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"A Comprehensive Review on Animal Models for Screening of Antihypertensive Drugs"

Suvidha s. Mane*, laxmikant m. Purane, vivekkumar k. Redasani
Department of pharmacology , yspm'syashoda technical campus , satara 415 011, maharashtra, india

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ABSTRACT
Hypertension is a major cause of death and disability, with cardiovascular disease and hypertension being the leading causes in wealthy nations. Animal models have been used to study its pathophysiology, aetiology, consequences, treatment, and antihypertensive medication evaluation. Genetically hypertensive rats are commonly used in therapeutic investigations. A summary of the traits and importance of both conventional and genetic animal models of hypertension is included as: In-Vitro Animal Models: Antagonism of Endothelin Receptors in Porcine Isolated Hearts and Monocrotaline induced pulmonary Hypertension. In-Vivo Animal Models: Rat Hypertension Models One-Kidney-Two Clip (Goldblatt hypertension, 2K1C), Rats with Chronic Renal Hypertension (1-kidney1-clip method), Dahl salt-sensitive rat model, Model of Fructose-induced Hypertension in rats, DOCO Salt rats , Pithed rats blood pressure model, Spontaneously Hypertensive Rats, Transgenic Rats Overexpressing Mouse Ren2 Gene (TGR (mRen 2) 27), Models of hypertension in dogs (Renal Chronic Hypertension), Neurogenic hypertension, Hypertension model of a monkey (Inhibition of renin in monkeys), Hypertension transgenic models , and Hypertension by chronic inhibition of nitric oxide. The most widely used animal models, their traits, and their importance are briefly summarized in this article on experimental models of hypertension, both genetic and traditional.
Keywords:cardiovascular; Pithed; Monocrotaline; genetic.

I. INTRODUCTION

The medical condition known as hypertension, which is characterized by a consistently elevated blood pressure, is referred to as "high blood pressure." The main causes of death are complications involving hypertension. The primary cause of essential hypertension in humans is mostly unclear. It is quite probable that the complex and diverse characteristics of hypertension result from the interplay of multiple genetic and environmental variables.Chronically high blood pressure is a major cause of chronic renal failure and a risk factor for heart attack, heart failure, arterial aneurysm and stroke. There are two types of hypertensions: essential and secondary. When a patient has essential hypertension, there is no clear medical explanation for their condition. If your blood pressure is depended on another condition, such as renal disease or some types of cancer, indicates that the high blood pressure was first produced by the other condition (particularly the adrenal gland)[1,2].

For those with diabetes mellitus or chronic kidney disease (CKD) who are 18 years of age or older, the recommended treatment threshold and goal blood pressures are the same as those for the general population under 60. This includes maintaining the target diastolic and systolic blood pressures below 140 mm Hg and 90 mm Hg, respectively, and the threshold systolic and diastolic pressures at 140 mm Hg and 90 mm Hg. There is no proof that lowering blood pressure in CKD patients can reduce the disease's surely, nor that keeping a systolic BP of less than 140 mm Hg benefits the health of persons with both diabetes and hypertension. Drug-Based Therapy Angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, calcium channel blockers, and angiotensin receptor blockers (ARBs) should all be a part of the first antihypertensive therapy for the general nonblack population, including those with diabetes. A calcium channel inhibitors or thiazide diuretic should be part of the first line of therapy for the general Black population, including those with diabetes.If the desired blood pressure is not reached within a month after beginning treatment, the first medication's dosage should be increased or another medication must be added. (ACE inhibitor or ARB, calcium channel blocker, thiazide diuretic;

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do not combine an ACE inhibitor with an ARB). Until the desired blood pressure is achieved, blood pressure should be tracked and the treatment plan modified as necessary. If necessary, a third medication should be added; however, antihypertensive medications from other classes (e.g., aldosterone antagonists, beta blockers) may be used if the goal blood pressure cannot be reached with just the drug types mentioned above. There is moderate evidence that ACE inhibitors and ARBs enhance renal-related outcomes in adults with hypertension and CKD, therefore these drugs should be used as initial or supplemental therapy. Eighth Joint

National Committee is the originator of the guidelines [3].
The new guidelines' classifications for blood pressure are:
• Normal: Normal: 120/80 mm Hg or below;
• Elevated: diastolic less than 80 and systolic between 120 and 129;
• Stage 1: either diastolic between 80 and 89 or systolic between 130 and 139;
• Stage 2:at least 90 mm Hg diastolic or 140 mm Hg systolic;
• A hypertensive crisis is defined as a systolic blood pressure of 180 and/or a diastolic blood pressure of 120.

