



# ANIMAL MODELS FOR HYPERTENSION RESEARCH

## SHORT REVIEW

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Hypertension is one of the most common diseases in the world and also an important risk factor for heart failure, renal failure and brain stroke. Hypertension is of a multifactorial and polygenic nature, and it is caused by mutual interactions between genetic and environmental factors, therefore its exploration needs experimental models of hypertension: genetic and non-genetic. Genetic models are based on transgenic techniques for the selection of genes which are suspected of being responsible for hypertension. Non-genetic models use selective breeding of animals that possess the demanded phenotype. A combination of genotypic and phenotypic strategies in animal models of hypertension allows them to be used in clinical practice.

**Key words:** animal models of hypertension, hypertension, rats

### INTRODUCTION

Hypertension is one of the most common diseases in the world and also an important risk factor for heart failure, renal failure and brain stroke. Hypertension is of a multifactorial nature and it is caused by mutual interactions between genetic and environmental factors. The pathogenesis of more than 90% cases of this common disease remains unknown. This type of hypertension is often named essential hypertension which may be

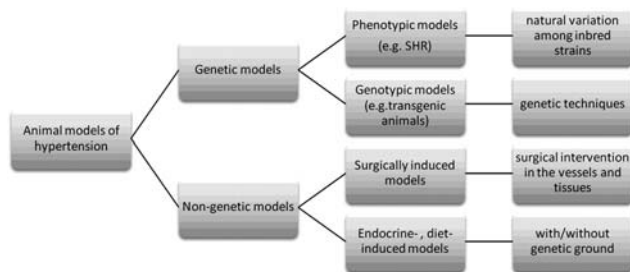
a genetic disorder. It has been shown that blood pressure is a phenotype-dependent parameter and its regulation is associated with the activity of several genes. The genes act indirectly through enzymes, receptors and other tissue mechanisms (CHOBANIAN et al., 2003; MANCIA et al., 2009). The cause of the remaining 10% of hypertension cases is well-known: underlying disease, injury, toxicity and others factors, and they are classified as secondary hypertension. Nevertheless, genetic as well as non-genetic factors play an

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important role in the progression and manifestation of the disease.

Scientific research on the interaction between genetic and environmental factors aims at the identification of early pathogenic mechanisms of hypertension. The hypertension studies require the availability of genetically modified animal models. The best hypertension animal model should be characterized by the hemodynamics that is identical with that of the human cardiovascular system (EUROPEAN SOCIETY OF HYPERTENSION, 2003), and it should also develop adaptive changes like those observed in humans with chronic hypertension. Currently, none of the species meet the above-mentioned requirements of the ideal animal hypertension model, and therefore it is very often the type of the experiment that determines the choice of an appropriate animal model.

Bearing in mind the fact that the development, progression and manifestation of hypertension depends on genetic and environmental factors, scientists use genetic and non-genetic animal models (Fig.1) (GUIDELINES COMMITTEE, 2007; ZANCHETTI, 2009).



**Fig.1.** The main categories of animal models of hypertension (LERMAN et al., 2005)

#### NON-GENETIC ANIMAL MODELS OF HYPERTENSION

In contrast to essential hypertension, secondary hypertension has an underlying and potentially correctable cause. Pathogenesis of secondary hypertension includes such diseases as endocrine disorders, kidney malfunction, e.g. renovascular hypertension induced by ischemia of kidneys and many other well-known disorders. Rarely, it also includes pheochromocytoma, hy-

peraldosteronism (Conn's syndrome), Cushing's syndrome, hyperparathyroidism, acromegaly, hyperthyroidism and hypothyroidism. Moreover, many classes of drugs may induce hypertension. Such drugs include steroids, sympathomimetic amines, immunosuppressive agents, nonsteroidal anti-inflammatory agents and also hormonal contraceptives.

