EDITORIAL

Insights Into the Development and Treatment of Cardiovascular Disease: A Role for Animal Models

Approximately one-third of the total deaths worldwide per annum, amounting to 16.6 million people, is due to cardiovascular disease [1], making it the number one cause of death [2]. Cardiovascular disease also has a major impact on morbidity [1]. Thus, reducing the incidence of deaths due to vascular disease/complications and developing better treatment strategies, remains a central goal for national economies worldwide [3, 4]. Consequently, several animal models have been developed to replicate human vascular diseases, in order to study the pathophysiology of disease progression and novel therapeutic options. This issue of The Open Cardiovascular Medicine Journal discusses some of these models. In this Editorial, each review article for the Special Issue will be briefly outlined, with consideration given to a few additional models.

Tsui describes genetically predisposed, chemical and physical animal models of abdominal aortic aneurysms (AAAs) [5]. This review focuses on the pathophysiological mechanisms that underlie the development and progression of AAAs and the different treatment modalities for their management.

Ou et al. discusses the development of animal models of myocardial infarction, dilated cardiomyopathy, heart failure, myocarditis and cardiac hypertrophy, emphasising the usefulness of stem cell therapy [6].

Karasu describes abnormal cardiac contractility and impaired vascular reactivity in animal models of diabetes mellitus and highlights the role of antioxidant therapy in preventing or delaying diabetic cardiovascular complications [7].

Grossman explores the use of the renal hypertension-Goldblatt kidney and uraemic cardiomyopathy animal models to look at the relationship between cardiovascular disease and renal pathophysiology [8].

Ameen and Robson describe the relationship between Duchenne Muscular Dystrophy and cardiovascular disease in spontaneous and transgenic animal models, outlining new treatment options [9].

Price et al. discusses the use of magnetic resonance imaging to follow the pathophysiology of myocardial ischaemia and atherosclerosis in animal models. Attention has also been given to imaging the rodent developing heart to assess the influence of genes and congenital diseases [10].

In addition, several other models have been developed for the study of vascular disease. This Editorial briefly addresses some of them.

1. ISCHEMIC AND HEMORRHAGIC STROKE

Strokes result from ischemic (brain infarction), as well as, intracerebral or subarachnoidal hemorrhage [11]. Ischemic stroke is often caused by occlusion of the middle cerebral artery or one of its branches. The most relevant animal model has emerged from isolated middle cerebral artery occlusion in rodents. One of the striking features of this model is the ease to perform both permanent and transient ischemia in a controlled manner [12]. Thromboembolic stroke, the most common stroke type in humans, can be mimicked in rodents and used for preclinical testing of thrombolytic agents [13-15], evaluation of the ischemic lesion under the effect of thrombolysis [16, 17], investigation of the consequences of thrombolysis such as hemorrhagic transformation [18], to test novel antithrombotic agents [19, 20] and combination therapies (e.g. thrombolytic agents and neuroprotective drugs) [21-23].

Strokes caused by intracerebral and subarachnoid hemorrhages are associated with high mortality and most survivors are burdened with severe disability. Several animal models have been developed to study intracerebral haemorrhages [24-27]. The most commonly used models involve: autologous blood or collagenase injection [28-30] or balloon inflation [31] into the desired brain region.

Subarachnoid haemorrhages have also been studied in various animal models [32-35].

The endovascular filament rupture of the basilar artery and intracranial internal carotid artery bifurcation models have become very popular [30, 36, 37].

In general, animal stroke models are able to reproduce important pathophysiological events relevant to the human situation and help in the development of novel treatment regimes.

2. HYPERTENSION

Hypertension is an important risk factor for cardiovascular and cerebrovascular disease. The availability of animal models for research on the pathophysiology and treatment of hypertension-induced disease has provided valuable information. Models
have been created following portal vein stenosis [38], renal surgery [39], high fructose diet [40] and the administration of deoxycorticosterone acetate salt [41]. However, spontaneously hypertensive rats represent the most common animal model [42-46]. Cerebrovascular changes, brain atrophy, loss of nerve cells in cerebrocortical areas is evident in these rats; allowing the assessment of the effectiveness of anti-hypertensive therapy on these changes.

3. PERIPHERAL ARTERIAL DISEASE

Animal models for hindlimb ischemia are useful for investigating many of the features of peripheral arterial disease (PAD) [47, 48], such as angiogenesis and arteriogenesis [49]. They have been used to evaluate the beneficial effect of autologous bone marrow cell infusion [50, 51], vascular endothelial growth factor [52] and platelet-derived endothelial cell growth factor [53] for the induction of angiogenesis. In addition, animal models have helped establish diagnostic tests for the evaluation and quantification of angiogenesis [54-57].