Patients should be hospitalised very away if there are signs of organ damage, or their medications should be changed promptly if no other issues are present.

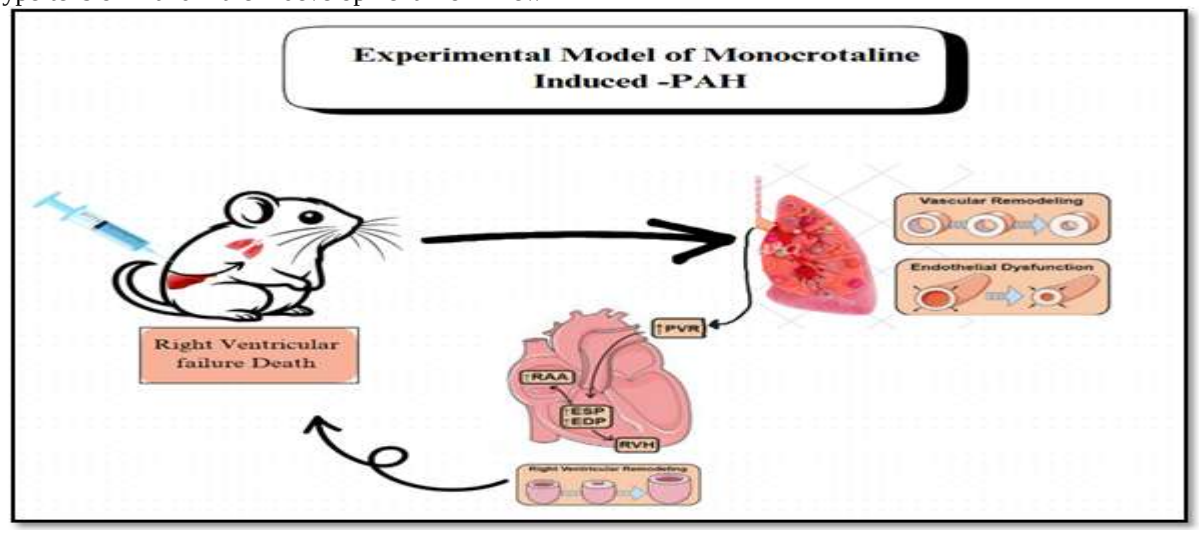
Research on the pathogenesis of hypertension and the development of new therapeutics have both benefited from the use of animal models. Human-like hemodynamic, cardiovascular anatomy, and physiology, human-like high blood pressure features and consequences, investigations of chronic stable HTN, and the ability to measure relevant hemodynamic and biochemical parameters are all requirements for the perfect animal model for HTN research[4,5]. The aetiological aspects were used in the design of many of these models —such as RAAS hyperactivity, high salt intake, and genetic aspects—that are believed to be responsible for clinical hypertension.Several animal models of hypertension have been covered in this study, each with unique advantages and disadvantages[6].

METHODS (ANIMAL MODELS) FOR SCREENING OF ANTIHYPERTENSIVE DRUGS

❖ **IN -VITRO ANIMAL MODELS –**

I. Monocrotaline-Induced Pulmonary Hypertension-

Rats are exposed to monocrotaline, a hepatotoxic and pneumotoxic drug, to induce pulmonary hypertension. A single injection of this pyrrolizidine alkaloid, which is derived from the Crotalaria spectabilis plant, results in Heart attack, progressive pulmonary hypertension, and right ventricular hypertrophy [7,8]. The pulmonary arteries and arterioles likewise show ultrastructural changes, including muscularization, perivascular oedema, fragmentation and endothelial cell senescence, and RBC extravasation.



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An Experimental Model of Pulmonary Arterial Hypertension (Pah) Induced on By Monocrotaline. Vascular Remodelling and Endothelial Dysfunction After Monocrotaline Injection Cause Rats' Pulmonary Vascular Resistance (Pvr) To Gradually Rise, Which in Turn Causes Right Ventricular Hypertrophy (Rvh), Elevated Rv Systolic and Diastolic Pressures, And an Increase in Right Atrial Area (Raa). The Animal Eventually Dies of Rv Failure as A Result of Rv Function Gradually Declining Due to The Progressive Increase in Pvr. End-Diastolic Pressure (Edp); End-Systolic Pressure (Esp)[9].

