International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2024.1350.1364

Review Article
Evaluation of Various Experimental Models in Antihypertensive Drug Development: Recent Update

[1]Sheryar Afzal, [2]Ali Attiq, [3,4]Yuan Seng Wu, [1,5]Ahmed Omer Alameen, [1]Ibrahim Albokhadaim, [1,6]Mahmoud Kandeel, [1]Samir Alhojaily, [1,7]Yassir Ali Almofti and [1,8]Saad Shousha

[1]Department of Biomedical Science, College of Veterinary Medicine, King Faisal University, Saudi Arabia
[2]Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Gelugor 11800, Penang, Malaysia
[3]Department of Medical Education, School of Medical and Life Sciences, Sunway University, Subang Jaya 47500, Selangor, Malaysia
[4]Sunway Microbiome Centre, School of Medical and Life Sciences, Sunway University, Subang Jaya 47500, Selangor, Malaysia
[5]Department of Physiology, Faculty of Veterinary Medicine, University of Khartoum, 13314, Shambat, Sudan
[6]Department of Pharmacology, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh 33516, Egypt
[7]Department of Biochemistry, Faculty of Veterinary Medicine, University of Bahri, Khartoum, Sudan
[8]Department of Physiology, Faculty of Veterinary Medicine, Benha University, Benha 13736, Egypt

Abstract

Hypertension is either primary or secondary hypertension. One of the main causes of cardiovascular disease is hypertension, as secondary hypertension brings illnesses, including kidney disease, cardiac disease, endocrine dysfunction and other underlying medical disorders. Several animal models are being used to investigate the pathophysiology and therapies of hypertension. The major goal of the review is to elaborate on the various experimental animal models used for investigating, understanding hypertension and studying therapies for hypertension. Currently, the most often animals used to study hypertension are rat's sensitive to Dahl salt and rats with hypertension caused by Ang II, DOCA salt rats, L-NAME-induced hypertensive rats, transgenic rats and fructose fed/fructose-induced hypertensive rats. In conclusion, the animal models used in study of development of hypertension are considered as splendid tool for studying the pathophysiology of hypertension. Animal models are also used as first approach to investigate a potential new therapy and to evaluate the existed drug. Despite the fact that the animal models are distinctive from the human and often characterized by some limitations such as animal size, cost and availability. The researchers are still rely on animal models, as they can be readily tested, autopsied and biopsied easily. The genetic and environmental background of animal models are already known. However, all researchers must obey the ethical limits when using animal models in an experiment. The use of animal model is only allowed when they are necessary and prevent causing pain, distress and lasting harm.

Key words: Hypertension, DOCA models, Dahl sensitive models, renal models, hypertensive rats

Citation: Afzal, S., A. Attiq, Y.S. Wu, A.O. Alameen and I. Albokhadaim *et al.*, 2024. Evaluation of various experimental models in antihypertensive drug development: Recent update. Int. J. Pharmacol., 19: 1350-1364.

Corresponding Author: Sheryar Afzal, Department of Biomedical Science, College of Veterinary Medicine, King Faisal University, Saudi Arabia

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hypertension is a common chronic condition that can raise the risk and severity of Cardiovascular Disease (CVD)-related death[1]. High sodium diets, inadequate potassium intake, obesity, age and stress are risk factors for primary hypertension; nevertheless, these are not the main causes of hypertension[2]. Secondary hypertension, portal hypertension, pulmonary hypertension, malignant hypertension and other kinds of hypertension exist in addition to primary hypertension. Although they only account for a small percentage of hypertension instances, they nonetheless account for many cases when compared to other disorders. Although genetic inheritance of hypertension is extremely rare in the population, it does help us understand the importance of blood pressure-regulating mechanisms in the body. Over the past 20 years, several scientific studies on such unusual subtypes of hypertension have been conducted and monogenic causes of hypertension have been revealed as a result of these studies. Somatic mutations in primary aldosteronism, as well as mutations in the APOLI genes, placental growth factor and soluble fms-like tyrosine kinase-1 caused placental insufficiency, which resulted in hypertension in pregnancy[2]. Animal models were used/developed as like hypertensive response found in people to study and understand the pathophysiology of hypertension as and also to develop therapeutics for hypertension[3]. These models help researchers to understand the process, progress and causes of hypertension and also to analyze potential antihypertensive drugs. These models were helpful in studying hypertension in humans which includes excessive salt intake, hyper-reaction of RAAS (renin-angiotensin-aldosterone system) and genes flow through hereditary[4].

The pathogenesis of primary hypertension is studied using spontaneously hypertensive rats (SHR), Dahl salt-sensitive, etc. while the underlying mechanisms of primary hypertension are studied using transgenic models and other molecular models such as gene knockout strains, consomic and congenic strains. Pharmacological models such as Deoxycorticosterone acetate salt (DOCA-salt) model, Angiotensin II-induced hypertensive model (Ang II rat), etc., are used for studies of pharmacologically induced hypertension. For the purpose of studying hypertension brought on by renal illnesses, renal models such as the 2 Kidneys-1 Clip Hypertension model (2K-1C), the 1 Kidney-1 Clip Hypertension model (1K-1C) and the 2 Kidney-2 Clip Hypertension model (2K-2C) have been developed and used. Animal models for stress, environment, cold temperature and diet-induced hypertension are also introduced to the research on hypertension[5].

The main objective was to abridge the existing information on animal models that have been developed to study and understand the mechanism of hypertension and to develop therapeutic interventions for hypertension. This study also aims to review the utilities of different types of experimental animals. Several animal models were used, as shown in Fig. 1.

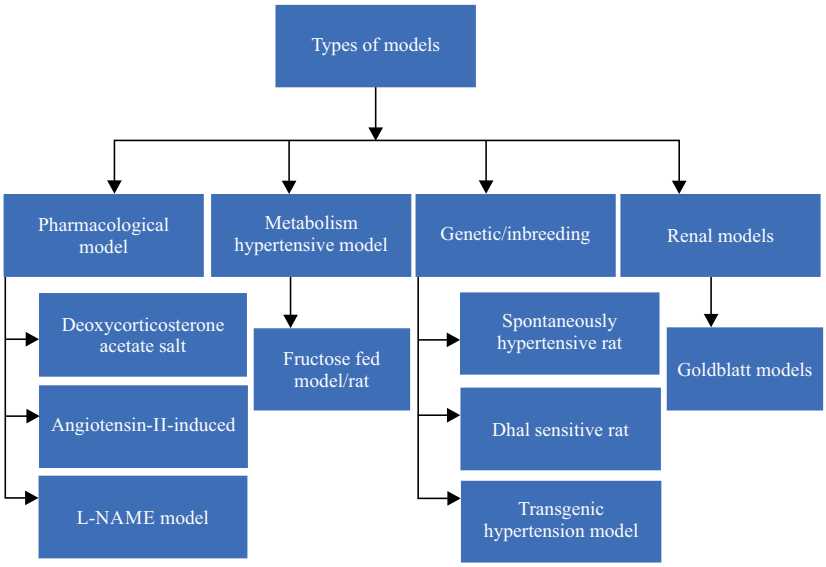

Fig. 1: Types of animal models used for hypertension studies

Table 1: DOCA salt hypertensive models

Type of animal model and objective	Study period	Outcome	References
Deoxycorticosterone acetate salt (DOCA-salt) rat for investigation of angiotensin-1-7 and its antihypertensive action	21 days	Salt was given as angiotensin-converting enzyme inhibitors, baro-reflex regulation of heart rate was enhanced (1-7) DOCA-salt rats given Ang-treatment showed a significant reduction in blood pressure (1-7)	Guimaraes *et al.*[82]
DOCA-salt rat to find the role of renal nerve in hypertension emergence	2 months	DOCA-salt animals with renal denervation had reduced mean arterial pressure to 50%	Jacob *et al.*[83]
DOCA-salt rat for studying the role of sympathetic nervous system in hypertension	21 days	Mean arterial pressure was significantly increased than normotensive rats	Kandlikar *et al.*[6]
DOCA-salt female rat to study the role of AT2-R angiotensin system in prevention of hypertension	4 weeks	Male rats were not affected by AT2-R antagonist injections into the Intra-cerebroventricular, where as female rats saw a substantial increase in DOCA/salt pressor effects	Dai *et al.*[84]
DOCA-salt rat for understanding the antihypertensive effects of mycophenolate mofetil	4 weeks	After 4 weeks of therapy, DOCA-salt animals' mean arterial pressure was significantly lower because MMF medication inhibited the rise in blood pressure starting on day 11 of the experiment	Moes *et al.*[85]

Pharmacological model types

Deoxycorticosterone acetate salt (DOCA-salt) model: One of the most often used experimental animal models is Deoxycorticosterone acetate (DOCA) salt animals for the investigation of pharmacologically induced hypertension[6]. High dose of DOCA (300 to 1000 mg/kg) are given to the animal model, mostly rat models followed with 0.6 to 1% of Sodium Chloride (NaCl) through drinking water to induce high reabsorption of sodium and water by kidney resulting in hypervolemia. It is usually coupled with reduction of renal mass by surgery such as uninephrectomy in order to increase the onset of DOCA-induced hypertension[7]. These DOCA-salt models are being used to study the two major pathways 1. Renin-angiotensin system (RAS) and 2. Sympathetic nervous system, which is critical in the pathogenesis of secondary hypertension. In most cases, an overactive sympathetic nervous system and an imbalance in the renin-angiotensin system are responsible for the induction of hypertension, according to numerous human and animal research. The DOCA-induced hypertension is a volume overloaded hypertension with low renin.

