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SPONTANEOUSLY HYPERTENSION RAT MODELS - AN OVERVIEW.

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ABSTRACT: Hypertension is the most common cause of mortality in both developed and developmental countries. Experimental animal models of hypertension have become a valuable tool for providing information on etiology, pathophysiology, and complications of the diseases and on the efficacy of various drugs and compounds used in the therapy. Compared to human model, animal model is easily manageable, as compounding effects of dietary and environmental factor can be controlled. Cardiac tissue and blood samples can be taken for thorough experimental and bimolecular review from such animal models. An animal model is often resolute by the research object, as well as financial and technical factors. A complete understanding of animal model used and complete analysis must be validated so that the data can be extrapolated to humans. Animal models of hypertension are invaluable in improving our understanding of cardiovascular diseases and developing new pharmacological therapies. Among this the most studied model is SHR (spontaneous hypertension in rat) model. SHR was established and discovered as a result of the deliberate inbreeding of rats with the greatest blood pressure and the development of a novel technique for monitoring rat blood pressure.

***Index terms*:** Hypertension, SHR model, Pathophysiology, Neurotransmitter, Rat.

INTRODUCTION

Raised blood pressure, also known as hypertension, is a serious medical condition that raises the risk of kidney, heart, and other disorders. Pre-clinical animal models have greatly improved our understanding of disease processes since they allow for the manipulation of many risk factors. Numerous animal models of hypertension exist (Figure 1), but only a handful historically noteworthy model systems have considerably enhanced our understanding of the condition. The Spontaneously Hypertensive Rat (SHR) Model is among these models that is extrem ely popular.[1]

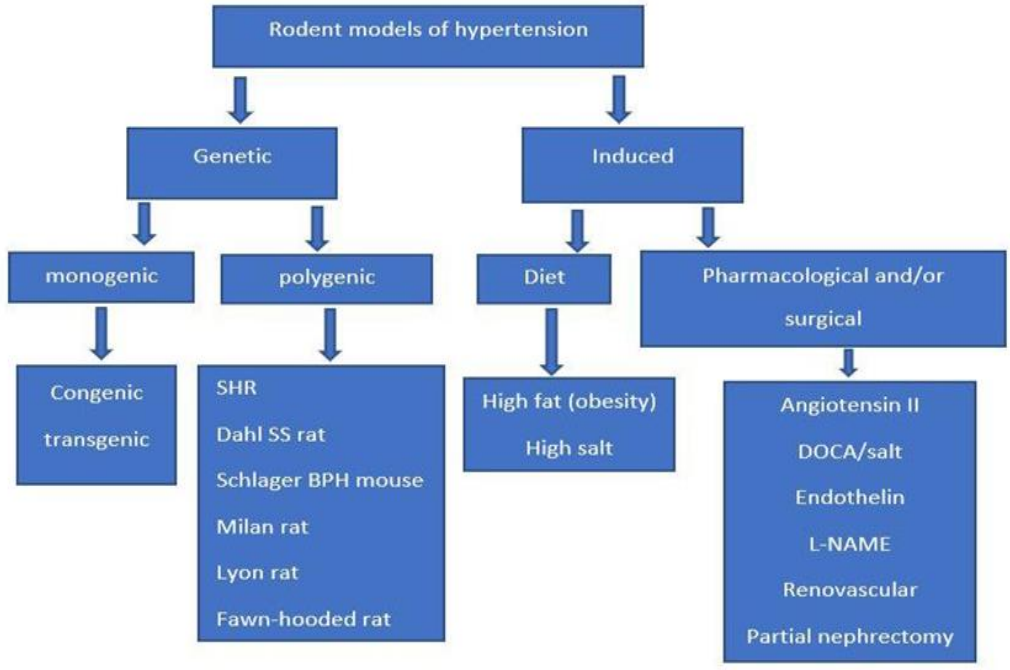


Figure :1. Different types of hypertension model

HISTORY AND DEVELOPMENT OF SHR MODEL

SHR strain was produced by OKAMOTO and AOKI. The SHR is inbred genetic model of experimental hypertension similar to human essential hypertension. The SHR is most commonly used model to study hypertension. This model is generally related to Wistar-Kyoto (WKY) rat, widely accepted that the WKY is the most appropriate control for studies using the SHR. However, there is some concern about genetic differences in WKY & SHR rats [2].