In rats, monocrotaline administration can result in pleural effusion, ascites, and severe right ventricular hypertrophy. Monocrotaline Administration A single subcutaneous injection of monocrotaline at a dose of 100 mg/kg is administered to 200–225 g Sprague Dawley rats after they have been fed the test medication for a week. The animals are killed four, seven, or fourteen days after receiving a high dose of anaesthesia (hexobarbital sodium), and their hearts and lungs get removed from the thoracic cavity. The major rightextrapulmonary artery, intrapulmonary artery, and pulmonary artery are among the pulmonary artery segments that are identified by weighing the left ventricle and lung.Each vessel is suspended between stainless steel hooks in tissue baths that contain Krebs-Henseleit buffer that is aerated with 5% carbon dioxide 95% oxygen and at 37 °C. Vessel segments are cleaned, weighed, and measured at the end of the study. Tissue weight and diameter are used to determine an artery's cross-sectional area. After an hour, theKCl (6 × 102 M) causes the arteries to narrow.The maximum active force produced by an artery is shown as a function of applied force using force displacement transducers, which also measure and record changes in isometric force on a polygraph.

Contractile as well as relaxant agonist responses are measured in the pulmonary arteries. Plots of the cumulative concentration-response curves for AT, noradrenaline, KCI, and angiotensin II are plotted. The force generated per cross sectional area and active tension development are used to measure contractions. Plotting of the relaxation and contractile responses against the negative logarithm of agonist concentration is done. A t-test for grouped data is employed to compare mean response differences [10,11].

II. ANTAGONISM OF ENDOTHELIN RECEPTORS IN PORCINE ISOLATED HEARTS

Cardiovascular disease aetiology has been connected to endothelin (ET). The isolated coronary artery in a pig is employed in this model because the ETA receptors are situated in the artery's smooth muscle. ET induces isolated blood vessel strips to contract powerfully and consistently[12]. Studies conducted both in vivo and in vitro have shown that endothelin peptides arise blood pressure.The study included six 12-week-old domestic crossbred female pigs weighing between 30 and 40 kg. The pigs are sedated using xylazine (0.03 mg/kg/min) and ketamine (0.2 mg/kg/min). A left thoracotomy is used to reveal the heart. Porcine hearts are used to isolate the left anterior descending coronary arteries. Before they are cleaned, the connective tissue and fat are removed. The arteries that have lost endothelium are sliced into spiral strips that are 1 mm broad and 10 mm long. The intimal surface of the spiral rings is gently scraped with filter paper to remove the vascular endothelium. A Krebs Henseleit solution bubbled with 95% O2/5% CO is used to hang each strip at 37 °C. 50 mM KCl is used for obtaining isometric contraction after stabilizing the isolated substance.The ET-1 concentration response curves are produced by adding ET-1 cumulatively.Twenty minutes prior to the administration of ET-1, test drugs and endothelin receptor antagonists are introduced to the organ bath, and the concentration response curve is recorded. Schild plot analysis shows pA, values, and slopes[13].

❖ IN-VIVO ANIMAL MODELS

I. Dahl Salt-Sensitive Rat Model

The kidneys can efficiently eliminate the daily salt load without significantly raising extracellular volume. However, general epidemiological studies have shown that the average sodium intake in a population will rise along with the prevalence of hypertension.Rats with chronically excessive salt intake develop hypertension, which morphologically resembles human hypertension.

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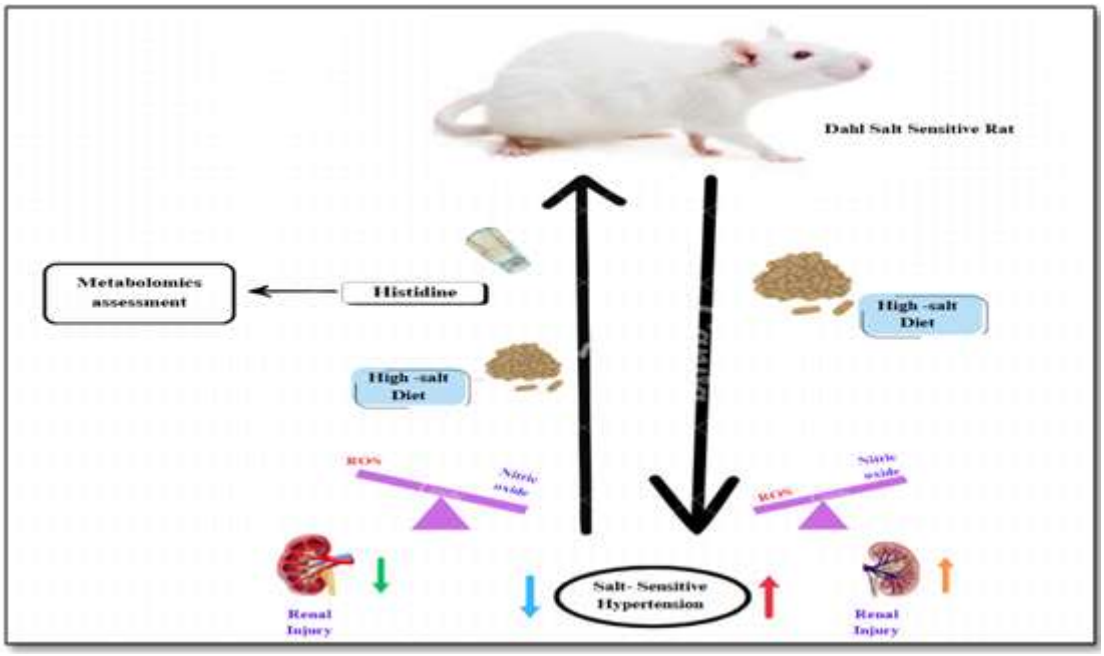

