mediated by its sustained release and tissue targeting profiles. BPS nanoparticles may be useful for the treatment of PAH patients due to reduced dosages and frequency of BPS administration.

Conclusion

CVD animal models remain the best tool to understand the mechanism of human CVD and validate the novel pharmacological therapeutics. No single animal model can perfectly duplicate the human disease and there are other concerns to be considered when choosing animal models such as cost, infrastructure, and the requirement for specialized personnel. Choosing a model that best

Table 5 I/R animal models used in the study of nanoparticles for the treatment of myocardial I/R injury

Type of IR model	Animal	Nano-delivery system	Carried drugs	Administration route/dose	Measurement	Results	Refs
I/R Animal	Adult male Sprague Dawley (SD) rats	PLGA nanoparticles	Pitavastatin	Intravenous injection	1) Electrocardiogram 2) Echocardiography 3) Serum parameters measurement 4) Histological analysis	Pitavastatin-NP induced phosphorylation of Akt and GSK3β, and inhibited inflammation and cardiomyocyte apoptosis in the IR myocardium.	(Nagaoka et al. 2015)
	Male Sprague Dawley rats	Silver nanoparticles (AgNP)	None	Intratracheal instillation		AgNP increased circulating levels of several cytokines, which may contribute to persistent expansion of I/R injury.	(Holland et al. 2015)
	Male FVB mice	stock and PEG-modified polystyrene nanoparticles	None	Intravenous injection		Nanoparticles with a core diameter in the 20–200 nm range were optimal for rapid passive targeting of the I/R-injured left ventricle.	(Lundy et al. 2016)
	Male C57/B mice	PVAX and HPOX Nanoparticles	None	Intraperitoneal injection		PVAX effectively suppressed the generation of ROS caused by I/R, and PVAX significantly reduced the level of NADPH oxidase (NOX) 2 and 4 expression, which favors the reduction in ROS generation after I/R.	(Bae et al. 2016)
	Adult male C57BL/6J mice	PLGA nanoparticles	Irbesartan	Intravenous injection		Treatment with irbesartan-NP, but not with control nanoparticles or irbesartan solution inhibited the recruitment of inflammatory monocytes to the I/R heart, and reduced the infarct size via PPARγ-dependent anti-inflammatory mechanisms, and Ameliorated left ventricular remodeling 21 days after I/R.	(Nakano et al. 2016)
	Male C57BL/6J (wild–type; WT) and cyclophilin D knockout (CypD-KO) mice	PLGA Nanoparticles	Mdivi1	Intravenous injection		Mdivi1-NPs had cardioprotective effect against I/R injury through inhibition of Drp1-mediated Bax translocation to the mitochondria, namely, through MOMP, even in mice lacking a CypD/MPTP opening.	(Ishikita et al. 2016)
	Male C57BL/6J and cyclophilin D$^{-/-}$ mice	PLGA Nanoparticles	CsA	Intravenous injection		Treatment with CsA-NP at the onset of reperfusion enhanced cardioprotection against I/R injury through the inhibition of mitochondrial permeability transition pore opening.	(Ikeda et al. 2016)
	Male Wistar rats	silica nanoparticles	Adenosine	Intravenous infusion		Immobilization of adenosine on the surface of silica nanoparticles decreased the infarct size in the rat model.	(Galagudza et al. 2012)
	Male Sprague Dawley rats	NIPAAm-MMA nanoparticles	Visnagin	Intravenous injection		Visnagin-NP treatment induced cardioprotection, reducing the size of the MI and ameliorating cardiac dysfunction through the induction of autophagy and the inhibition of apoptosis.	(Fu et al. 2018)
	Male Sprague Dawley rats	Plasm exosomes	None	Intravenous injection		The exosome-rich fraction was powerfully cardioprotective in I/R rats.	(Vicencio et al. 2015)
	Bama mini-pigs	PLGA nanoparticles	Pitavastatin	Intravenous injection		Pitavastatin-NP significantly reduced infarct size without obvious adverse side effects.	(Ichimura et al. 2016)
Langendorff I/R Heart	Male Wistar rats	PGMA nanoparticles	AID Peptide	Via a recirculation System		Curcumin and the AID peptide in combination effectively reduced muscle damage, decreased oxidative stress and superoxide production in cardiac myocytes.	(Hardy et al. 2015)

Table 5 (continued)

Type of IR model	Animal	Nano-delivery system	Carried drugs	Administration route/dose	Measurement	Results	Refs
	Male C57BL/6J (wild-type) and cyclophilin D knockout (CypD-KO) mice	PLGA Nanoparticles	Mdivi1	Intravenous injection		Mdivi1-NPs have cardioprotective effect against IR injury through inhibition of Drp1-mediated Bax translocation to the mitochondria, namely, through MOMP, even in mice lacking a CypD/MPTP opening.	(Ishikita et al. 2016)
	Male Sprague Dawley rats	Plasm exosomes	None	Via a recirculation System		The exosome-rich fraction was powerfully cardioprotective in isolated I/R hearts.	(Vicencio et al. 2015)

PLGA, poly-lactic/glycolic acid; *PGMA*, poly (glycidyl methacrylate); *Mdivi1*, mitochondrial division inhibitor 1; *CsA*, cyclosporine A; *NIPAAm-MMA*, N-isopropylacrylamide and methacrylic acid

reflect on the aspect of disease being investigated can certainly help to explore how nanoparticles can be best used for CVD. The effects of nanoparticles in various preclinical animal models of CVD approved that nanoparticles as a delivery vehicle can significantly improve the therapeutic efficacy of the drug and reduce doses and frequency of drug administration through sustained release and tissue-specific targeting. Nanoparticles are also ideal delivery carrier for the gene therapy. Therefore, nanoparticles possess a strong potential for clinical translation in CVD. However, establishing more reliable large animal models and choosing more effective therapeutic genes or drugs should be prioritized when testing the nanoparticle application.

Declarations

Conflict of interest The authors declare no conflict of interest.

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