This model helps us understand sodium (salt) function as hypertension advances linked with hypervolemia and hyperaldosteronism[4]. There are limitations with these models as they are not suitable for chronic studies as severe hypertension and hypertrophy is very rapid. The dose requirement of the DOCA used to induce hypertension and hypertrophy is very high, surgical removal of renal mass is required and the ingestion of large amounts of sodium chloride (salt) required, are also considered as limitations of this model[7]. The uses and studies done using DOCA models were listed in Table 1.

Angiotensin-II-induced hypertensive model: Peripheral blood vessel vasoconstrictor, blood pressure regulator and vascular tone, Angiotensin II (Ang II) promotes the growth of vascular and blood vessels smooth muscle cells and helps in physiology of cardiovascular homeostasis and a final mediator in renin-angiotensin system (RAS). It's known to play a role in pathological disorders like heart failure and hypertension[8], diabetic complications[9] and oxidative stress[10]. Angiotensin II induces hypertension in a slow manner in 6 to 10 days. Baroreflex-mediated sympatho inhibition is created after Ang II-induced hypertension develops to prevent the sympathetic nervous system from responding to high BP[11].

Epidermal growth: The epidermal growth factor receptor antisense (EGFR-AS) was examined in rats given Ang II to induce hypertension and ascertain its impact on hypertension[12]. The role of soluble epoxide hydrolase (SEH) in Ang II-induced hypertension development, while inhibition of SEH partially inhibits the effect of Ang II[13]. According to Sarr *et al.*[14], in Ang II-induced hypertensive rats, red wine polyphenols prevent vascular oxidative stress by inhibiting the production of NADPH oxidase, hence limiting the development of hypertension and endothelial dysfunction. The Ang II induced hypertension can be prevented by attenuation of pro-inflammatory cytokines and overexpression of ACE2 in the hypothalamic paraventricular[15]. The effectiveness of brain TNF inhibition is in attenuating the development of Ang II induced hypertension was examined with the use of Ang II induced hypertensive rats[16]. Additionally, a study was conducted on the Ang II-induced hypertensive rats to ascertain the involvement of collecting duct renin in blood pressure[17]. The effect of blocking of central Melanocortin 3 and 4 Receptors (MC3/4R) in attenuating development of hypertension in Ang II rats was determined and the result showed that blocking of central MC3/4R does not attenuate development of hypertension in Ang II rats[18].

Table 2: Ang II hypertensive models

Type of animal model	Study period	Outcome	References
Ang II induced hypertensive rats for examining Na^+/H^+ Exchanger 3 (NHE3) in the proximal tubule	14 days	Blood pressure in rats lacking the proximal tubule-specific Na^+/H^+ exchanger 3 significantly decreased	Li *et al.*[20]
Ang II induced hypertensive rats to analyze RAAS on maternal gestational hypertension and pro-inflammatory cytokines in adult offspring	2 weeks	Angiotensin-converting enzyme inhibitor captopril or renal denervation effectively lowered blood pressure increases in hypertensive rats pups	Xue *et al.*[19]
Nitric oxide synthase inhibitor rat (L-NAME) and Ang II induced hypertensive rats to determine the blocking of central MC3/4R	2 months	Inhibition of MC3/4R considerably lowered blood pressure in L-NAME rats but had no effect on Ang II rats	da Silva *et al.*[18]
Ang II induced hypertensive rats to analyze epoxide hydrolase (SEH) in hypertension	2 weeks	Rats that were made hypertensive by Ang II had their blood pressure dramatically lowered by AUDA (a SEH inhibitor)	Jung *et al.*[13]

Renal denervation and angiotensin-converting enzyme inhibitor attenuate the Ang II-induced hypertension in rat offspring caused by maternal gestational hypertension[19]. The antihypertensive effect of knockout of Na^+/H^+ exchanger 3 (NHE3) in the proximal tubule was examined in Ang II-induced hypertensive rats as animal model[20].

There are some advantages of this model. First, Angiotensin II-induced hypertension that occurred in this model is like that in human body, thus this model is suitable for studying underlying factors that induce the Ang II-induced hypertension. It is a great model for examining the *in vivo* functions of angiotensin receptors and the signaling cascades that follow. Second, the short-term intravenous infusion of Ang II combined with chronic subcutaneous administration produces a comprehensive profile of protein vascular and renal function when renin-angiotensin-aldosterone system (RAAS) is activated[2]. Third, the preparation of Ang II-induced hypertensive rats is very simple as it is done by infusion of Ang II with desired concentration and no specific and complicated technique is needed. However, this model is only limited to the study of Ang II-induced hypertension. Various Ang II models used in hypertension studies were shown in Table 2.

Nitric oxide synthase inhibitor (NOS inhibitor-L-NAME model): Nitric oxide (NO), a chemical which induces vasodilation and helps in reducing resistance in vascular system and helps in maintaining a healthy blood pressure[21]. A NOS inhibitor, such as NG-Nitro-L-Arginine Methyl Ester (L-NAME), reduces the production of nitric oxide, which increases the development of hypertension by vasoconstriction[22]. With this idea, L-NAME-induced hypertensive model was proposed and developed by Paulis *et al.*[23]. This model was developed by long term oral administration of NG-Nitro-L-Arginine Methyl Ester (L-NAME). It promoted marked increase of blood pressure associated with renal injury as it also promotes renal vasoconstriction[24]. Low dose of L-NAME produces volume-dependent hypertension due to renal constriction while a high dose of L-NAME promotes volume-and salt-independent hypertension caused by systemic[25]. There are advantages and limitations that need to be considered for the use of L-NAME model. Preparation of this model is simple and reproducible and promotes development of systemic and severe hypertension. It can be utilized to investigate the damage to target organs in hypertension. However, L-NAME may contribute to some processes aside from NOS inhibition and those processes remain unclear. Furthermore, the emergence of hypertension in this particular model is quick, usually within a few hrs of L-NAME infusion; in contrast, human hypertension development is delayed and occurs after several years[2]. Consequently, it is unsuitable for researching primary hypertension. Various L-NAME models for hypertension studies were tabulated in Table 3.

Metabolism hypertensive model

Fructose-fed model/rat (FFR): The fructose-fed rat serves as an animal model of hypertension and displays several metabolic syndrome symptoms[26] (Table 4). When given a fructose-rich diet, the rat developed hypertension, insulin resistance and even hyperinsulinemia[27]. Numerous studies have shown an increase in systolic blood pressure in laboratory rats after substitution of starch content with fructose in their diets. Increase in mean arterial pressure was also observed in 4-8 weeks. The fructose-fed induced hypertension is concentration-and time-dependent and the effect is maintained up to 12 weeks[28]. However, the chronic effect of fructose feeding is infatuated as the hypertensive effect of fructose is not maintained after 40 weeks of fructose feeding[26,28]. Since there is no weight gain during the fructose treatment in rats during treatment period, this rat model is suitable for reviewing the relationship between hypertension and metabolic impairment without contribution of obesity and genetic factor.

Table 3: L-NAME hypertensive models

L-NAME-induced hypertensive rats uses	Study period	Outcome	References
Examining the antihypertensive effects of *Cinnamomum zeylanicum*	4 weeks	When MECZ was administered both acutely and continuously to hypertensive rats induced by L-NAME, a significant reduction in blood pressure was seen. Additionally, MECZ stopped the loss of NO tissue concentration	Nyadjeu *et al.*[86]
Find role of Ang-(1-7) as antihypertensive agent	4 weeks	In L-NAME-treated rats, captopril reduced the rise in blood pressure, but captopril combined with Ang-(1-7) totally reversed the L-NAME-induced rise in blood pressure	Benter *et al.*[87]
Analyze the anti-hypertensive effects of vanillic acid (VA)	30 days	VA treatment brought the blood pressure levels of the L-NAME-induced hypertensive rats back to baseline	Kumar *et al.*[88]
Study the effect of *Lagenaria siceraria* fruit in L-NAME against hypertension	28 days	Systolic blood pressures were increased by L-NAME. In both drug treated groups systolic and diastolic blood pressures were reduced significantly compared to L-NAME. In L-NAME group significantly elevated cholesterol, which was reduced by LS treatment. In L-NAME group inflammation and necrosis was present in heart whereas there was no change in myocardium of LS and L-arginine treated rats	Mali *et al.*[89]