Many useful experimental animal models have been developed and based on non-genetic, secondary factors of hypertension. These models make it possible to examine the influence of chronically persisting hypertension on damage to different organs. In 1934 GOLDBLATT et al. (1934) introduced the first animal model of hypertension. It was a non-genetic model, obtained by surgery. Scientists achieved unilateral renal artery stenosis in dogs by using a special clip on the artery. This model was called the high-resistance hypertension model – 2K1C. Very soon after their achievement such a model was induced in rats (WILSON and BYROM, 1939), rabbits (PICKERING and PRINZMETAL, 1937), pigs (LERMAN et al., 1999), monkeys (PANEK et al., 1991) and also mice (WIESEL et al., 1997). The most successful results were obtained with rats because these animals relatively easily and quickly developed hypertension.

In successive years a modification to the 2K1C model was introduced, consisting in additional contralateral nephrectomy. The model with one kidney and a renal artery clip was called the volume-dependent hypertension model – 1K1C (THURSTON and SWALES, 1976). Both the 2K1C and 1K1C models showed a susceptibility to a high-sodium diet. Depending on the model, the target organ damage was different. In the 1K1C model left ventricles were hypertrophied with normal plasma renin activity (PRA), while in the 2K1C model PRA was elevated but the morphology of the left ventricle was normal (unchanged). In both cases disruption of laminar blood flow and endothelial dysfunction were observed. In 1939 PAGE (see DIAMOND, 2001), by wrapping the kidney in cellophane or silk, developed another model of hypertension. Such a state leads to interstitial renal inflammation, reduction of kidney weight and also to elevation of the RAS and endothelin-1 (ET-1) activity (DIAMOND, 2001; HALL et al., 2003). This model is successfully induced in dogs, cats, rabbits, and monkeys.

Other non-genetic models are characterized by endocrine-induced hypertension. The most popular method is the administration of mineralocorticoids (PITZALIS et al., 2001; BIAN et al., 2005; ULF et al., 2009), especially desoxycorticosterone acetate (DOCA). The DOCA-induced hypertension model in rats and dogs additionally requires partial resection of the renal mass and a high-sodium diet. In this model, during high blood pressure development (increased volume and cardiac output), characteristic organ damage and dysfunctions, such as cardiac hypertrophy, endothelial dysfunction, renal glomerulosclerosis and proteinuria are observed (GHOSH et al., 2004). Hypertension may also be induced by administration of glucocorticosteroids, e.g. dexamethasone (DEXA) (ZHANG et al., 2004). This method is used in rats and mice (HU et al., 2006; FAN et al., 2009; ULF et al., 2009). An increase in blood pressure in this case is probably induced by the renin-angiotensin-aldosterone system (RAAS) activation. However, this method is less efficient than the DOCA model. Chronic infusions of RAS components is another method used to induce high blood pressure. In 1965 McCUBBIN et al. (1965) demonstrated (THOMAS, 2007) that the infusion of angiotensin II results in a slow and gradual increase in blood pressure, probably as a result of increased oxidative stress (SAINZ et al., 2005; ULF et al., 2009).

**High-sodium** and **high-fructose** diets are also used for hypertension induction. Additionally, a high-fructose diet induces both insulin resistance and hypertension in Sprague-Dawley and Wistar - Kyoto (COSENZI et al., 2002) rats, possibly due to down-regulation of insulin receptors and the up-regulation of type 1 angiotensin receptor (AT1). The high-fructose diet also induces hypertriglyceridemia and fatty liver in rats.

#### GENETIC ANIMAL MODELS OF HYPERTENSION

Sequencing of the human and mouse genomes led to the creation of two categories of genetic models, one is based on the phenotype and the other – on the genotype. Phenotypic models are created using the natural genetic variation among inbred strains (SUGIYAMA et al., 2001), while ge-

notypic model creation is based on changes in specific genes. Genetic engineering enabled the isolation of specific genes and thus the determination of their primary sequences. Therefore, it is possible to determine where overexpression or ablation of the specific gene occurs.