The creation of a novel tool for measuring rat blood pressure and the deliberate inbreeding of rats with the highest BP led to the establishment and discovery of SHR (Aoki SHR). A similar device for measuring rats' blood pressure was created in 1959. A male SHR was found while measuring the BP of approximately ten Wistar rats from Kyoto University's Animal Centre to check the new tool's accuracy. To produce SHR offspring, a female rat was reared with a male SHR. Brother-sister inbreeding resulted in rats with spontaneous hypertension, and the rats with the highest blood pressure were chosen among the progeny. All of the tertiary and succeeding groups' offspring developed hypertension. The development and establishment of the SHR strain. From the progeny, the rats with the highest blood pressure were chosen, and brother-sister inbreeding produced rats with spontaneous hypertension. The tertiary and succeeding groups' progeny all developed hypertension. By 1963, the SHR strain had grown significantly and been established [3].

PATHOPHYSIOLOGY

Hypertensive development begins around 5 to 6 weeks of age, reaching systolic pressures between 180 and 200 MmHg in the adult age phase. Starting between 40 and 50 weeks, SHR develops characteristics of cardiovascular disease, such as cardiac hypertrophy and vascular.

The kidney has some relationship to hypertensive development. A normotensive Wistar rat receiving a kidney transplant from a SHR experiences a rise in blood pressure. On the other hand, giving a Wistar kidney to a SHR rats returns their blood pressure to normal [4].

MECHANISMS INVOLVED IN THE DEVELOPMENT OF SHR MODEL

Neurogenic mechanism

Studies on the Kyoto (SHR) and the New Zealand (GHR) strains of genetically predisposed hypertensive rats have shown that in the SHR neurogenic influences, primarily of higher central origin, play an important role in the initiation of hypertension. Studies on human essential hypertension indicate that this may also be true for man, although it is far from being the sole explanation.

In the SHR model, environmental factors like stress and salt loading speed up hypertension,This hypertension develops in large part due to the autonomic nervous system. The brainstem's noradrenergic inhibitory mechanisms for controlling blood pressure may not be enough, causing peripheral vasomotor tone to initially increase and lead to labile hypertension .The increased noradrenalin level or dopamine-beta-hydroxylase activity in the blood further supported the conclusion that the neural factor was primarily responsible for the development or early stage of hypertension.

Vascular and cardiac hypertrophy

Arterial cell hypertrophy and/or hyperplasia have been implicated as playing a central role in the vascular abnormalities noted in (SHR). The accelerated protein metabolism of the vascular wall serves as a relay for the initial neurogenic stimuli and subsequent involvement of nonneurogenic variables. Experimental evidence demonstrating the influence of neural innervation on the elevated lysine incorporation into the non-collagenous protein of the mesenteric arteries found in the prehypertensive SHR. Hypertension was stabilised by the peripheral vascular resistance's structural component.[6] Regardless of the nature of the initiating factors, these secondary but rapidly established changes occur and greatly contribute to the maintenance and acceleration of the hypertensive state. The vascular changes can even be regarded as a common denominator for chronic hypertension and serve as an element which, in fact, reinforces the initiating mechanisms. An increased wall thickness of the resistance vessels implies a vascular hyper reactivity to constricting influences which, in turn, rapidly brings the blood pressure. Moreover, impaired endothelial function and oxidative stress appears 7to be a cause and/or consequence of hypertrophy development in this animal model [5].

RENAL DYSFUNCTION

A common pathophysiological feature shared by models of renovascular hypertension is the motorist of hypertension and target-organ damage a reduction in blood flow to the kidneys, resulting in declined perfusion pressure and starting the RAAS, leading to vasoconstriction and salt and water retention, Systemic hypertension induces progressive endothelial dysfunction, stretch, and organ damage, whereas long-term reduction of blood flow to the kidneys leads to tissue ischemia and subsequent release of hypoxia-stimulated factors and oxidative stress that trigger inflammation. These processes in turn induce microvascular remodelling, fibrosis, and loss of renal function, which likely play a dual role by both maintaining hypertension and promoting target-organ injury. Blockade of the RAAS with angiotensin-converting enzyme inhibition normalizes BP in both young male and female SHRs. [6,7].