Oral Histidine's Protective Action Against Hypertension In Rats Having Dahl Salt Sensitivity Induced on By A High-Salt Diet[14].

Salt-sensitive Dahl rats that are fed high-sodium diets develop severe and occasionally fatal hypertension, while salt-resistant Dahl rats do not suffer from the same type of hypertension.Regular salt consumption causes the salt-sensitive rats to develop hypertension, demonstrating that this is a model of hereditary hypertension with the added characteristic of salt sensitivity [15].For this study, 250–300 g Sprague Dawley rats are used. The drinking water is replaced with a saline solution that contains 8% NaCl. Salt is added to a regular meal in a laboratory diet to make a high-Dahl salt diet. The animals are given unlimited access to the 8% NaCl solution and preparedmeal. Blood pressure fluctuations between the various experimental groups are recorded at pre-established intervals. Blood pressure continuously increases after a week, reaching systolic values of 160–180 mm Hg later four weeks. The animals are divided into two groups:the sham control group, which got no therapy, and the treated group, which received the drug orally for a month.At the conclusion of the experiment, the animals from both groups—those who received therapy and those that received a sham treatment—are slaughtered. The weight of the right and left ventricles, and overall cardiac mass, are measured and compared after their hearts are removed. Rats fed salt (8% NaCl) have an extreme rise in blood pressure, which only slightly lowers their levels comparedto rats with spontaneous hypertension (up to 32%). The test drug's ability to reverse these changes is being examined [16].

II. Model of DOCO Salt Rats

Mineralocorticoids enhance extracellular volume and plasma, which results in hypertension. In rats, unilateral nephrectomy and salt loading increase the hypertensive effects. When a high-sodium diet and unilateral nephrectomy are combined with the mineralocorticoid deoxycorticosterone acetate (DOCA), hypertension results. Increased salt and water reabsorption carried on by DOCA led to a rise in blood volume and, ultimately, BP. Additionally, there is a rise in vasopressin secretion, which results in vasoconstriction and water retention. Furthermore, altered RAAS activity leads to increased sympathetic activity. Compared to the high renin levels in the other model, the renin levels in this model are low. Male Sprague Dawley rats weighing between 250 and 280 g are anaesthetised using ether. The left kidney was removed by making a cut along its flank. For four weeks, deoxycorticosterone acetate (20 mg/kg) diluted in olive oil was injected subcutaneously into rats twice a week. Use 1% NaCl solution instead of drinking water. Blood pressure arises to rise after a week, and after four weeks, the systolic blood pressure reaches about 160 to 180 mm Hg. DOCA implants or pellets in silastic devices can be used as

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an alternative to repeated injections. Animals are randomly allocated to either the sham control (untreated) or treatment (test drugs given orally for one month) groups. Blood pressure is recorded in each of the various experimental groups at scheduled intervals throughout the experiment.At the end of the experiment, the animals are slaughtered and their hearts are weighed. Changes in renal function (including glomerulosclerosis and proteinuria) and blood pressure, are recorded and compared between the two groups to assess the effectiveness of the test drug in lowering blood pressure [17].