Table 4: Fructose fed rats models

Fructose fed rats (FFRs) and it uses	Study period	Outcome	References
Analyze contribution of thromboxane A2 in hypertension	6 weeks	At the end of drug treatment, blood and aorta were collected from each animal. Plasma Thromboxane B2 (TXB2), a stable TXA2 metabolite, increased significantly in FHR and was reduced to control level by both chronic bosentan and dazmegrel treatment. Protein expression of COX2 was elevated significantly in FHR aortas and treatment with bosentan and dazmegrel corrected these changes	Jiang *et al.*[90]
Investigate whether adding taurine supplements to your exercise routine can lower your blood pressure and boost your ability to exercise	4 weeks	Taurine supplementation and exercise (FET) group's elevated blood pressure was dramatically lowered and their ability to be active was significantly increased	Rahman *et al.*[91]
In hypertension rats caused by fructose, examine the anti-hypertensive effects of morin	7 weeks	After receiving morin, fructose-induced hypertension rats showed a decrease in systolic blood pressure	Kang *et al.*[92]
Look into the possibility of using human tissue kallikrein in gene therapy to treat fructose-induced	40 days	After receiving treatment with human tissue kallikrein, fructose-induced hypertension rats' systolic blood pressure and serum hypertension in FFRs insulin levels returned to normal	Zhao *et al.*[93]

Genetic/inbreeding models

Spontaneously hypertensive rat (SHR): An animal model that has been used extensively is the spontaneously hypertensive rat (SHR) genetically engineered to become hypertensive. The first spontaneously hypertensive rat was inbred by Okamoto and Aoki from Wistar rats with highest blood pressure. While 4 to 6 weeks are required for these rats to develop hypertension. The development of hypertension is totally unaffected by other factors that can cause hypertension such as high sodium diet[29]. The development of hypertension is affected by environmental factors. Given that the pathophysiology of this model is comparable to that of essential hypertension in the human body, it is significant for the research of essential hypertension. Higher cardiac output was associated with normal peripheral resistance in the early phases of hypertension in SHRs, according to *in vivo* observations. In SHRs, as their hypertension advances, the cardiac output is eventually returned to normal level, but the total peripheral resistance is increased due to blood vessel hypertrophy[30] and gradually, the structural alteration of heart with cardiac hypertrophy is developed by SHRs with advanced progression of hypertension[31].

There were several studies conducted by using this animal model. This model was used to assess the efficacy of alamandine in lowering hypertension[32]. By using SHRs model, the effect of lecithin derived from ω-3 PUFA fortified eggs on the development of hypertension was evaluated[33]. Over-expression of guanine nucleotide binding protein Gi-alpha-2 was determined to be accountable for the emergence of hypertension in hypertensive rats[34,35]. The effect of acupuncture on development of hypertension was examined by using spontaneously hypertensive rats as the animal model[36]. The anti-hypertensive effect of flavonoid quercetin was also examined with the use of spontaneously hypertensive rats as the animal model[37].

Tetrahydrobiopterin showed its anti-hypertensive effect in spontaneously hypertensive rats[38]. It was discovered that carotid body input contributes significantly to the onset and maintenance of hypertension by studying the involvement of the carotid body in the onset of hypertension in rats with

Table 5: Spontaneously hypertensive rats models

Spontaneously hypertensive rats and their uses	Study period	Outcome	References
Determine alamandine role in reducing hypertension	6 weeks	Systolic, diastolic and mean arterial pressure in SHRs markedly decrease in 2 to 6 weeks after alamandine infusion.	Liu *et al.*[32]
Analyze the effects of lecithin derived from eggs fortified with -3 PUFA on the emergence of hypertension in rats who already have hypertension on their own	12 weeks	Lecithin treatment resulted in lower blood pressure in spontaneously hypertensive rats than in the control group. (157/104 mmHg versus 178/121 mmHg)	Nowacki *et al.*[33]
Determine how the guanine nucleotide binding proteins Gi-alpha-2 and Gi-alpha-3 contribute to the emergence of hypertension	9 weeks	Gi-alpha-2 protein knockdown prevented hypertension from developing in SHRs, while Gi-alpha3 protein knockdown did not	El-Basyuni *et al.*[34]
Find out which genes in SHRs and SHR-SP contribute to the onset and progression of hypertension	3 weeks	Between SHR-SP rats and Wistar-Kyoto rats, 83 up-regulated 44 up-regulated and 254 down-regulated genes were found. Between SHR-SP rats and Wistar-Kyoto rats, 83 up-regulated and 207 down-regulated genes were found. Between SHRs rats and SHR-SP rats, 36 up-regulated and 24 down-regulated genes were found	Ikawa *et al.*[35]
Acupuncture effect on the progression of hypertension	6 weeks	Use of acupuncture to treat spontaneously hypertensive rats lowered blood pressure (185 5.6 mm of mercury).The level of serum angiotensin II in SHRs was decreased by acupuncture	Leung *et al.*[36]

spontaneous hypertension[39]. Stroke-Prone Spontaneously Hypertensive Rats (SHR-SP) are a sub-strain that is developed with higher blood pressure and a high chance of dying from stroke[7]. It is a unique and utilized animal model used to study spontaneous stroke such as spontaneous occurrence of stroke lesions experiments for prevention of stroke[39,40]. This model is applied to the studies of the occurrence of stroke in humans as stroke observed in SHR-SP model is similar to stroke occurring in human essential hypertension[41]. This model also can be used to study on prophylaxis of essential hypertension and its complications and holds the advantage of reviewing the changes of pathophysiology in SHR model which is similar to human essential hypertension. The absence of a suitable control that has been genetically altered but is disease-free, as well as the complexities of the genetic modifications that have influenced not only blood pressure but many other regulatory systems, are critical faults in this model[7]. Various SHRs model used in hypertension studies are tabulated in Table 5.

Dahl-sensitive rats: Dahl salt-sensitive rat was originated by Dr. Lewis Kitchener Dahl from Sprague-Dawley rats. This model focuses on developing hypertension with high salt intake. When these rats are fed with a normal quantity of salts, they will develop hypertension as they are genetic models with high salt sensitivity. Two strains of animal models were further developed on the basis of previous model, they are Dahl salt-sensitive rat and Dahl salt-resistant rat[42]. Hypertension will be developed in Dahl salt-sensitive rats after high salt intake, while Dahl salt-resistant rats do not develop hypertension even with the same diet as Dahl salt-sensitive rats. The mechanisms of salt-sensitive hypertension in genetic aspect are not yet fully known[43].

There were several studies conducted by using this animal model. Metformin decreases blood pressure and reduces plasma norepinephrine concentration in Dahl salt-sensitive rats[44]. By using the Dahl salt-sensitive rats as an animal model, it was found that exogenous norepinephrine (NE) can induce the development of hypertension in salt-sensitive rats through an alpha 1-adrenoceptor-gated signalling pathway that promotes Na^+Cl^- cotransporter (NCC)[45]. Prolyl-hydroxylase 2 (PHR2) gene may be a specific gene for inducing hypertension while targeting of PHR2 gene can attenuates salt-sensitive hypertension in Dahl salt-sensitive rats[46]. The role of NADPH Oxidase 4 (Nox4) gene in salt-induced hypertension was also examined by researchers and they concluded that knocking out of Nox4 gene can attenuate salt-induced hypertension in Dahl salt-sensitive rats[47]. The mammalian Target of Rapamycin Complex 1 (mTORC1) pathway was found to be responsible for development of salt-induced hypertension in Dahl salt-sensitive rats with a high salt diet by Kumar and his colleagues while rapamycin can attenuate the induction of salt-induced hypertension in Dahl salt-sensitive rats. They also conducted an experiment to examine the effect of compound PP242 in the inhibition of Mammalian Target of Rapamycin Complex 2 (mTORC2) on salt-sensitive hypertension in Dahl salt-sensitive rats. The role of fumarase-NO pathway in development of hypertension was also conducted by using the Dahl salt-sensitive rats[48,49]. Methylglyoxal increased the systolic blood pressure after administration of MG for 12 weeks in Dahl salt-sensitive rats[50]. The ability of exenatide analogue AC3174 attenuate the development of hypertension was proven in Dahl salt-sensitive rats[51]. The T lymphocyte in kidney can develop hypertension in dahl salt-sensitive rats by increasing the production of Ang II. Suppression of T lymphocyte infiltration can reduce hypertension in the dahl's rat[52]. Dahl salt-sensitive rat is best for investigating the pathogenesis of primary

hypertension due to innate salt sensitivity of humans. No specific technique is needed for preparation of the Dahl salt-sensitive rat aside from providing high salt diet and drinking water. The limitation of this model is this model is only suitable for studies on genetic factor results in essential hypertension. Some of the Dahl salt sensitive rats used in hypertension studies were shown in Table 6.