INCREASED PLATELET LIPOXYGENASE

Hypertension in SHR is linked to improve production rate of platelet 12-HETE. Acute BP drop reached during lipoxygenase inhibition but not by angiotensin converting enzyme inhibition leads to a attendant reduction in the manufacture of platelet 12-HETE. We venture that since rat arterial tissue produces 12-HETE, enlarged 12-lipoxygenase activity in SHR may contribute to the maintenance of elevated arterial pressure in SHR [8].

THE GENOME SEQUENCE OF THE SHR

Genes that were exaggerated by major changes in their coding sequence were vastly enriched for genes related to transport, ion-transport and plasma membrane localization, providing intuitions into the likely molecular and cellular basis of hypertension to the SHR strain. Genes that were affected by major alterations in their coding sequence were highly enriched for genes related to ion transport, transport, and plasma membrane localization, providing insights into the likely molecular and cellular basis of hypertension and other phenotypes specific to the SHR strain. This near complete catalog of genomic differences between two extensively studied rat strains provides the starting point for complete elucidation, at the molecular level, of the physiological and pathophysiological phenotypic differences between individuals from these strains. *Cacnala* gene, which encodes the voltage-dependent $Ca_v2.1$ (α1A), P/Q-type Ca^{2+} channel. The SHR gene *Kcnj1*, which encodes the inwardly rectifying potassium channel, contains three different single-base deletions in its coding region. *Echdc2* gene, whose product catalyses' the second step in the physiologically important beta-oxidation pathway of fatty acid metabolism [9].

APPLICATIONS, BENEFITS AND LIMITATIONS

Despite the fact that this model was created a long time ago, it is still extensively employed due to its benefits. In 2020, greater SHR model utilisation was shown by statistical analysis of the data collected (Figure:2).

Applications:

1. SHRs have been used to determine the genes responsible for hypertension
2. To evaluate complications of target organs
3. To study the transition from compensated hypertrophy to failure of the Heart.
4. The screening potential pharmacological agents for treatment.

Benefits:

1. Wide availability
2. Low maintenance cost
3. Short generation time means less time consuming
4. Easy housing & handling
5. Does not require surgical procedures or pharmacological intervention.

Limitations

Small body size limits frequent blood collection and increases difficulty of small arteries

1. Highly inbreed, homogeneous and mostly monogenic.
2. Limited available & expensive
3. Require sophisticated maintenance

FURTHER DEVELOPMENTS IN SHR MODEL:

1.The stroke prone SHR

Stroke prone SHR (SHR-SP) is a more expansion of SHR that has even advanced blood pressure than SHR and a solid propensity to perish from stroke [10].

2.Attention Deficit Hyperactivity Disorder

The (SHR) Spontaneously Hypertensive Rat is similarly used as a model of attention-deficit hyperactivity disorder. Many studies have shown that the SHR shows the full range of ADHD-like symptoms, including increased motor activity, decreased & impulsiveness decreased attention. It also shows biological features that similar those seen in ADHD patients such as smaller brains and altered activity in dopaminergic, norepinephrine and ionic/energetic exchange genes. SHR is strong signal of its validity as a model of ADHD [11,12].

3.Model for anxiety

Spontaneously hypertensive rats show behavioural differences. These changes include reduced anxiety-like behaviour in SHR. while improved performance and behavioural deficits have been reported in learning/memory studies. The modifications in anxiety levels can modify retention performance in animal models of memory. SHR shows lesser anxiety levels.