III. Rat Hypertension Models One-Kidney-Two Clip (Goldblatt Hypertension, 2K1C)

Blood pressure rises when renal ischaemia activates the renin-angiotensin system. Rats' renal arteries can be constricted for four hours to cause renal hypertension. The sympathetic nervous system and peripheral RAAS system are activated by this process. Reopening the vessel causes stored renin to be released into the bloodstream, which leads to acute hypertension.When sympathetic activity increases, the kidneys release renin. Angiotensinogen is converted into angiotensin L via renin. Blood pressure is raised when angiotensin-I is converted to angiotensin-II (ACE) through the angiotensin converting enzyme.Aldosterone production is also triggered by angiotensin-II, which increases blood pressure and increases water and salt retention [18,19]. This model is used to evaluate a drug's ability to lower blood pressure. To give anaesthesia in 300-g Sprague Dawley rats, 100 mg/kg of hexobarbital sodium is administered intraperitoneally.In the left lumbar area, an incision is made toward the flank, parallel to the rat's long axis. Which renal they are is known. A PVC-coated clip connects the kidney's left hilum to the back muscles. Blocking the renal artery takes 3.5 to 4 hours. Ganglionic blocking is carried out using pentolinium, and after the blood pressure has stabilized at a lower level, the "renal arterial clip" is removed. The animals are subsequently given pentobarbitone sodium intraperitoneally (30–40 mg/kg) to cause anaesthesia. The trachea is cannulated to promote spontaneous breathing.A pressure transducer is used for measuring blood pressure in the carotid artery.The test substance is administered by cannulating the jugular vein. An increased plasma renin level causes blood pressure to rise as a result. The test drug is administered via intravenous routes. Blood pressure is continuously monitored.Blood pressure was shown to rise afterwards the reopening of the renal artery and fall after the administration of the test drug. calculated the % reduction in blood pressure from baseline levels with drug therapy. Only one side of the renal artery is narrowed; the other kidney (or artery) remains uninjured. Plasma rennin activity increases as a result. However, there is no retention of water or salt because the other healthy kidney continues to function regularly. Consequently, the ensuing hypertension is now dependent on renin-angiotensin [20,21].

IV. Rats With Chronic Renal Hypertension (1-Kidney-1-Clip Method)

Renal ischaemia results in hypertension, as was previously mentioned. The process has changed in different ways for various species of animals. The one-kidney, one-clip method is one of the most effective adaptations for removing a single kidney in rats. The opposing renal is removed, and one side of the renal artery is constricted.The blood pressure rises after a few minutes. Since there is no second kidney, there is rapid water and salt retention and no pressure diuresis or natriuresis. Usually, plasma rennin activity is normal.It produces volume dependency in rats with chronic renal hypertension (1-kidney-1-clip technique) very quickly.

As previously reported, hypertension is a result of renal ischaemia. For several kinds of animal species, the process has been documented in multiple forms.The one-kidney, one-clip method is among the most effective adaptations in rats when one kidney is removed. Renal artery narrows on one side results in the removal of the contralateral kidney.The blood pressure rises a few hours later. Rapid salt and water retention results from pressure diuresis and natriuresis, which are prevented by the absence of a second kidney. The norm is normal plasma rennin activity. The onset of volume dependence in hypertension is rapid. The anaesthesia is given intraperitoneally to 200–250 g Sprague Dawley rats using pentobarbitone sodium (50 mg/kg).The kidneys are exposed by making a flank incision in the left lumbar area, which runs parallel to the rat's long axis. The renal artery is visible when the kidney retracts. The renal artery is cleaned, dissected, and then inserted near the aorta with a U-shaped silver clip.The internal gap can be altered to be between 0.25 and 0.38 nm by changing the clip's size. Prior to the removal of the right kidney, the renal pedicel is tied off. Four to five weeks after clipping, rats are divided into many groups and administered different dosages of

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the test drugs, and their blood pressure is also measured.Every dose uses a different animal as the control. The test chemicals are administered over the course of three days.Before and two hours after administering the drug, blood pressure is measured.The antihypertensive effect of the test medication is evaluated by compared the treatment blood pressure measurement with the pre-drug blood pressure on day 1. To compare values and identify if they are statistically significant, the paired t-test is utilized [22,23].

V. Model of Fructose- Induced Hypertension in Rats

Giving Sprague-Dawley rats a high-fructose diet in order to cause insulin resistance and hypertension.Fructose also causes hypertriglyceridemia, insulin resistance and hyperinsulinemia in healthy rats. Angiotensin-Il Type (AT) receptor expression increases in adipose tissue when fructose is consumed by normal or well-fed animals, resulting in hypertension.AT receptors are involved in the pathophysiology of the hemodynamic and metabolic alterations caused by fructose consumption.The 200–250 g Wistar rats are kept in cages with a 12-hour dark-light cycle, a bed war diet, and continuous eating. Fructose solution makes about 10% of the water we drink. Every week while the rats are on drug therapy, their body weight, fluid intake and food, and other data are recorded. The pulse rate and systolic blood pressure are measured using the radiotelemetry or tail-cuff method. Blood is drawn to check insulin, glucose, and lipid levels before and every other week during treatment [24].

