Review

Animal models for the study of arterial hypertension

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Hypertension is one of the leading causes of disability or death due to stroke, heart attack and kidney failure. Because the etiology of essential hypertension is not known and may be multifactorial, the use of experimental animal models has provided valuable information regarding many aspects of the disease, which include etiology, pathophysiology, complications and treatment. The models of hypertension are various, and in this review, we provide a brief overview of the most widely used animal models, their features and their importance.

[Dornas WC and Silva ME 2011 Animal models for the study of arterial hypertension. *J. Biosci.* **36** 731–737] **DOI** 10.1007/s12038-011-9097-y

1. Introduction

Owing to the high occurrence of hypertension and problems originating from this disease over the years, a series of experimental models have been developed (Doggrell and Brown 1998). The use of relevant models to mimic human cardiovascular disease may offer useful information by allowing an understanding of the cause and progression of the disease status as well as potential therapeutic interventions (Badyal *et al.* 2003). However, an effective study of particular cardiovascular alterations emerging in the course of the developmental process requires the use of adequate animal models. Accordingly, it should be mentioned that each one of the studied models involves a different role in the development of the disease (Fazan *et al.* 2001).

2. Genetic hypertension

2.1 *Spontaneously hypertensive rat*

Spontaneously hypertensive rats (SHRs) were originally inbred from Wistar rats and their Wistar–Kyoto (WKY) inbred non-hypertensive controls (Okamoto and Aoki 1963). These rats develop hypertension at about 4–6 weeks of age without physiological, pharmacological or surgical intervention (Zicha and Kunes 1999); however, environmental factors affect the development of hypertension, and the importance of this model has been attributed to the similarity of its pathophysiology with essential hypertension in humans (Trippodo and Frohlic 1981).

In vivo studies have shown that in the early stages of hypertension, SHRs have an increased cardiac output with normal total peripheral resistance. As the SHR progresses into the established hypertension state, the cardiac output returns to normal values and the hypertrophied blood vessels produce an increase in the total peripheral resistance (Smith and Hutchins 1979). With the advance of hypertension, the SHR progressively develops (between 6 and 24 months of age) structural alterations in the heart, which are associated with progressive cardiac hypertrophy (Engelmann *et al.* 1987). As this is not a strictly inbred strain, individual variations in the genetic background of both SHR and particularly of their control strain may significantly influence the resulting end-organ changes, what can be seen in figure 1.

Keywords. Blood pressure; cardiovascular disease; experimental models; hypertension

Abbreviations used: ANG II, angiotensin II; BHR, borderline hypertensive rat; CBF, cerebral blood flow; DOCA, 11-desoxycorticosterone acetate; DR, Dahl salt-resistant rat; DS, Dahl salt-sensitive rat; EDCF, endothelium-derived constricting factor; EDRF, endothelium-derived relaxing factor; HR, heart rate; LV, left ventricle; MAP, mean arterial pressure; PRA, plasma rennin activity; RAAS, rennin–angiotensin–aldosterone system; ROS, reactive oxygen species; RSNA, renal sympathetic nerve activity; SAD, sinoaortic baroreceptors; SHR, spontaneously hypertensive rat; SHRSP, stroke-prone spontaneously hypertensive rat; SOD, superoxide dismutase; WKY, Wistar–Kyoto

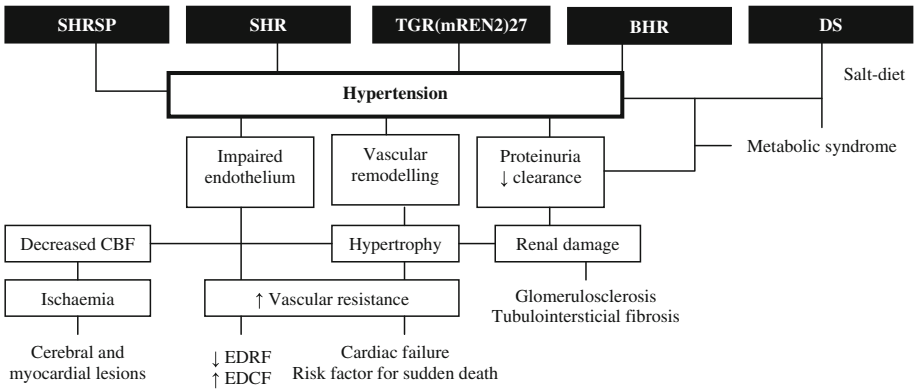

Figure 1. End-organ damage as affected by different experimental genetic models of hypertension: Cerebral blood flow (CBF); endothelium-derived relaxing factor (EDRF) and endothelium-derived constricting factor (EDCF).

