Journal of the American Society of Hypertension 3(3) (2009) 158–165

Review Article

Experimental animal models of hypertension

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Manuscript received December 7, 2008 and accepted February 12, 2009

Abstract

Hypertension (HTN) and cardiovascular disease are the most common causes of death in developed countries. The use of experimental animal models of HTN has provided valuable information regarding many aspects of HTN, including etiology, pathophysiology, complications, and treatment. Because the etiology of HTN is heterogeneous, many experimental animal models have been developed to mimic the many facets of human HTN. The choice of animal model will be determined by the research question, monetary limitations, and technical expertise. The categories of models of HTN are: renovascular, renal parenchymal, pharmacologically induced, environmentally induced, and genetic. There are considerable differences between HTN in animals and humans, including differences in homeostatic mechanisms and pathophysiology; therefore, a thorough understanding of the animal models and rigorous analysis is required before extrapolating the finding in animals to humans. J Am Soc Hypertens 2009;3(3):158–165.

Keywords: Renovascular; renal parenchymal; mineralocorticoid; genetic.

Introduction

The difficulty in studying a disease process such as hypertension (HTN) begins with the fact that the etiology of HTN is heterogeneous. HTN can be primary (''essential''), the etiology of which is unclear and thought to be resulting from the interaction of multiple genetic and environmental factors, or secondary to a defined process, such as renal artery stenosis. The pathophysiology of essential HTN is also heterogeneous and varies by age, renin status, sodium dependency, and other characteristics.[1] Therefore, several experimental models have been developed to mimic the many facets of human HTN.

The ideal animal model for HTN research should have human-like cardiovascular anatomy, hemodynamics, and physiology; develop the human HTN characteristics and complications; allow studies in chronic stable HTN; and allow measurement of relevant hemodynamic and biochemical parameters.[2,3] Understandably, no species can consistently meet all these needs, and research design and other constraints usually dictate the choice of the animal models. The aim of this review is to summarize the most widely used animal models of HTN.

The Major Experimental Models of HTN

The most widely used animal models of HTN can be grouped into primary and secondary, based on the etiology of the HTN. Secondary causes are a small percentage of human HTN, and they are represented by models in which the HTN is induced by interventions such as renal artery occlusion. The most common human form, primary HTN, is represented by the genetic models of HTN, such as spontaneously hypertensive rat (SHR).

Renovascular HTN

The pioneering work of Goldblatt[4] led to the development of 1 of the first animal models of HTN. He induced the HTN in dogs by unilateral clamping of the renal artery. This was followed by similar production of HTN in other

This study was supported by the National Institute of Health Grant no. HL73251.

Conflict of interest: none.

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1933-1711/09/$ – see front matter
doi:10.1016/j.jash.2009.02.003

species. These models are classified as 2-kidney, 1-clip (2K-1C), 2-kidney, 2-clip (2K-2C), and 1-kidney, 1-clip (1K-1C) Goldblatt HTN models.

2K-1C Model

In the 2K-1C model, both native kidneys are left intact, but a constricting clip (to resemble a clinical stenosis) is placed on 1 renal artery. In the absence of damage to the contralateral kidney, this model represents a classic renin dependent model, at least in the initial phases.[5] In the rat, 2K-1C HTN is characterized by an initial increase in plasma renin activity (PRA) because of the decreased renal arterial pressure in the clipped kidney, followed by a return to near-normal levels.[6,7] This is followed by a chronic phase of elevated PRA. The PRA in humans with renal artery stenosis tends to follow a similar pattern.[8]

1K-1C Model

In the 1K-1C model, unilateral nephrectomy is followed by placement of a constricting clip on the renal artery of the remaining kidney. This model resembles patients who have only a solitary kidney and a significant renal artery stenosis in that kidney. The initial elevation of blood pressure (BP) in the 1K-1C model is also renin-angiotensin system (RAS) dependent. However, because of the absence of a functioning kidney, no compensatory increase in sodium and water excretion can occur, so the fluid volume is retained. Thus, the chronic 1K-1C model is a volume-dependent model that is less dependent on the RAS, as evidenced by a decrease in PRA and inability of angiotensin-converting enzyme (ACE) blockade to prevent development of chronic HTN.[9,10] This model is particularly useful for studying the role of volume expansion in the development of HTN.

2K-2C Model

This model, in which both renal arteries are constricted, is less often used. It differs relatively little from the 1K-1C model in hemodynamic and neurohumoral features and parallels bilateral renal artery stenosis in humans.

Renal Parenchymal HTN

Reduced Renal Mass Salt-Induced Model

Clinically, the most common secondary cause of HTN is a loss of renal function from any cause.[1] The animal model that most closely approximates this clinical condition is the reduced renal mass model,[11] most commonly studied in the rat and dog. In this model, a renal mass reduction of >85% is required. This is achieved by unilateral nephrectomy followed by surgical removal of two-thirds of the remaining kidney. By itself, this degree of renal mass reduction results in only a slight BP increase compared with sham-operated, normotensive control animals.[12] A further increase in BP is provoked by the administration of excess salt in the drinking water or in the food.

In the reduced renal mass salt-induced model, PRA is low and the HTN is salt-dependent.[12,13] Nevertheless, blockade of the RAS with ACE inhibitors[14] or angiotensin receptor blockers[15] results in a lowering of BP in this model. Explanations of this apparent paradox include the blocking effects of anti-RAS drugs on the tissue RAS, decreased sympathetic nervous system (SNS) activity by the attenuation of the central nervous system (CNS) angiotensin II effects.[16]

Other Renal Models

Although not as commonly used for experimental purposes, there are other renal animal models of experimental HTN, such as renal ischemia induced by microembolization[17] and perinephric fibrosis model (Page HTN) induced by wrapping the kidney in cellophane.[18] Page HTN limits the renal pulsatility and may mimic the intense fibrosis and HTN that occurs in the occasional posttransplant patient.

Pharmacologically Induced HTN

Deoxycorticosterone Acetate-Salt (Mineralocorticoid)–Induced Model

The most common model studied is the mineralocorticoid-salt or deoxycorticosterone acetate (DOCA)-salt model. This model resembles the clinical situation of aldosterone excess. HTN is produced by the unilateral nephrectomy followed by administration of DOCA along with excess salt (usually, 0.9% NaCl drinking water).[19] The Yucatan miniature swine model of DOCA-induced HTN differs from the rodent models in that it involves increased SNS activity,[20] and excess dietary salt is not required for the development of sustained HTN.

This is a low-renin model that is sodium dependent. As in other models, non-sodium–dependent mechanisms have been suggested to play a role in the pathogenesis, including activation of SNS,[21] vasopressin,[22] upregulation of central angiotensin II receptors,[23] endothelin,[24] and oxidative stress.[25]

The primary advantage of this model is that it represents a low-renin volume overload form of HTN, with a different natural history, and a different response to antihypertensive agents[26] when compared with high-renin models such as 2 K-1C. The disadvantages of this model include the need for nephrectomy, large doses of DOCA-salt, and salt ingestion.

Glucocorticoid-Induced Model

The glucocorticoid induced HTN model is produced by the administration of excess glucocorticoids to