VI. Pithed Rats Blood Pressure Model

The pithed rat model loses the neurogenic reflex control that could change the primary pharmacological effect. It is often used to evaluate the effectiveness of medications on the cardiovascular system[25].

Male Wistar rats weighing 250–350 g is put to sleep with halothane. The carotid artery is cannulated in order to collect blood samples and monitor blood pressure.After the animal's trachea is cannulated, artificial breathing (60 cycles per minute) is maintained using a ventilator pump. Additionally, the test medication is also given by cannulating the jugular vein. In order to do pithing, a steel rod of 11 cm in length and 2.2 mm in diameter is passed through the spinal canal, orbit and foramen magnum.inspired air is made more oxygen-rich,by passing an oxygen flow through a T-piece connected to the ventilation pump's air inlet. 0.3 ml of blood is drawn from the carotid cannula 30 minutes after spitting in order to assess the bicarbonate, pH, pO2, and pCO2 concentrations using a blood gas analyser. The carotid artery is used to assess cardiac frequency and blood pressure.The carotid artery is used to monitor heart rate and blood pressure. To quantify a and an antagonism, initial DRC are recorded for the selective an agonists BHT 920 phenylephrine (0.1-30 g/kg, iv route) as well as (1 1000 g/kg, iv route). 15 minutes following the intravenous administration of the test drug, the agonist DRC are repeated. The response of blood pressure to the agonist curve is obtained. DRC are plotted using logarithmic probit scales. The potency ratio is determined using the DRC [26].

VII. Spontaneously Hypertensive Rat Model

Okamoto and Aoki developed the SHR strain of spontaneously hypertensive Wistar rats by mating a strain of spontaneously hypertensive Wistar with a female that had a slightly elevated blood pressure. Thorough genetic inbreeding was used to make SHR, and 100 percentage of the progeny consistently had naturally occurring high blood pressure. Since then, various expert panels have declared the fact that SHR is a great example of experimental high blood pressure and might be utilised as a model for hypertension problems as well as an alternative to clinical primary hypertension[27].

When these rats are 5 to 6 weeks old, their blood pressure starts to rise and keeps rising until it reaches a high systolic of 180 to 200 mm Hg.Multiple symptoms of hypertensive end organ damage manifest in the SHR, including renal impairment, heart hypertrophy and heart failure. However, they don't have any overt vascular problems. Other than decreased endothelium-dependent relaxations, they do not typically experience strokes, develop vascular thrombosis, or develop macroscopic atherosclerosis vascular thrombosis. The SHR stroke prone (SHR SP), a more severe sub-strain, has a higher risk of stroke death and higher blood pressure.A variety of genes that seem to co-segregate in various crossings have been identified using the SHR, which has been commonly used to evaluate genetic factors in hypertension. However, this has not always been confirmed. Other models of genetically determined spontaneous hypertension include the Milan hypertensive (MHS),New Zealand strain of genetic hypertension (GH-Smirk), the Dahl's salt susceptible (S) and salt resistant (S) strains, the stroke-prone and stroke-resistant sub strains of

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SHR (SHRSP and SHRSR), the arteriolipoidosis-prone SHR (SHRLP'), the Lyon' stain, the obese SHR stain, and the Smirk with the Wistar Kyoto strain, extensive expertise has been gained [28].

VIII. Neurogenic Hypertension Model

Baroreceptors in the aortic arch and carotid sinus play a major role in controlling blood pressure. Along the 9th and 10th cranial nerves, baroreceptor afferents move. The medulla oblongata's nucleus tractus soloitarius (NTS) is the location where the first synapses are located. The nucleus tractus soloitarius gets information from the periphery and has complex synaptic connections and innervations from many different parts of the brain, making it more than simply a relay centre. Vasodilation, bradycardia, and hypotension are the results of baroreceptor activation, which suppresses the vasomotor centre. Blood pressure increases gradually as baroreceptor nerves are separated. As a result, dogs that adopt this technique suffer acute neurogenic hypertension [29]. Adult dogs weighing 10 to 15 kg are anesthetized with a mixture of 60 mg/kg sodium pentobarbital, 15 mg/kg thiopental and 200 mg/kg sodium barbital. The femoral vein is cannulated to receive test chemicals, while the femoral artery is utilized for measuring heart rate and arterial pressure. The common carotid artery can be utilised to measuredP/dt and left ventricular pressure using a Millar microtip pressure transducer. Pmax and cardiac output are also estimated. At this stage, external and internal carotid arteries separate. A bilateral vagotomy is performed, and the carotid sinus nerves are located, ligated, and sectioned in order to induce neurogenic hypertension.afterwards a 30-minute equilibration period, an intravenous bolus of the test medication takes place. It is required to measure the blood pressure, heart rate, P, left ventricular pressure, and maximal dP/dt for 90 minutes. Modified cardiovascular parameters are displayed as a % of their pre- and post-drug values [30].