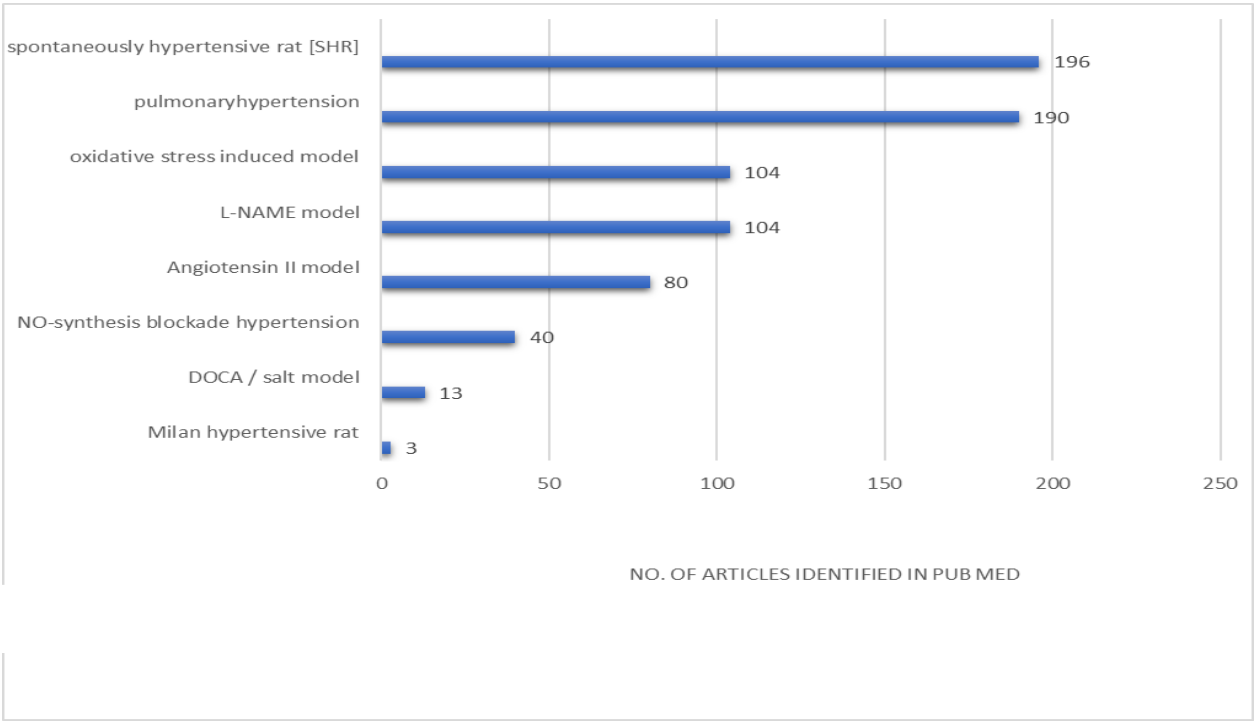
4.Cognitive impairment

The SHR has been used to change models in the [CNS] related with cognitive-related disorders. Current animal and human studies indicate a probable connection between insulin resistance, cognitive deficits and hypertension. By Evolving feature of 2-way shuttle box evasion in the spontaneously hypertensive rat and normotensive rat. The combined influence of hypertension and aging had an additive detrimental effect on cognitive functions. Notwithstanding these deficiencies in learning and memory, SHR have seldom been used as a model in the screening of drugs with therapeutic potential for treatment of disorders of cognitive processes [13].

5.SHR Model for Evaluating Kidney Diseases

The hypertensive damage in the SHR is pressure-dependent and shows how initial vascular damage leads to a loss of autoregulation and arterial hypertrophy in the juxtamedullary cortex while the outer cortical structures are relatively protected. Progressive arteriolar media hypertrophy then leads to the collapse of some glomeruli followed by tubular atrophy. The reduced glomerular filtration, thus, leads to compensatory hyperfiltration in another population of glomeruli which develop proteinuria and glomerulosclerosis [14].

Figure 2: different hypertensive models used in preclinical research in year 2020.