Stroke-prone spontaneously hypertensive rats (SHRSP), bred from SHR developed with even higher levels of BP and a strong tendency to die from stroke, are extreme examples of cerebrovascular lesions developing spontaneously in animal models (Okamoto *et al.* 1974). It is the most utilized animal model of spontaneous stroke and is regarded as a unique animal model in which prevention of stroke can be studied experimentally as the incidence of spontaneous occurrence of stroke lesions in these models reach 80% in males and 60% in females, with extensive cerebral arteriosclerosis (Yamori 1989).

Because of the high mortality rate of stroke in humans, and of the similarity of stroke in SHRSP to that observed in human essential hypertension, this model has been applied to studies of stroke in human beings (Yamori *et al.* 1976). Hypertrophy leads to increased vascular resistance (figure 1) and wall sheer rates. As blood vessels become less functionally responsive and more extensively filled with atherosclerotic plaques, there is a risk for complications such as cerebral hemorrhage, thrombosis, nephrosclerosis and myocardial lesions in SHRs and especially cerebral lesions in SHRSPs (Henning *et al.* 2010). Therefore, these models can be used to study not only the pathogenesis and therapy but also prophylaxis in essential hypertension and its complications.

2.2 *Dahl salt-sensitive rats*

Another model is the Dahl salt-sensitive rat (DS), originally derived by Dahl from the Sprague–Dawley stock on the basis of developing hypertension with a high NaCl diet. When fed normal salt diet, these rats become hypertensive, indicating that this is a genetic model of hypertension with the feature of salt sensitivity. On the basis of these considerations, Dahl *et al.* (1962) selected from endocrossings of Sprague–Dawley rats and, on the basis of pressure levels associated with a diet high in salt (8% NaCl), two strains of animals: the Dahl salt-sensitive rats (DS) and the Dahl salt-resistant ones (DR).

The DS animals develop a systemic arterial hypertension after ingesting a high-salt diet, while the DR animals can maintain BP within normal limits even with the same diet. The mechanisms of genetic salt-sensitive hypertension of the Dahl strain rats are not yet fully known. In addition, DS rats are possibly insulin resistant even before hypertension is fully established, and salt-sensitive models of hypertension manifest a decrease in afferent arteriolar resistance and a rise in glomerular pressure in response to an increase in BP (Campese 1994). This could indicate that insulin resistance and hypertension may be inherited as separate traits that develop in a parallel but independent manner (Channa *et al.* 2004).

Dahl salt-hypertensive rats are prone to hypertensive nephropathy (figure 1). Hypertensive glomerular lesions were conventionally characterized by mesangial proliferation, matrix accumulation and glomerulosclerosis, in addition to endothelial dysfunction (Nagase *et al.* 2006).

2.3 *Transgenic hypertension models*

Transgenic hypertension models can be generated by overexpression of a specific gene. This is an excellent model to study the role of a specific gene in the pathogenesis of hypertension. A representative of this type of hypertension is the TGR(mREN2)27 transgenic rat developed by Mullins *et al.* (1990), which suppresses endogenous renal renin (Bader *et al.* 1992). TGR develops fulminant hypertension (200 to 260 mmHg mean systolic BP) beginning at the 5th week of age, exhibits more myocyte hypertrophy and, only to a small extent, hyperplasia, and more endothelial dysfunction than age- and BP-matched SHR (Mullins *et al.* 1990).

Structural lesions of the nephron in TGR are moderate in both sexes at an age of 4 months, except for an overall increase in wall thickness of the larger arterioles and arteries

(Bachmann *et al.* 1992). Although the model is not representative of human hypertension, it does allow *in vivo* analysis of the consequences of severe, monogenetic activation of the Ras and allows identification of the types of hypertensive damage that can be expected from an activated Ras (figure 1).

2.4 *Borderline hypertensive rat*

Investigations using the borderline hypertensive rat (BHR) have demonstrated the important role genetic factors can play in mediating both the behavioural and cardiovascular responses to environmental stressors.