IX. Hypertension Transgenic Models

Transgenic models of hypertension can be produced by overexpressing a certain gene. This model allows you to investigate the role that a specific gene plays in the pathophysiology of conditions such as hypertension. The following are examples of this kind of hypertension: The TGR (mREN2)27 transgenic rat, created by Mullins, inhibits endogenous renal renin. It was initially reported by et al. in 1992 in "Bader et al [31]. Starting on the fifth heartbeat, TGR patients develop full-blown hypertension (200–260 mmHg means systolic blood pressure), more endothelial dysfunction and only a week of age-matched hyperplasia and more myocyte hypertrophy,less severe than age- and blood pressure-matched SHR,4 months old with structural nephron lesions.Despite the model's limitations, it allows for in vivo analysis of the consequences of severe, monogenetic hypertension, which is representative of human hypertension, with the exception of a general variation in the growth of myocyte hypertrophy at week of age. When the Ras is activating, it is possible to identify the type of harm associated with hypertension that can be expected when the Ras is active [32].

X. Transgenic Rats with Mouse Ren2 Gene Overexpression (TGR (Mren 2)

The ability to create transgenic animals and insert particular genetic constructs has opened up new research directions in the field of hypertension. A transgenic rat recently developed after the entire mouse Ren2d gene was introduced [33].The introduction and overexpression of the mouse Ren-2 gene in homozygous rats causes severe hypertension, which is harmful. Two significant features of this rat model are that it is a genetically inherited form of hypertension for which only one genetic event is known, and that even though this genetic change is well understood, the exact mechanism triggering hypertension is still unknown. The high blood pressure and subsequent harm to the end organs in this hypertensive paradigm are caused by increased local angiotensin II production,it responses effectively to suppression of RAS. The degree of hypertension is slightly affected by the genetic composition of the rats used to breed the TGR (mRen2) 27. An accelerated and malignant form of hypertension develops when these rats are crossed with Sprague-Dawley rats. In other transgenic models, the presence of both human angiotensinogen and renin causes high blood pressure in rats and mice. The knockout models no longer contain the genes for Nitric Oxide (NO)-Synthase and Atrial Natriuretic Factor (ANF). Rats without the ANF receptor exhibited salt-sensitive hypertension, as compared to rats lacking the type A ANF receptor, which developed salt-independent hypertension. These models can be used to screen for various antihypertensive drugs [34,35].

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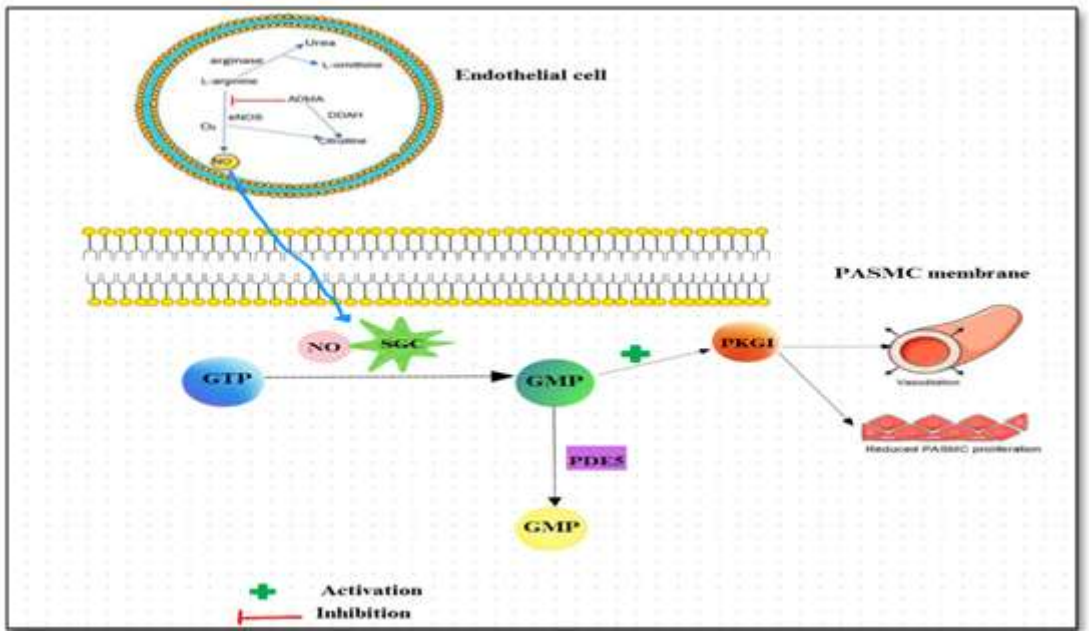
XI. Hypertension by chronic suppression of nitric oxide