Transgenic hypertension model: Transgenic hypertension models are created by over-expressing a specific gene that causes hypertension. This model is useful for examining the role of individual genes in the aetiology of hypertension[42]. There are some examples of specific genes used to develop transgenic hypertension model such as TGR (mREN2)27, Cyp1a1-Ren-2 and MC4R genes. The Cyp1a1-Ren-2 model is an excellent model for studying the execute of renin-angiotensin system in the pathophysiology of hypertension as this model induces hypertension by expressing the Ren-2 gene renin gene with the help of Cyp1a1 promoter[53]. Expression of Cyp1a1 promoter is enhanced rapidly associated with increased Ren-2 renin gene expression in the liver after the administration of oral indole-3-carbinol (I3C) and further develops Ang II-dependent malignant hypertension[54]. There are some advantages to the use of transgenic hypertension rats (Table 7). First, it models the development of hypertension in a controlled environment. Second, specific genes are targeted for studying the development of hypertension due to genetic factors. This model also replicates the symptoms and pathology of the hypertension caused by targeted gene. There are limitations to this model as well. Limited human hypertension is modelled by the transgenic rats or it may develop differently in the transgenic rat. The new drugs that are effective on the modelled hypertension might not be effective on humans as there is a biological difference between humans and rats.

Renal models

Goldblatt models: Kidney plays vital part in blood pressure regulation by controlling electrolytes and fluid balance in our bodies. They are also responsible for renin secretion, which is critical in the renal-angiotensin system (RAS). Since 1934, Goldblatt and his team have developed renal-induced model with hypertension by constricting the renal artery partially. His technique includes constriction of one or both renal arteries with the use of tiny silver clamp[51]. Two Kidney-1 Clip (2K-1C), 1 Kidney-1 Clip (1K-1C) and 2 Kidney-2 Clip are the three types of hypertensions caused by renal artery constriction (2K-2C). The primary cause of hypertension in the 2 Kidney-1 Clip paradigm is unilateral renal artery stenosis[55]. It will also enhance renin and Angiotensin II synthesis[56]. For 1 kidney-1 clip model, one kidney is removed from the rat and renal artery of another kidney is constricted to produce 1K-1C Goldblatt hypertension. This model is ideal for studying the role of volume expansion in hypertension development[57].

Severe renal ischemia is induced in the 2K-2C model and occasionally activates the RAS and sympathetic nervous system and increases the production of serum vasopressin, which leads to elevated blood pressure[58]. Studying with this model is possible for spontaneous stroke as it has a higher incidence of spontaneous stroke[42]. There were several studies conducted using this animal model. The investigation of the anti-hypertensive effect and nitric oxide synthesis enhancing effect of garlic was conducted by using 2 Kidneys-1 Clip rats[59]. Two Kidneys-1 Clip rats is used as an animal model to determine whether the up-regulation of collecting duct renin is affected by hypertension or by high Ang II content[56]. Using 2K-1C rats, the effects of long-term therapy with an inhibitor of Nicotinamide Adenine Dinucleotide Phosphate (NADPH)-dependent oxidase (apocynin) and a superoxide dismutase (SOD) mimic (tempol) were assessed with regard to the development of hypertension, endothelial dysfunction and oxidative damage[60]. Renal injury contributes to development of hypertension in 2K-1C rats while mesenchymal stem cells (MSC) treatment is effective for treating the renovascular hypertension[61]. The 2K-1C rat was also used as animal model to examine the anti-hypertensive and vasorelaxation effect of rice bran peptides (RBP)[62]. Over-expression of macrophage migration inhibitory factor (MIH) in the nucleus of the solitary tract (NTS) can inhibit the development of hypertension in 2 Kidneys-1 Clip rats[63]. The evaluation of anti-hypertensive effect of novel nitrate 1, 3-bis (hexyloxy) propan-2-yl nitrate (NDHP) in the development of hypertension was conducted by using 2 Kidneys-1 Clip rats[64].

The major advantage of Goldblatt models is the underlying mechanism is similar to the renal arterial stenosis (RAS) from human. The 2K-1C model is resembling to unilateral renal arterial stenosis in human which one renal artery is constricted. The 2K-2C model resembles to the bilateral renal arterial stenosis in human where both renal arteries are constricted. While 1K-1C model is resembling to the patients who suffered from renal arterial stenosis after unilateral nephrectomy[5]. There is limitation of these models. Specific skill is required for clipping of renal arteries and removal of kidney in the rats. This model is also not suitable for studying of primary hypertension. Literature review on various models and their efficiency as hypertensive models has been studied. Some of the Goldblatt (2K-1C) models in hypertension studies were given in Table 8.

Table 6: Dahl salt sensitive hypertensive models

Type of animal model	Uses of Dahl salt-sensitive rats	Study period	Outcome	References
Dahl salt-sensitive rats	Determine the effect of metformin	6 weeks	Metformin reduces plasma norepinephrine levels and blood pressure in hypertensive rats. Metformin also lessens oxidative stress in the hypothalamus paraventricular nucleus of hypertensive rats (PVN)	Yu *et al.*[43]
Dahl salt-sensitive rats	Find out role of inhibition of the prolyl-hydroxylase 2 (PHR2) gene in hypertension	2 weeks	Prolyl hydroxylase 2 short hairpin RHA decreased PHR2 levels and salt-sensitive hypertension in Dahl salt-sensitive rats	Zhu *et al.*[45]
Dahl salt-sensitive rats	Investigate the involvement of the Nox4 gene in hypertension and renal damage	21 days	Salt-sensitive rats with the Nox4 gene deletion demonstrated a reduction in salt-induced hypertension and renal impairment after 21 days of consuming a diet containing 4.0% sodium chloride	Cowley *et al.*[46]
Dahl salt-sensitive rats	Blocking of rapamycin Complex 1 and hypertension	21 days	Upregulation of mTORC1 in the kidney was found in salt-sensitive rats fed a diet containing 4.0% sodium chloride. After 21 days of rapamycin therapy, salt-induced hypertension in salt-sensitive rats is decreased	Kumar *et al.*[47]
Dahl salt-sensitive rats	Blocking of rapamycin complex 1 and role of impact of chemical PP242 in hypertension	21 days	In salt-sensitive rats on a standard salt diet, PP242 decreased mean arterial pressure. For 21 days, a high-salt meal was given to salt-sensitive rats, however PP242 had no impact on the animals' mean arterial pressure	Kumar *et al.*[94]

Table 7: Transgenic rat model

Transgenic rat and its uses	Study period	Outcome	References
Find out if Cyp1a1-Ren2 transgenic rats may avoid developing Ang II-dependent hypertension by using prolonged direct renin inhibition with aliskiren	16 days	Aliskiren inhibited the onset of hypertension in Cyp1a1-Ren2 transgenic rats. Aliskiren treatment resulted in noticeably decreased blood pressure in Cyp1a1-Ren2 transgenic rats	Huang *et al.*[95]
Determine the antihypertensive effects of the tripeptides valyl-prolyl -proline (VPP) and isoleucyl-prolyl-proline (IPP) in double transgenic rats (dTGR)	3 weeks	Because fermented milk has ACE inhibitory characteristics, it prevented dTGR from developing hypertension	Jauhiainen *et al.*[96]
Analyze how Cyp1a1-Ren2 transgenic inhibition affects the onset of Angiotensin II-dependent hypertension	2 weeks	cis-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy] is an inhibitor in the development of hypertension. to cause hypertension rats with Cyp1a1-Ren2 transgenes	Honetschlägerová *et al.*[97]
Examine whether transgenic mice over expressing renal RAS can cause hypertension and kidney injury by itself (rAng)	83 days	Transgenic animals overexpressing renal (rAng) were found to have significantly higher blood pressure than non-transgenic mice. In transgenic mice, renal damage was seen when the kidneys were examined	Sachetelli *et al.*[98]
Analyze whether rosuvastatin can prevent Ren2 transgenic rats from developing pulmonary arterial hypertension	30 days	In Ren2 transgenic rats with pulmonary arterial hypertension, the rise in Right Ventricular Systolic Pressure (RVSP) was dramatically reduced by rosuvastatin	DeMarco *et al.*[99]

Table 8: Goldblatt (2K-1C) hypertensive models

2 Kidneys-1 Clip rats and its uses	Study period	Outcome	References
Analyzing the novel nitrate 1, 3-bis (hexyloxy) propan-2-yl nitrate (NDH) antihypertensive's effects in hypertension	14 days	Nitrate 1, 3-bis (hexyloxy) propan-2-yl nitrate (NDHP) infusion decreased blood pressure in the 2 kidneys as compared to normotensive rats. 1) clip rats	Paulo *et al.*[64]
Check whether hypertension or a high Ang II concentration impacts the up-regulation of collecting duct renin	25 days	Despite having high blood pressure, 2 kidneys-1 clip rats had more renin than rats with normal blood pressure did	Prieto-Carrasquero *et al.*[56]
Examine the antihypertensive and vaso-relaxing effects of rice bran peptides (RBP)	6 weeks	All of the animals had vaso-relaxation due to RBP. The RBP treatment reduced peripheral vascular resistance and blood pressure in 2K-1C rats	Boonla *et al.*[62]
Examine the effects of garlic on lowering blood pressure and increasing the generation of nitric oxide	2 weeks	Garlic reversed the hypertensive effects of L-NAME in rats, both normotensive and 2K-1C rats	Al-Qattan *et al.*[100]
Determine whether mesenchymal stem cells (MSC) can prevent the development of hypertension and its associated effects on the kidneys	6 weeks	Mesenchymal stem cells dramatically decreased proteinuria, sympathetic hyperactivity and averted further elevations in arterial pressure in 2K-1C animals	Oliveira-Sales *et al.*[61]

MEASUREMENT OF HYPERTENSION IN MODELS

Blood pressure in animals must be measured repeatedly. In acute experiments, the animals are often given anaesthetise and their blood pressure is monitored during the experiment by identifying a navigable artery and putting a catheter in it attached to a pressure gauge or a mercury manometer transducer[65]. The person taking the measurements needs to have patience and be adept at handling clients, animals and equipment. The veterinarian must understand numerous variables involved in measuring blood pressure.