BHR is a genetic model of environmentally induced hypertension and it is the first filial offspring of the SHR and the normotensive WKY rat, possessing genetic information from both parents (Sanders and Lawler 1992). The mechanisms by which environmental stress produces hypertension in BHR have not been identified. However, the sympathetic nervous system has been implicated. Increases in plasma norepinephrine concentration during acute environmental stress have been observed in BHR, and changes in vascular reactivity induced by stress may contribute to the differential hemodynamic adaptations to stress observed in WKY rats and BHR (Fuchs *et al.* 1998). BHR are characterized by a high plasma concentration of vasopressin, exogenous vasopressin-induced hyperpressor action and cardiac hypertrophy (figure 1).

3. Renal hypertension

3.1 *Renovascular hypertension*

Since 1934, when Goldblatt and his coworkers induced an elevation of BP by partial constriction of the renal artery of dog, many renal-induced models of hypertension have been successfully established. Goldblatt's technique consists of constricting one or both renal arteries by use of a small adjustable silver clamp (Goldblatt *et al.* 1934). Generally, renal-induced experimental hypertension includes two-kidney one-clip hypertension (2K1C; constriction of one renal artery while the contralateral kidney is left intact), one-kidney one-clip hypertension (1K1C; one renal artery is constricted and the contralateral kidney is removed), and two-kidney two-clip hypertension (2K2C; constriction of aorta or both renal arteries).

As the clip is not severe enough to cause ischaemia in the 2K1C Goldblatt model, hypertension is induced by unilateral stenosis of the renal artery. However, the reduced renal perfusion pressure stimulates increased renin synthesis and angiotensin II (ANG II), via its direct vascular effects, acutely increases total peripheral resistance and raises BP and also has actions on almost every organ system (Guyton 1991).

Constricting the renal artery of the remaining kidney in uninephrectomized rats produces 1K1C Goldblatt hypertension. This hypertensive model has been generally considered to be sodium-fluid volume-dependent, and is an ideal model for studying the role of volume expansion in the development of hypertension; owing to the absence of the other normal kidney, no compensatory increase in sodium and water excretion can occur, and hence, fluid volume is retained (Liard *et al.* 1974).

When of the aorta or both renal arteries are constricted, there is severe renal ischaemia caused by renal clipping, occasioning the activation of renin-angiotensin and the sympathetic nervous system and the elevation of serum vasopressin, leading to increased BP (Suzuki *et al.* 1987). The 2K2C, with a high incidence of spontaneous stroke, can be used as SHRSP independent of a genetic deficiency. The lesioned small artery or arteriole with thrombotic occlusion is the main cause of cerebral infarction in 2K2C, and this may be similar to lacunar infarction in the human brain (Zeng *et al.* 1998).

3.2 *Renoprival hypertension*

Significant reduction of nephron mass by subtotal nephrectomy in experimental animals or by various diseases in humans triggers a chain of events that lead to glomerulosclerosis, tubulointerstitial injury, proteinuria and progression to end-stage renal disease (Quiroz *et al.* 2008).

Unilateral nephrectomy causes neither hypertension nor cardiovascular lesions. However, hypertension caused by renal arterial stenosis, exacerbated by high amounts of protein and salt in the diet and/or by high volumes of water consumed, as well as removal or not of the adrenal gland, can affect the severity of renoprival hypertension. Removal of one kidney and approximately two-thirds of the other is followed by a slow increase in BP. In these animals, intravascular volume increases and the resulting hypertension may have the same pathogenesis as renoprival hypertension (Ledingham and Pelling 1970). Since a bilateral nephrectomy leads to hypertension with vascular lesions, especially if the animal's life is prolonged after the complete removal of the kidneys (Ferrario *et al.* 2009).

4. Endocrine hypertension

4.1 *Salt and mineralocorticoids*

Mineralocorticoids cause retention of sodium and water in the body until escape diuresis occurs due to increased pressure on the kidneys and suppression of renin secretion. The renal effects of this model are similar to hyperaldoster-

onism in humans. 11-desoxycorticosterone acetate (DOCA) and a high-salt diet cause increase of BP within 3 weeks in isolated perfused cortical collecting ducts, and can cause a 30-fold increase in sodium absorption (Garwitz and Jones 1982). Moreover, there is a reduced plasma rennin activity (PRA), which is expected in a model of volume-dependent hypertension, and oxidative stress also may be involved in DOCA salt hypertension by the increase of superoxide formation (Ortiz and Garvin 2001).