CONCLUSION:

The SHR model is produced in an easy and effective manner. A genetic inbreed model of experimental hypertension is the SHR. Multiple genes are involved in causing the blood pressure elevation in the SHR, which makes it a suitable model for researching essential hypertension in humans. The stability of the hypertensive state and the repeatability of trial effects make the hypertensive rat an acceptable model for studies on hypertension. It is a generally effective paradigm for evaluating antihypertensive drugs. Additionally, the spontaneously hypertensive rat serves as a model for stroke, anxiety, ADHD, and renal dysfunction. Crosses between the Okamoto strain and the Sprague-Dawley rat have been shown to have mutations that cause obesity, hyperlipidaemia, and early atherosclerosis.
This SHR models are effective in various research, but they are most beneficial in certain aspects (primarily those related to hypertension) of memory problems, especially those in which cholinergic function is compromised. The creation of mutant Okamoto strain rats with haemorrhages, myocardial infarctions, and brain relaxation would enable the testing of particular medicinal medicines with less side effects.

REFERENCES:

1. Hypertension Key Facts https://www. who. int/news-room/fact-sheets/detail/hypertension.

2.Franklin T. B., Russig H., Weiss I. C., et al. Epigenetic transmission of the impact of earlystress across generations. Biological Psychiatry. 2010;68(5):408–415. doi: 10.1016/j.biopsych.2010.05.036. - DOI – PubMed.

3. Okamoto K and Aoki K (1963) Development of a strain of spontaneously hypertensive rats. Jpn Circ J 27:282–293.

4.(Kawabe K, Watanabe TX, Shiono K, Sokabe H (November 1978). "Influence on blood pressure of renal isografts between spontaneously hypertensive and normotensive rats, utilizing the F1 hybrids". Japanese Heart Journal. 19(6): 886–94. doi:10.1536/ihj.19.886. PMID 374777.)

5.Dommett EJ, Rostron CL (November 2011). "Abnormal air righting behaviour in the spontaneously hypertensive rat model of ADHD". Experimental Brain Research. 215 (1): 45–52. doi:10.1007/s00221-011-2869-7. PMID 21931982. S2CID 18981985.

6.Page IH. A method for producing persistent hypertension by cellophane. Science. 1939; 89:273–274. [PubMed] [Google Scholar]

7. DeForrest JM, Scalese RJ, Oehl RS, Waldron TL, Mitch S, Brittain RJ, Free CA, Asaad M, Burkett D. Perinephritis hypertension in Macaca fascicularis (cynomolgus monkey): studies of the renin-angiotensin-aldosterone axis and renal hemodynamic function. J Hypertens. 1989; 7:763–767. [PubMed] [Google Scholar]

8.Kriska T, Cepura C, Magier D, Siangjong L, Gauthier KM, Campbell WB. Am J Physiol Heart Circ Physiol. 2012 Jun 1;302(11):H2428-38. doi: 10.1152/ajpheart.01120.2011. E pub 2012 Mar 30. PMID : 22467300 Free PMC article.

9. Agnihotri G, Liu HW 2003. Enoyl-CoA hydratase. Reaction, mechanism, and inhibition. Bioorg Med Chem 11: 9–20 [PubMed] [Google Scholar]re back to supra normal levels as soon as therapy.

10.Churchill PC, Churchill MC, Griffin KA, et al. (May 2002). "Increased genetic susceptibility to renal damage in the stroke-prone spontaneously hypertensive rat". Kidney International. 61 (5): 1794–800. doi:10.1046/j.1523-1755.2002.00321x. PMID 11967029.

11. Berger DF, Sagvolden T: Sex differences in operant discrimination behaviour in an animal model of attention-deficit hyperactivity disorder. Behav Brain Res. 1998, 94: 73-82. 10.1016/S0166-4328(97)00171-X.

12. Sagvolden T, Johansen E, Woien G, Walaas S, Storm-Mathisen J, Bergersen L, Hvalby O, Jensen V, Aase H, Russell V: The spontaneously hypertensive rat model of ADHD - The importance of selecting the appropriate reference strain. Neuropharmacology. 2009, 57 (7-8): 619-26. 10.1016/j.neuropharm.2009.08.004.

13. Mondon CE, Reaven GM. Evidence of abnormalities of insulin metabolism in rats with spontaneous hypertension. Metabolism. 1988;37(4):303–5. doi:10.1016/0026-0495(88)90127-8.

14. Leh S, Hultström M, Rosenberger C, Iversen BM.Virchows Arch. 2011 Jul;459(1):99-108. doi: 10.1007/s00428-011-1100-3. E pub 2011 Jun 10. PMID: 21660521