Direct methods of measuring of hypertension: Radiotelemetry methods or indwelling catheters attached to externally mounted transducers can be used to measure blood pressure directly. It is the "gold standard" technique[66]. An important step forward in the study of hypertension has been made possible by the commercial availability of dependable and simple-to-use wireless radio telemetric equipment over the past 10 to 15 years for BP measurements in laboratory animals[67]. For the radiotelemetry system (TS) to measure blood pressure, a catheter must be surgically implanted into a mouse artery, typically the infrarenal abdominal aorta or the left common carotid artery[68]. Radiotelemetry uses small sensors and transmitters to detect and send biological signals from animals to a nearby receiver. The receiver converts the analog signal into a digital signal in order to send the analogue frequency signal into a computational data collecting system[69].

This method is difficult due to the necessity for anesthesia close to the time of recording restraint, as well as problems associated with any surgical operation, despite being accurate and able to detect minute changes in blood pressure[70].

Measurement of blood pressure using indwelling catheters provides an exact measurement of the arterial blood pressure. However, the cardiovascular system's response to anesthesia is unpredictable and creates concern[71]. Mice can be recorded continuously or semi-continuously over intervals ranging from a few weeks to many months. The technology allows recorded blood pressure data to be stored and automatically analyzed as waveforms, beat-to-beat systolic, mean and diastolic pressures, or any combination of these[72]. Telemetry is significantly more expensive than using tail cuffs, calls for specialized knowledge and has high mortality and morbidity rates (Fig. 2)[73].

Indirect methods of measuring of hypertension: For high-throughput experimental designs like mutagenesis screens and genetic crosses, the American Heart Association guidelines for blood pressure measurement in experimental animals[1] recommended indirect blood pressure measurement. Indirect blood pressure measurements accuracy can, however, differ significantly[73,74]. This method is widely used in spontaneously hypertensive rats[72]. It includes constraint and minimal heat stress to dilate the tail bed's blood vessels. The approach provides a single point measurement and can be used to accurately measure just systolic pressure[73]. A sensor at the base of the tail senses when blood flow starts and stops and a computer regulates the tail cuff's inflation and deflation. At the end of the screen, we obtain an average systolic blood pressure based on 60 measurements[68]. It is a non-invasive method and most suitable for blood pressure measurement in animal models[74,77]. The rat must be held using the tail cuff method for the duration of the experiment; any observations may reveal stressed blood pressure. There is proof that dietary restriction throughout development can change the cardiovascular reactions triggered by stress[78]. Prior to measurements taking place over the next two days, mice must first be taught to the device for a total of three days. Mice have been on the high-fat diet for 2 weeks at the end of this experiment. The

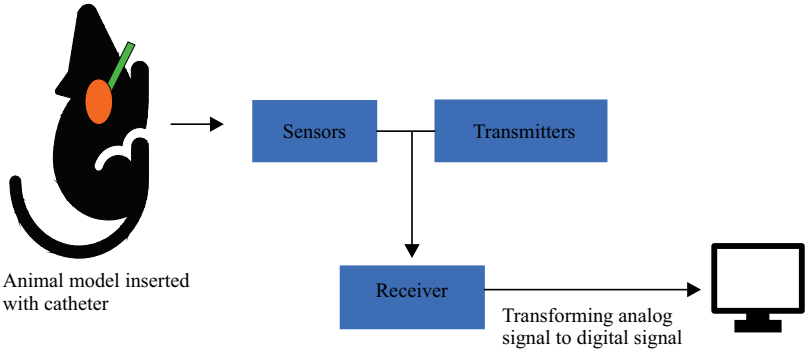

Fig. 2: Indwelling catheters for blood pressure measurement

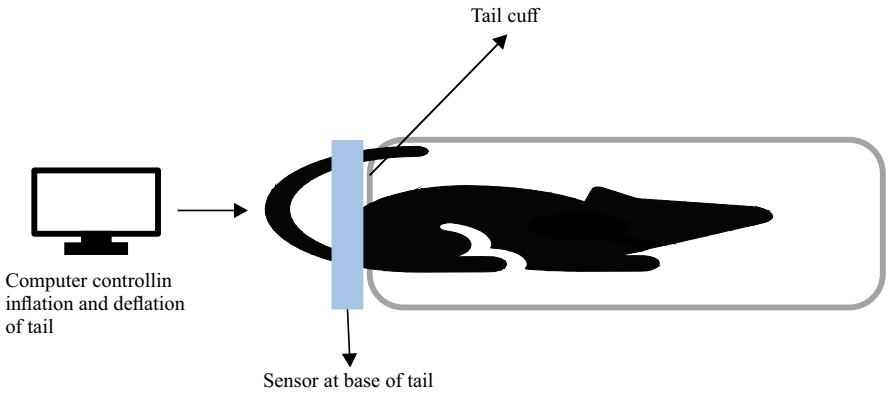

Fig. 3: Tail cuff for blood pressure measurement

detection equipment comprises of four mice that have not been given anesthesia and are being held captive by a magnetic restraint that has an open nose end on a heated platform. A sensor near the base of the tail detects when blood flow starts and stops and this information is used by a computer to manage the inflation and deflation of the tail cuff. Each platform has four mice and each training and measurement session lasts for 20 min in the morning. At the bottom of the screen, we obtain an average systolic blood pressure based on sixty readings[3,75]. Tail cuff for blood pressure measurement method was shown in Fig. 3.

EFFECT ON MODELS

Today, any novel antihypertensive medication will first go through multiple hypertension models of research. clinical studies When evaluating antihypertensive activity, it is crucial to ensure the medication is dispensed in accordance with a set schedule, which corresponding to the length of its action[61,65]. Particularly, it is difficult to obtain accurate blood pressure readings, especially in small experimental animal models[79]. Cerebrovascular tree structural alterations caused by hypertension in SHR and SHRSP may buffer the cerebrovascular tree from the negative effects of persistently increased arterial blood pressure. However, structural changes may prevent normal cerebrovascular function once treatment returns blood pressure to normal ranges[80]. The cannabinoid receptor agonist WIN 55,212-2 causes age-and strain-dependent locomotor effects in rats after acute systemic treatment. With no effects on adult SHR, it specifically improves the locomotion of adolescent SHR at low dosages. Adolescent rats of both strains experience hypoactivity when given a greater dose[81]. Effects of drugs on animal models not only in case of anti-hypertensive drugs but also for other drugs must be observed clearly and also the quantity provided must be checked. However, this aims to be the preliminary stage before subjecting to human population, it also can cause adverse effect on animals which must be monitored.

CONCLUSION

The animal models used in study of development of hypertension are considered as splendid tool for studying the pathophysiology of hypertension. Animal models are also used as first approach to investigate a potential new therapy and to evaluate the existed drug. Despite the fact that the animal models are distinctive from the human and often characterized by some limitations such as animal size, cost and availability. The researchers are still relying on animal models as they can be readily tested, autopsied and biopsied easily. The genetic and environmental background of animal models are already known. However, all researchers must obey the ethical limits when using animal models in an experiment. The use of animal model is only allowed when they are necessary and prevent causing pain, distress and lasting harm.

SIGNIFICANCE STATEMENT

According to the reviewed studies, the type of animal models used in a study is determined by which factor that causes the development of hypertension in human body. After one of the factor is targeted by the researcher, the animal model used in the study will be developed to mimic that particular mechanism and pathophysiology of hypertension. For instance, the researcher simulates the aldosteronism in a rat by administering DOCA (deoxycorticosterone acetate) salt for the study of hypertension caused by primary aldosteronism in human body. Sufficient data in this review suggests that every type of animal model can only mimic one of causative factors in development of hypertension in human, but not multiple.

ACKNOWLEDGMENT

This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia under Annual Research Track (Grant No. A465).