DOCA salt models progress quickly to severe hypertension and hypertrophy and are therefore not suited for long-term studies in chronic, stable disease; there should be minimal mortality due to the procedures alone. Thereby, the major limitations of the DOCA salt model are: (1) the pharmacological (large) doses of drug required, (2) the requirement for surgical reduction of renal mass and (3) the ingestion of a large amount of NaCl required. Moreover, it is not a very realistic model for many human hypertensive patients (Doggrell and Brown 1998).

4.2 *Psychosocial and environment-induced hypertension*

It has been reported that elevation of BP resulting from repeated exposure to stressful situations may lead to a state of persistent hypertension (Smith and Hutchins 1979).

Several mechanisms such as the resetting of the baroreceptor reflexes and structural autoregulation in the peripheral vasculature may operate to sustain BP at a high level once it is raised, but these account less convincingly for the initial elevation. However, if psychosocial factors are involved in the development of hypertension, they are likely to be linked with the early, triggering stages of the pathophysiological sequence (Steptoe 1986).

Chronic social stress in a modern world represents an important risk factor for the development of cardiovascular disease. Its deleterious effects depend on the critical period of exposure, duration and type, as all these factors may alter functions of the basic autoregulatory stress response components in the hypothalamic–pituitary–adrenal axis, sympathoadrenal medullar system, rennin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (Zimmerman and Frohlich 1990; McCarty and Gold 1996; Esch *et al.* 2002).

Different types of stress have been applied, such as emotional stimuli, psychosocial stress, immobilization stress, food deprivation and electric stimuli, air jet noise, flashing lights, cold, and interaction of members of a social group as they compete for food and water (Henry 1975; Friedman and Dahl 1975; Papanek *et al.* 1991; Henry *et al.* 1993; Tucker and Hunt 1993; Bechtold *et al.* 2009).

5. Neurogenic hypertension

Evidence suggests that the central nervous system participates in the genesis of hypertension. Neurogenic hypertension can be defined as a permanent increase in BP resulting from a primarily neural change. Denervation of sinoaortic baroreceptors (SAD) is the neurogenic model of hypertension most often used. The details of these control mechanisms have been studied by observing steady state changes in mean arterial pressure (MAP), heart rate (HR) and renal sympathetic nerve activity (RSNA) at various times after complete disruption of these reflexes (DiBona and Jones 2001), and in association with other models to obtain a global analysis of the baroreceptor-sympathetic reflex (table 1).

Table 1. Association of baroreceptor denervation and other models of experimental hypertension

Baroreceptor denervation and angiotensin-II-induced hypertension
Sustained decrease in RSNA during angiotensin II infusion is baroreflex mediated (Barrett *et al.* 2005).
Sinoaortic denervation and administration L-NAME
Baroreflexes play an important role in the long-term control of BP, and one mediator of this control is nitric oxide (Ramchandra *et al.* 2003).
Sinoaortic denervation in chronic one-kidney, one-clip hypertensive
Central and peripheral components of the baroreflex are acting efficiently at higher BP when the aortic nerve is maximally stimulated or the activity is abolished, suggesting that baroreceptor resetting may not be complete in chronic hypertension (Trindade *et al.* 2009).
Sinoaortic denervation and stress in BHR
Baroreflex resetting prevents a fall in BP when cardiac output is reduced during stress (Hatton *et al.* 1997).
Sinoaortic denervation with unilateral nephrectomy and administered NaCl
Vasopressin and neurogenic stimuli work together in some manner to elevate vascular resistance in salt-induced hypertension (Ryuzaki *et al.* 1991).
Sinoaortic denervation and administered NaCl
Baroreceptor reflex is required to prevent chronic salt-induced increases in arterial pressure (Osborn and Provo 1992).

In rats, SAD leads to marked and sustained increase in BP, and the increase of BP in rat is not accompanied by as marked a tachycardia as that observed in dog (Krieger 1964). Thus, an increase in MAP stimulates baroreceptors and causes a reciprocal reduction in sympathetic outflow to resistance vessels and the heart so as to restore MAP to the normal level and, therefore, cause neurogenic hypertension (Thrasher 2002).

6. Hypertension by chronic inhibition of nitric oxide

Nitric oxide (NO) plays an important role in regulating systemic vascular resistance by exerting a tonic vasodilator effect (Török 2008).