**Phenotypic rat model** is the most commonly used genetic model in hypertension researches and it is of great importance for the determination of the polygenic basis of this popular disease. The development of homozygous strains of rats with hypertension is achieved by crossing inbred strains. The breeding of specific animals with the desired phenotype is performed this way. Such breeds of rats have been named the Wistar strain. Homogeneity of different strains is stable by maintaining their specific characteristics for about 20 generations. The same approach was used to develop other models based on Wistar rats, one is named SHR (Spontaneously Hypertensive Rats) and the other – SHRSP (Stroke Prone Rats). These models are used to evaluate blood pressure and cardiovascular diseases (SHR and SHRSP), metabolic diseases, renal disorders, insulin resistance, hypertriglyceridemia, hyperinsulinemia, hypercholesterolemia (SHR), stroke, nephropathy, and osteoporosis (SHRSP) (FORTEPIANI et al., 2003). Another important model obtained using the same technique includes salt-sensitive rats named Dahl and Sabra (DAHL, 1972). From the medical point of view, animal models where other hypertension-related disorders coexist are of particular importance. Such models include rats with a tendency to obesity development, i.e.: Sprague-Dawley (DOBRIAN et al., 2003), Zucker, Wistar-fatty (FRUHBECK, 2004).

**Genotypic Models.** Genetic engineering enabled better understanding of the genetic basis of hypertension pathogenesis (VADOLAS et al., 2005). Direct intervention in the structure of the genome made it possible to obtain two types of animal hypertension models: the transgenic (HABIBI et al., 2008) and knock-out (KASI et al., 2007) models. The transgenic model (with overexpression of the specific gene) was developed by placing the gene responsible for renin synthesis into the rat genome. This gene is named *Ren-2* and is derived from mice. The knock-out model was obtained by eliminating the genes responsible for synthesis of vasoactive substances.

**Antihypertensive agents in different hypertension models.** Current scientific literature suggests that spontaneous hypertensive rats (SHR) are most widely used as a hypertension model. Despite some similarities, other rat models are rarely used due to many important differences between the particular models (PINTO

et al., 1998). In each model animals develop hypertension and cardiac hypertrophy. Nevertheless, only in some models significant changes in the organs, such as heart failure, stroke or renal failure are observed. It is noteworthy that various drugs act differently in different models (Tab. 1). Currently it is thought that effective hypoten-

**TABLE 1.** Activity of antihypertensive drugs in animal models.

Animal models of hypertension	Activity in:				
	hypertension	cardiac hypertrophy	heart failure	proteinuria	endothelial dysfunction
SHR	A +	A +	A +	A +	A +
	B -	B +	B +		C +
	C +	C +	C + ?		D - ?
	D -	D -	E +/-	E +	
	E -			F -	F -
	F +	F -			
DOCA	A -	A -	A -	C +	A -
	B -				
	C +	C +			
	D +	D +			
	E +	E +			
	F +	F -			
2K1C	A +	A +			
	B -	B -			
	C +	C +			
	D - ?				
	E -				
	F +	F -			
TGR mRen2)27 <sup>1</sup>	A +	A +			A +
	B -	B -			B -
	C -	C -			
	F -	F -			F -
Dahl	A +	A +		A +/-	
	B +/-			B -	
	C -	C -		C -	
	D +	D -		D -	D +
	E + ?			E -	
	F +				F +

"1" transgenic model with overexpression of *Ren2* gene

"+" protective effect

"-" no effect

A = ACE inhibitors, B =  $\beta$ -blockers, C = calcium channel blockers, D = diuretics, E = endothelin antagonists, F = arterial vasodilators

sive drugs also protect the target organs against damage. However, there are some divergences. Insufficient number of studies that directly compare all classes of antihypertensive drugs in each animal model make unambiguous interpretation difficult.

As mentioned above, morphological changes in the organs depend probably on rat breeding, genetic factors and even interspecies differences. A multitude of different animal hypertension models enables scientists to choose the one that is most suitable for their specific purposes. Nevertheless, an appropriate approach to the interpretation of the obtained results is necessary. Unfortunately, it is often impossible to relate the results obtained in animal hypertension models to those obtained in humans with hypertension. Moreover, it has been shown that very often the selection of a given model significantly affects the obtained results. Therefore, before starting an experiment, scientists should know the exact specification of a given animal model and then they should consider its relevance to the planned objectives. It seems to be reasonable to select more than one model for the experiment because such an approach makes it possible to obtain more complete and comparable results.

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