REFERENCES

1. Fuchs, F.D. and P.K. Whelton, 2020. High blood pressure and cardiovascular disease. Hypertension, 75: 285-292.
2. Lerman, L.O., T.W. Kurtz, R.M. Touyz, D.H. Ellison and A.R. Chade*et al*., 2019. Animal models of hypertension: A scientific statement from the American Heart Association. Hypertension, 73: e87-e120.
3. Lerman, L.O., A.R. Chade, V. Sica and C. Napoli, 2005. Animal models of hypertension: An overview. J. Lab. Clin. Med., 146: 160-173.
4. Leong, X.F., C.Y. Ng and K. Jaarin, 2015. Animal models in cardiovascular research: Hypertension and atherosclerosis. BioMed Res. Int., Vol. 2015. 10.1155/2015/528757.
5. Lin, H.Y., Y.T. Lee, Y.W. Chan and G. Tse, 2016. Animal models for the study of primary and secondary hypertension in humans (Review). Biomed. Rep., 5: 653-659.
6. Kandlikar, S.S. and G.D. Fink, 2011. Mild DOCA-salt hypertension: Sympathetic system and role of renal nerves. Am. J. Physiol. Heart Circ. Physiol., 300: H1781-H1787.
7. Sun, Z.J. and Z.E. Zhang, 2005. Historic perspectives and recent advances in major animal models of hypertension. Acta Pharmacol. Sin., 26: 295-301.
8. Mehta, P.K. and K.K. Griendling, 2007. Angiotensin II cell signaling: Physiological and pathological effects in the cardiovascular system. Am. J. Physiol. Physiol., 292: C82-C97.
9. Afzal, S., M. Abdul Sattar, S. Akhtar, N.A.B. Abdullah, O.A. Eseyin, M.H. Abdulla and E.J. Johns, 2018. Effect of pioglitazone on vasopressor responses to adrenergic agonists and angiotensin II in diabetic and non-diabetic spontaneously hypertensive rats. Pak. J. Pharm. Sci., 31: 747-754.
10. Afzal, S., M. Abdul Sattar, E.J. Johns, O.A. Eseyin and A. Attiq, 2021. Antioxidant potential of adiponectin and full PPAR-γ agonist in correcting streptozotocin-induced vascular abnormality in spontaneously hypertensive rats. PPAR Res., Vol. 2021. 10.1155/2021/6661181.
11. McBryde, F.D., S.J. Guild, C.J. Barrett, J.W. Osborn and S.C. Malpas, 2007. Angiotensin II-based hypertension and the sympathetic nervous system: The role of dose and increased dietary salt in rabbits. Exp. Physiol., 92: 831-840.
12. Staruschenko, A., O. Palygin, D.V. Ilatovskaya and T.S. Pavlov, 2013. Epidermal growth factors in the kidney and relationship to hypertension. Am. J. Physiol. Renal Physiol., 305: F12-F20.
13. Jung, O., R.P. Brandes, I.H. Kim, F. Schweda and R. Schmidt *et al*., 2005. Soluble epoxide hydrolase is a main effector of angiotensin II-induced hypertension. Hypertension, 45: 759-765.
14. Sarr, M., M. Chataigneau, S. Martins, C. Schott and J. El Bedoui*et al*., 2006. Red wine polyphenols prevent angiotensin II-induced hypertension and endothelial dysfunction in rats: Role of NADPH oxidase. Cardiovasc. Res., 71: 794-802.
15. Sriramula, S., J.P. Cardinale, E. Lazartigues and J. Francis, 2011. ACE2 overexpression in the paraventricular nucleus attenuates angiotensin II-induced hypertension. Cardiovasc. Res., 92: 401-408.
16. Sriramula, S., J.P. Cardinale and J. Francis, 2013. Inhibition of TNF in the brain reverses alterations in RAS components and attenuates angiotensin II-induced hypertension. PLoS ONE, Vol. 8. 10.1371/journal.pone.0063847.
17. Ramkumar, N., D. Stuart, S. Rees, A. van Hoek, C.D. Sigmund and D.E. Kohan, 2014. Collecting duct-specific knockout of renin attenuates angiotensin II-induced hypertension. Am. J. Physiol. Renal Physiol., 307: F931-F938.
18. da Silva, A.A., J.M. do Carmo, J.H. Dubinion, M. Bassi, K. Mokhtarpouriani, S.M. Hamza and J.E. Hall, 2015. Chronic central nervous system MC3/4R blockade attenuates hypertension induced by nitric oxide synthase inhibition but not by angiotensin II infusion. Hypertension, 65: 171-177.
19. Xue, B., H. Yin, F. Guo, T.G. Beltz, R.L. Thunhorst and A.K. Johnson, 2017. Maternal gestational hypertension-induced sensitization of angiotensin II hypertension is reversed by renal denervation or angiotensin-converting enzyme inhibition in rat offspring. Hypertension, 69: 669-677.
20. Li, X.C., D. Zhu, X. Chen, X. Zheng and C. Zhao *et al*., 2019. Proximal tubule-specific deletion of the NHE3 (Na^+/H^+exchanger 3) in the kidney attenuates Ang II (angiotensin II)-induced hypertension in mice. Hypertension, 74: 526-535.
21. Tousoulis, D., A.M. Kampoli, C.T.N. Papageorgiou and C. Stefanadis, 2012. The role of nitric oxide on endothelial function. Curr. Vasc. Pharmacol., 10: 4-18.
22. Ahmad, A., M.Z. Abdul Sattar, H.A. Rathore, A.I. Hussain and S.A. Khan *et al*., 2015. Antioxidant activity and free radical scavenging capacity of L-arginine and NaHS: A comparitive *in vitro* study. Acta Poloniae Pharm. Drug Res., 72: 245-252.
23. Paulis, L., J. Zicha, J. Kunes, S. Hojna and M. Behuliak *et al*., 2008. Regression of L-NAME-induced hypertension: The role of nitric oxide and endothelium-derived constricting factor. Hypertens. Res., 31: 793-803.
24. Chade, A.R., 2017. Small vessels, big role: Renal microcirculation and progression of renal injury. Hypertension, 69: 551-563.

25. Elijovich, F., M.H. Weinberger, C.A.M. Anderson, L.J. Appel and M. Bursztyn *et al*., 2016. Salt sensitivity of blood pressure: A scientific statement from the American Heart Association. Hypertension, 68: e7-e46.
26. Tran, L.T., V.G. Yuen and J.H. McNeill, 2009. The fructose-fed rat: A review on the mechanisms of fructose-induced insulin resistance and hypertension. Mol. Cell. Biochem., 332: 145-159.
27. Basciano, H., L. Federico and K. Adeli, 2005. Fructose, insulin resistance, and metabolic dyslipidemia. Nutr. Metabol., Vol. 2. 10.1186/1743-7075-2-5.
28. Madero, M ., S.E. Perez-Pozo, D. Jalal, R.J. Johnson and L.G. Sánchez-Lozada, 2011. Dietary fructose and hypertension. Curr. Hypertens. Rep., 13: 29-35.
29. Rust, P. and C. Ekmekcioglu, 2016. Impact of Salt Intake on the Pathogenesis and Treatment of Hypertension. In: Hypertension: From Basic Research to Clinical Practice, Shahidul Islam, M. (Ed.), Springer International Publishing, Cham, Switzerland, ISBN: 978-3-319-44251-8, pp: 61-84.
30. Schiffrin, E.L., 2020. How structure, mechanics, and function of the vasculature contribute to blood pressure elevation in hypertension. Can. J. Cardiol., 36: 648-658.
31. Saheera, S. and P. Krishnamurthy, 2020. Cardiovascular changes associated with hypertensive heart disease and aging. Cell Transplant., Vol. 29. 10.1177/0963689720920830.
32. Liu, C., C.X. Yang, X.R. Chen, B.X. Liu and Y. Li *et al*., 2018. Alamandine attenuates hypertension and cardiac hypertrophy in hypertensive rats. Amino Acids, 50: 1071-1081.
33. Nowacki, D., H. Martynowicz, A. Skoczyńska, A. Wojakowska and B. Turczyn *et al*., 2017. Lecithin derived from ω-3 PUFA fortified eggs decreases blood pressure in spontaneously hypertensive rats. Sci. Rep., Vol. 7. 10.1038/s41598-017-12019-w.
34. El-Basyuni, Y.A., Y. Li and M.B. Anand Srivastava, 2016. Knockdown of inhibitory guanine nucleotide binding protein Giα-2 by antisense oligodeoxynucleotides attenuates the development of hypertension and tachycardia in spontaneously hypertensive rats. J. Am. Heart Assoc., Vol. 5. 10.1161/JAHA.116.004594.
35. Ikawa, T., Y. Watanabe, D. Okuzaki, N. Goto and N. Okamura *et al*., 2019. A new approach to identifying hypertension-associated genes in the mesenteric artery of spontaneously hypertensive rats and stroke-prone spontaneously hypertensive rats. J. Hypertens., 37: 1644-1656.
36. Leung, S.B., H. Zhang, C.W. Lau and Z.X. Lin, 2016. Attenuation of blood pressure in spontaneously hypertensive rats by acupuncture was associated with reduction oxidative stress and improvement from endothelial dysfunction. Chin. Med., Vol. 11. 10.1186/s13020-016-0110-0.
37. Perez-Vizcaino, F., J. Duarte, R. Jimenez, C. Santos-Buelga and A. Osuna, 2009. Antihypertensive effects of the flavonoid quercetin. Pharmacol. Rep., 61: 67-75.
38. Rubio-Guerra, A., H. Vargas-Robles, L.M. Ramos-Brizuela and B.A. Escalante-Acosta, 2010. Is tetrahydrobiopterin a therapeutic option in diabetic hypertensive patients? Integr. Blood Pressure Control, 3: 125-132.
39. Abdala, A.P., F.D. McBryde, N. Marina, E.B. Hendy and Z.J. Engelman *et al*., 2012. Hypertension is critically dependent on the carotid body input in the spontaneously hypertensive rat. J. Physiol., 590: 4269-4277.
40. Stanisavljevic, A., J.M. Schrader, X. Zhu, J.M. Mattar and A. Hanks *et al*., 2022. Impact of non-pharmacological chronic hypertension on a transgenic rat model of cerebral amyloid angiopathy. Front. Neurosci., Vol. 16. 10.3389/fnins.2022.811371.
41. Amenta, F. and D. Tomassoni, 2011. Spontaneously Hypertensive Rat (SHR): An Animal Model of Vascular Brain Disorder. In: Animal Models of Dementia, de Deyn, P.P. and D. van Dam (Eds.), Humana Press, Totowa, New Jersey, ISBN: 978-1-60761-898-0, pp: 577-611.
42. Dornas, W.C. and M.E. Silva, 2011. Animal models for the study of arterial hypertension. J. Biosci., 36: 731-737.
43. Yu, X.J., Y.N. Zhao, Y.K. Hou, H.B. Li and W.J. Xia *et al*., 2019. Chronic intracerebroventricular infusion of metformin inhibits salt-sensitive hypertension via attenuation of oxidative stress and neurohormonal excitation in rat paraventricular nucleus. Neurosci. Bull., 35: 57-66.
44. Frame, A.A., F. Puleo, K. Kim, K.R. Walsh, E. Faudoa, R.S. Hoover and R.D. Wainford, 2019. Sympathetic regulation of NCC in norepinephrine-evoked salt-sensitive hypertension in Sprague-Dawley rats. Am. J. Physiol. Renal Physiol., 317: F1623-F1636.
45. Zhu, Q., J. Hu, W.Q. Han, F. Zhang, P.L. Li, Z. Wang and N. Li, 2014. Silencing of HIF prolyl-hydroxylase 2 gene in the renal medulla attenuates salt-sensitive hypertension in Dahl s rats. Am. J. Hypertens., 27: 107-113.
46. Cowley Jr., A.W., C. Yang, N.N. Zheleznova, A. Staruschenko and T. Kurth *et al*., 2016. Evidence of the importance of Nox4 in production of hypertension in Dahl salt-sensitive rats. Hypertension, 67: 440-450.
47. Kumar, V., C. Wollner, T. Kurth, J.D. Bukowy and A.W. Cowley Jr., 2017. Inhibition of mammalian target of rapamycin complex 1 attenuates salt-induced hypertension and kidney injury in Dahl salt-sensitive rats. Hypertension, 70: 813-821.
48. Xue, H., A.M. Geurts, K. Usa, F. Wang and Y. Lin *et al*., 2019. Fumarase overexpression abolishes hypertension attributable to endothelial NO synthase haploinsufficiency in Dahl salt-sensitive rats. Hypertension, 74: 313-322.