These models provide insight into the pathophysiology and management of PAD. Application of these preliminary results in humans holds implications for a different therapeutic approach to this disease in the future.

4. ERECTILE DYSFUNCTION

The association between erectile dysfunction (ED) and coronary heart disease has confirmed that it is another manifestation of atherosclerotic vascular disease. Interestingly, the same risk factors (e.g. diabetes mellitus, hypertension, dyslipidaemia, and smoking) predict both ED and vascular disease [58, 59]. These risk factors and their association with ED have been investigated in many animal studies.

The disruption of the nitric oxide (NO)/ cyclic guanosine monophosphate (cGMP) pathway seems to be a unifying factor in many of these conditions, resulting in a reduction in NO bioavailability and impaired corpus cavernosal smooth muscle relaxation, a cardinal component of the erectile process. The preservation of cGMP and the subsequent increase in smooth muscle relaxation, following treatment with phosphodiesterase type-5 (PDE5) inhibitors, represent an effective mode of treating diabetic ED [60]. One such drug, DA-8159 was found to ameliorate the development of ED in diabetic rats [61, 62].

Oxidative stress (OS) is also a feature of diabetes mellitus and ED, it is defined as an increase in the steady-state levels of reactive oxygen species, including superoxide anions (O$_2^-$), which occurs as a result of increased free radical generation and/or decreased anti-oxidant defense mechanisms. Not surprisingly antioxidant therapy has been pursued as a treatment option for diabetic ED. Low dose treatment with alpha-lipoic acid (antioxidant) and gamma-linolenic acid (omega-6-essential fatty acid) interacted synergistically to improve NO-mediated corpus cavernosal relaxation in diabetic rats [63]. While the antioxidant vitamin E enhanced the therapeutic effect of PDE5 inhibition, due to a reduction in OS in diabetic rats [64]. In vivo adenoviral gene transfer of EC-superoxide dismutase (SOD) reduced corporal O$_2^-$ levels and raise cavernosal cGMP levels by increasing NO bioavailability thus restoring erectile function in diabetic rats [65].

Many animal models of hypertension have revealed the close association between hypertension and ED. An increase in OS has been implicated in this relationship. For example, rats infused with angiotensin II developed hypertension and ED, due to an increase in NADPH activity (an inducible source of O$_2^-$ production). Apocynin an inhibitor of NADPH was found to exert protective effects on erectile function in this model [66]. Antioxidant treatment with alpha-tocopherol was found to improve erectile function in spontaneously hypertensive rats by increasing SOD activity, which reduced O$_2^-$ levels [67]. While, PDE5 inhibition with angiotensin II receptor blockade improved the function and morphology of erectile tissue taken from spontaneously hypertensive rats [68].

Rabbit models have been successfully used to demonstrate the link between hypercholesterolaemia and ED. A conscious rabbit model has been developed to assess the potential that intravenously administered drugs have for treating ED [69,70]. For example, the impaired erectile response exhibited by hypercholesterolaemic rabbits was improved following PDE5 inhibition [70]. This class of drugs was also effective in treating hypercholesterolaemic rats with ED [71].

The development of transgenic animal models, in particular the apolipoprotein E knockout mouse has provided a suitable model to illustrate atherosclerosis-associated ED and to develop new therapeutic strategies targeted at both atherosclerosis and ED [72, 73].

Evidence based analysis of the role of smoking in the development of ED, suggests that they are linked [74]. This is supported by a recent study using mice; animals that received short-term exposure to secondhand smoke were found to develop ED due to an increase in OS, which was improved by PDE5 inhibition [75].

It is clear that animal models play a pivotal role in the study of the pathophysiology of cardiovascular disease. The development of new models in the future will undoubtedly increase our understanding of the cellular/ molecular events involved in disease progression and aid the development of novel treatment strategies.
ABBREVIATIONS

AAA = Abdominal aortic aneurysms

CgMP = Cyclic guanosine monophosphate

DM = Diabetes mellitus

ED = Erectile dysfunction

NADPH = Nicotinamide adenine dinucleotide phosphate

NO = Nitric oxide

PAD = Peripheral arterial disease

OS = Oxidative stress

PDE5 = Phosphodiesterase type 5

SOD = Superoxide dismutase

$O_2^-$ = Superoxide anions

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