Chronic oral administration of an inhibitor of NO synthase, L-NAME, promoted a persistent hypertension associated with renal injury, characterized by glomerulosclerosis, glomerular ischaemia and interstitial infiltration in the kidney (Baylis *et al.* 1992; Ribeiro *et al.* 1992). This hypertension is associated with intense peripheral vasoconstriction and the consequent increase in peripheral vascular resistance. As for the cardiac output, some evidence seems to indicate a reduction even during chronic inhibition of NO synthase. A likely sympatho-excitatory action of central origin has also been proposed by Biancardi *et al.* (2007), who showed that vasoconstriction in response to L-NAME by the sympathetic tone plays an important role in the initiation and maintenance of hypertension.

In relation to cardiac abnormalities, the level of hypertrophy in this model is relatively minor as compared with other models with similar BP levels. L-NAME-induced pressure overload is associated with a distinct pattern of left ventricle (LV) remodelling characterized by a decrease in LV chamber size relative to wall thickness in the absence of an increase in LV mass (Bartunek *et al.* 2000).

7. Hypertension induced by ANG II

ANG II is known to play an important role in the physiological regulation of vascular tone and BP and in pathological conditions such as hypertension and heart failure, although the mechanisms by which ANG II chronically exerts its effects remain unclear. ANG II, the final mediator of the RAS, plays a pivotal physiological role in cardiovascular homeostasis. It is a potent vasoconstrictor of the peripheral vasculature and induces growth of smooth muscle cells of blood vessels and in the heart (Itoh *et al.* 1993).

This ANG II infusion rate does not cause immediate increases in systemic BP but it rather leads to a slowly developing hypertension over a period of 6–10 days. ANG-II-induced hypertension produces a presumably baroreflex-mediated sympathoinhibition corresponding to the increased BP, but with the added challenge of increased dietary salt, the sympathetic nervous system does not respond to the increase in pressure with the appropriate inhibition (McBryde *et al.* 2007).

8. Dietetically induced hypertension

It is known that long-term exposure to a special diet (high salt, fat or sugar) results in dietary hypertension in some animals or humans (Navarro-Cid *et al.* 1995; Kang *et al.* 2004; Giani *et al.* 2009).

High-salt intake is able to decrease both plasma levels and urinary excretion of nitrates (Fujiwara *et al.* 2000) and increased superoxide production in both vasculature and kidney blockade by superoxide dismutase (SOD)-enhanced endothelium-dependent relaxation Roberts *et al.* (2000) demonstrated the presence of oxidative stress and inactivation of NO in rats maintained on the high-fat or high-sugar diet, which may contribute to the development of hypertension by enhanced generation of reactive oxygen species (ROS). The reduction in NO availability in the high-fat and high-sugar diet-fed animals was associated with marked salt sensitivity, as evidenced by a significant rise in BP on the high-salt diet (Roberts *et al.* 2003).

Dietary intake of fats and carbohydrate, particularly the intake of simple sugars and the resultant effects of plasma insulin, adipokine and lipid concentrations, may affect cardiomyocyte size and function, especially with chronic hypertension (Sharma *et al.* 2007). High fructose consumption by animals produces a model of the metabolic syndrome with hypertension, hyperlipidaemia and insulin resistance, and this greatly accelerates progression of chronic kidney disease (Gersch *et al.* 2007).

9. Concluding remarks

Animal models can lead to understanding of the interactions of the principal regulatory factors in critical developmental periods of hypertension. Many of these models were developed by using etiologic factors responsible for human hypertension, although the cardiovascular response can be more easily obtained in animals than in human studies. Thus, limitations are found for a direct and simplified application of these results, which suggests that there is no evidence to support that any experimental model of hypertension exactly mimics all the symptoms of the human disease. Furthermore, many researches have shown that variables such as duration of exposure to causal factors and dose, differences in animal species, gender as well as age of the animal at the beginning of exposure, and the technique for BP monitoring greatly differ amongst the studies and may interfere with the results.

In this sense we suggest that the various models should be increasingly investigated, providing subsidies for new findings in the pathogenesis of hypertension, with a rational discussion about the advantages and disadvantages of each experimental model in order to allow the best choice for the study in question.

Acknowledgements

We are grateful to Dr Rinaldo Cardoso dos Santos for his critical reading of the manuscript.

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MS received 21 January 2011; accepted 16 May 2011

*e*Publication: 16 August 2011

Corresponding editor: Ashima Anand