49. Chen, X., T. Mori, Q. Guo, C. Hu and Y. Ohsaki *et al*., 2013. Carbonyl stress induces hypertension and cardio–renal vascular injury in Dahl salt-sensitive rats. Hypertens. Res., 36: 361-367.
50. Liu, Q., L. Adams, A. Broyde, R. Fernandez, A.D. Baron and D.G. Parkes, 2010. The exenatide analogue AC3174 attenuates hypertension, insulin resistance, and renal dysfunction in Dahl salt-sensitive rats. Cardiovasc. Diabetology., Vol. 9. 10.1186/1475-2840-9-32.
51. de Miguel, C., S. Das, H. Lund and D.L. Mattson, 2010. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. Am. J. Physiol. Regul. Integr. Comp. Physiol., 298: R1136-R1142.
52. de Miguel, C., C. Guo, H. Lund, D. Feng and D.L. Mattson, 2011. Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. Am. J. Physiol. Renal Physiol., 300: F734-F742.
53. Sporková, A., Š. Jíchová, Z. Husková, L. Kopkan and A. Nishiyama *et al*., 2014. Different mechanisms of acute versus long-term antihypertensive effects of soluble epoxide hydrolase inhibition: Studies in Cyp1a1-Ren-2 transgenic rats. Clin. Exp. Pharmacol. Physiol., 41: 1003-1013.
54. Jíchová, Š., Š. Doleželová, L. Kopkan, E. Kompanowska-Jezierska, J. Sadowski and L. Červenka, 2016. Fenofibrate attenuates malignant hypertension by suppression of the renin-angiotensin system: A study in Cyp1a1-Ren-2 transgenic rats. Am. J. Med. Sci., 352: 618-630.
55. Al-Suraih, M. and J.P. Grande, 2014. Management of renal artery stenosis: What does the experimental evidence tell us? World J. Cardiol., 6: 855-860.
56. Prieto-Carrasquero, M.C., F.T. Botros, J. Pagan, H. Kobori, D.M. Seth, D.E. Casarini and L.G. Navar, 2008. Collecting duct renin is upregulated in both kidneys of 2-kidney, 1-clip goldblatt hypertensive rats. Hypertension, 51: 1590-1596.
57. Elijovich, F., T.R. Kleyman, C.L. Laffer and A. Kirabo, 2021. Immune mechanisms of dietary salt-induced hypertension and kidney disease: Harry goldblatt award for early career investigators 2020. Hypertension, 78: 252-260.
58. Su, Y.Y., H.M. Li, Z.X. Yan, M.C. Li and J.P. Wei *et al*., 2019. Renin-angiotensin system activation and imbalance of matrix metalloproteinase-9/tissue inhibitor of matrix metalloproteinase-1 in cold-induced stroke. Life Sci., Vol. 231. 10.1016/j.lfs.2019.116563.
59. de Matos, V.S., A.L.R. do Nascimento, P.G. Pereira, K. Rabelo and C.B.V. Andrade *et al*., 2020. Aliskiren reduces the adrenal zona glomerulosa apoptosis and autophagy in Wistar rats with 2K1C hypertension. Int. J. Hypertens., Vol. 2020. 10.1155/2020/7684849.
60. Costa, C.A., T.A.S. Amaral, L.C.R.M. Carvalho, D.T. Ognibene and A.F.E. da Silva *et al*., 2009. Antioxidant treatment with tempol and apocynin prevents endothelial dysfunction and development of renovascular hypertension. Am. J. Hypertens., 22: 1242-1249.
61. Oliveira-Sales, E.B., E. Maquigussa, P. Semedo, L.G. Pereira and V.M. Ferreira *et al*., 2013. Mesenchymal stem cells (MSC) prevented the progression of renovascular hypertension, improved renal function and architecture. PLoS ONE, Vol. 8. 10.1371/journal.pone.0078464.
62. Boonla, O., U. Kukongviriyapan, P. Pakdeechote, V. Kukongviriyapan, P. Pannangpetch and S. Thawornchinsombut, 2015. Peptides-derived from Thai rice bran improves endothelial function in 2K-1C renovascular hypertensive rats. Nutrients, 7: 5783-5799.
63. Barbosa, R.M., G.F. Speretta, D.P.M. Dias, P.J. Ruchaya and H. Li *et al*., 2017. Increased expression of macrophage migration inhibitory factor in the nucleus of the solitary tract attenuates renovascular hypertension in rats. Am. J. Hypertens., 30: 435-443.
64. Paulo, L.L., J.C. Cruz, Z. Zhuge, A. Carvalho-Galvão and M.C.R. Brandão *et al*., 2018. The novel organic mononitrate NDHP attenuates hypertension and endothelial dysfunction in hypertensive rats. Redox Biol., 15: 182-191.
65. Badyal, D.K., H. Lata and A.P. Dadhich, 2003. Animal models of hypertension and effect of drugs. Indian J. Pharmacol., 35: 349-362.
66. Wilde, E., A.A. Aubdool, P. Thakore, L. Baldissera Jr. and K.M. Alawi *et al*., 2017. Tail-cuff technique and its influence on central blood pressure in the mouse. J. Am. Heart Assoc., Vol. 6. 10.1161/JAHA.116.005204.
67. Kurtz, T.W., K.A. Griffin, A.K. Bidani, R.L. Davisson and J.E. Hall, 2005. Recommendations for blood pressure measurement in humans and experimental animals. Part 2: Blood pressure measurement in experimental animals: A statement for professionals from the subcommittee of professional and public education of the American Heart Association Council on high blood pressure research. Hypertension, 45: 299-310.
68. Whitesall, S.E., J.B. Hoff, A.P. Vollmer and L.G. D'Alecy, 2004. Comparison of simultaneous measurement of mouse systolic arterial blood pressure by radiotelemetry and tail-cuff methods. Am. J . Physiol. Heart Circ. Physiol., 286: H2408-H2415.
69. Kays, R., S. Tilak, M. Crofoot, T. Fountain and D. Obando *et al*., 2011. Tracking animal location and activity with an automated radio telemetry system in a tropical rainforest. Comput. J., 54: 1931-1948.
70. Chau, K., M. Welsh, A. Makris and A. Hennessy, 2022. Progress in preeclampsia: The contribution of animal models. J. Hum. Hypertens., 36: 705-710.

71. Tan, Q., S. Zhao, X. Li, B. Gu and Z. Ni, 2021. Does non-invasive blood pressure measurement increase the complications and decrease indwelling time of peripheral intravenous catheters: A cohort study. J. Clin. Nurs., 30: 2287-2292.
72. Drüeke, T.B. and O. Devuyst, 2019. Blood pressure measurement in mice: Tail-cuff or telemetry? Kidney Int., Vol. 96. 10.1016/j.kint.2019.01.018.
73. Feng, M., S. Whitesall, Y. Zhang, M. Beibel, L. D' Alecy and K. DiPetrillo, 2008. Validation of volume-pressure recording tail-cuff blood pressure measurements. Am. J. Hypertens., 21: 1288-1291.
74. Afzal, S., M. Abdul Sattar, E.J. Johns and O.A. Eseyin, 2020. Renoprotective and haemodynamic effects of adiponectin and peroxisome proliferator-activated receptor agonist, pioglitazone, in renal vasculature of diabetic spontaneously hypertensive rats. PLoS ONE, Vol. 15. 10.1371/journal.pone.0229803.
75. Afzal, S., M. Abdul Sattar, O.A. Eseyin, A. Attiq and E.J. Johns, 2022. Crosstalk relationship between adiponectin receptors, PPAR-γ and α-adrenoceptors in renal vasculature of diabetic WKYs. Eur. J. Pharmacol., Vol. 917. 10.1016/j.ejphar.2021.174703.
76. Nathanielsz, P.W., 2006. Animal models that elucidate basic principles of the developmental origins of adult diseases. ILAR J., 47: 73-82.
77. Afzal, S., M. Abdul Sattar, E.J. Johns, M.H. Abdulla, S. Akhtar, F. Hashmi and N.A. Abdullah, 2016. Interaction between irbesartan, peroxisome proliferator-activated receptor (PPAR-γ), and adiponectin in the regulation of blood pressure and renal function in spontaneously hypertensive rats. J. Physiol. Biochem., 72: 593-604.
78. Pervanidou, P. and G.P. Chrousos, 2012. Metabolic consequences of stress during childhood and adolescence. Metabolism, 61: 611-619.
79. Pickering, T.G., J.E. Hall, L.J. Appel, B.E. Falkner and J. Graves *et al*., 2005. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the subcommittee of professional and public education of the American Heart Association Council on high blood pressure research. Circulation, 111: 697-716.
80. Henning, E.C., S. Warach and M. Spatz, 2010. Hypertension-induced vascular remodeling contributes to reduced cerebral perfusion and the development of spontaneous stroke in aged SHRSP rats. J. Cereb. Blood Flow Metab., 30: 827-836.
81. Pandolfo, P., F.A. Pamplona, R.D.S. Prediger and R.N. Takahashi, 2007. Increased sensitivity of adolescent spontaneously hypertensive rats, an animal model of attention deficit hyperactivity disorder, to the locomotor stimulation induced by the cannabinoid receptor agonist WIN 55,212-2. Eur. J. Pharmacol., 563: 141-148.
82. Guimaraes, P.S., N.M. Santiago, C.H. Xavier, E.P.P. Velloso, M.A.P. Fontes, R.A.S. Santos and M.J. Campagnole-Santos, 2012. Chronic infusion of angiotensin-(1-7) into the lateral ventricle of the brain attenuates hypertension in DOCA-salt rats. Am. J. Physiol. Heart. Circ. Physiol., 303: H393-H400.
83. Jacob, F., L.A. Clark, P.A. Guzman and J.W. Osborn, 2005. Role of renal nerves in development of hypertension in DOCA-salt model in rats: A telemetric approach. Am. J. Physiol. Heart Circ. Physiol., 289: H1519-H1529.
84. Dai, S.Y., W. Peng, Y.P. Zhang, J.D. Li, Y. Shen and X.F. Sun, 2015. Brain endogenous angiotensin II receptor type 2 (AT2-R) protects against DOCA/salt-induced hypertension in female rats. J. Neuroinflammation, Vol. 12. 10.1186/s12974-015-0261-4.
85. Moes, A.D., D. Severs, K. Verdonk, N. van der Lubbe, R. Zietse, A.H.J. Danser and E.J. Hoorn, 2018. Mycophenolate mofetil attenuates DOCA-salt hypertension: Effects on vascular tone. Front. Physiol., Vol. 9. 10.3389/fphys.2018.00578.
86. Nyadjeu, P., E.P. Nguelefack-Mbuyo, A.D. Atsamo, T.B. Nguelefack, A.B. Dongmo and A. Kamanyi, 2013. Acute and chronic antihypertensive effects of *Cinnamomum zeylanicum* stem bark methanol extract in L-NAME-induced hypertensive rat. BMC Complementary Altern. Med., Vol. 13. 10.1186/1472-6882-13-27.
87. Benter, I.F., M.H.M. Yousif, J.T. Anim, C. Cojocel and D.I. Diz, 2006. Angiotensin-(1-7) prevents development of severe hypertension and end-organ damage in spontaneously hypertensive rats treated with L-NAME. Am. J. Physiol. Heart Circ. Physiol., 290: H684-H691.
88. Kumar, S., P. Prahalathan and B. Raja, 2011. Antihypertensive and antioxidant potential of vanillic acid, a phenolic compound in L-NAME-induced hypertensive rats: A dose-dependence study. Redox Rep., 16: 208-215.
89. Mali, V.R., V. Mohan and S.L. Bodhankar, 2012. Antihypertensive and cardioprotective effects of the *Lagenaria siceraria* fruit in N^G-nitro-L-arginine methyl ester (L-NAME) induced hypertensive rats. Pharm. Biol., 50: 1428-1435.
90. Jiang, J., L. Tran, H. Vasudevan, Z. Xia, V.G. Yuen and J.H. McNeill, 2007. Endothelin-1 blockade prevents COX_2 induction and TXA_2 production in the fructose hypertensive rat. Can. J. Physiol. Pharmacol., 85: 422-429.
91. Rahman, M.M., H.M. Park, S.J. Kim, H.K. Go and G.B. Kim *et al*., 2011. Taurine prevents hypertension and increases exercise capacity in rats with fructose-induced hypertension. Am. J. Hypertens., 24: 574-581.
92. Kang, D.G., M.K. Moon, E.J. Sohn, D.H. Lee and H.S. Lee, 2004. Effects of morin on blood pressure and metabolic changes in fructose-induced hypertensive rats. Biol. Pharm. Bull., 27: 1779-1783.

93. Zhao, C., P. Wang, X. Xiao, J. Chao, L. Chao, D.W. Wang and D.C. Zeldin, 2003. Gene therapy with human tissue kallikrein reduces hypertension and hyperinsulinemia in fructose-induced hypertensive rats. Hypertension, 42: 1026-1033.
94. Kumar, V., L.C. Evans, T. Kurth, C. Yang and C. Wollner *et al*., 2019. Therapeutic suppression of mTOR (mammalian target of rapamycin) signaling prevents and reverses salt-induced hypertension and kidney injury in Dahl salt-sensitive rats. Hypertension, 73: 630-639.
95. Huang, L., C.G. Howard and K.D. Mitchell, 2012. Chronic direct renin inhibition with aliskiren prevents the development of hypertension in Cyp1a1-Ren2 transgenic rats with inducible Ang II-dependent hypertension. Am. J. Med. Sci., 344: 301-306.
96. Jauhiainen, T., T. Pilvi, Z.J. Cheng, H. Kautiainen and D.N. Müller *et al*., 2010. Milk products containing bioactive tripeptides have an antihypertensive effect in double transgenic rats (dTGR) harbouring human renin and human angiotensinogen genes. J. Nutr. Metab., Vol. 2010. 10.1155/2010/287030.
97. Honetschlägerová, Z., Z. Husková, Z. Vaňourková, A. Sporková and H.J. Kramer *et al*., 2011. Renal mechanisms contributing to the antihypertensive action of soluble epoxide hydrolase inhibition in Ren-2 transgenic rats with inducible hypertension. J. Physiol., 589: 207-219.
98. Sachetelli, S., Q. Liu, S.L. Zhang, F. Liu and T.J. Hsieh *et al*., 2006. RAS blockade decreases blood pressure and proteinuria in transgenic mice overexpressing rat angiotensinogen gene in the kidney. Kidney Int., 69: 1016-1023.
99. DeMarco, V.G., J. Habibi, A.T. Whaley-Connell, R.I. Schneider and J.R. Sowers *et al*., 2009. Rosuvastatin ameliorates the development of pulmonary arterial hypertension in the transgenic (mRen2)27 rat. AJP: Heart Circ. Physiol., 297: H1128-H1139.
100. Al-Qattan, K.K., M. Thomson, S. Al-Mutawa'a, D. Al-Hajeri, H. Drobiova and M. Ali, 2006. Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. J. Nutr., 136: 774S-776S.