Nitric oxide (NO) has a major effect on regulating the consequences of systemic vascular resistance by functioning as a tonic vasodilator. LNAME, an oral nitric oxide synthase inhibitor administered over a longer period of time, was linked to glomerular renal with ischaemia and glomerulosclerosis,interstitial infiltration, and chronic hypertension. The hypertension is related to significant peripheral vasoconstriction and the subsequent rise in peripheral vascular resistance [36]. Even with long-term NO synthase inhibition, there seems to be some evidence of a drop in cardiac production. The body's vasospasm ' action to NG-Nitroarginine methyl ester has also been shown to be a likely fundamental genesis of sympatho-excitatory activity, as it plays a major role in the development and maintenance of hypertension and sympathetic tone [37]. In terms of cardiac abnormalities, the degree of hypertrophy in this animal is actually quite low when compared to other models with similar blood pressure readings. A particular pattern of left ventricular (LV) remodelling, characterized by a decrease in LV chamber size in relation to wall thickness without an increase in LV mass blood pressure, is associated with pressure overload brought on by l-NAME [38]. However, the sympathetic nervous system is unable to appropriately control its response to the increase in blood pressure due to the increased difficulty of consuming more salt in the diet [39].



The Lack of a Pathway. Soluble Guanylate Cyclase, Nitric Oxide, Sgc, Gtp, Guanosine Triphosphate, Cgmp, Cyclic Guanosine Monophosphate, Pde5, Phosphodiesterase 5, Gmp, Guanosine Monophosphate, Pkgi, And Protein Kinase Ii. Enos, Pulmonary Arterial Smooth Muscle Cell, O2, Oxygen, Adma, Asymmetric Dimethylarginine, Ddah, Dimethylarginine Dimethylaminohydrolase, And Endothelial Nitric Oxide Synthase[40].

XII. Monkey Hypertension Model (Monkey Renin Inhibition)

Renin inhibition changes the renin-angiotensin system, which is mainlyimportant for blood pressure regulation.Renin, an aspartyl protease, hydrolyses angiotensinogen in order to produce angiotensin-I. Angiotensin I is subsequently changed into angiotensin II by the angiotensin converting enzyme. The renin inhibitors that are now on the market only slightly block renin in sub-primate animals and are quite selective for primate renin. This suggests that renin inhibitors cannot be evaluated in vivo using the most commonly used experimental animals, such as dogs and rats [41]. Marmosets (Callithrix jacchus) weighing between 300 and 400 g are supplemented with fruits and fed a pellet diet. The animals are put to sleep two days before to the experiment, and catheters are placed in the femoral artery to take blood pressure measurements.The

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lateral tail vein is cannulated in order to receive test drugs. An IV dose of furosemide (5 mg/kg) is administered 30 minutes prior to the experiment in order to promote Renin's release. The marmosets are kept in isolation boxes during the study and administered diazepam (0.3 mg/kg, ip) to induce them anaesthesia. Continuous recordings are taken of the average heart rate and blood pressure. Methods for Drug Testing Measurement are made at predetermined times. Both the standard medicine and test drug are administered intravenous infusion or by orally. Blood pressure is measured 30 minutes into the intravenous infusion and 30 minutes after the infusion ends. Variations from baseline values are observed when comparing various medication dosages. Dose-response curves can be created [42].

XIII. Dog Hypertension Model (Renal Chronic Hypertension)

Hypertension developed in dogs whose arteries of the kidneys were partially constricted. A modified version of this method is called the "wrapping technique." The kidney is wrapped in cellophane, which is fastened to the renal hilus with loosely knotted silk sutures.It is possible to wrap one kidney while removing the other, or to wrap both kidneys. The tissue's reaction to the foreign material leads a fibro collagenous shell growing around the kidney in 3–5 days. This shell reduces renal vascular pressure by compressing the renal parenchyma. As a result, the extracellular volume increases, which raises blood pressure and peripheral resistance [43].

Dogs weighing 8 to 12 kg are put to sleep by intravenous administration of 15 mg/kg of thiopental.After a midline abdominal incision, one kidney is seen.It is wrapped in cellophane then replaced. Before being removed, the contralateral kidney gets exposed and the vein, ureter, and artery ureter are tied.After that, the abdomen is closed and tied back together. The animals are given drugs and allowed time to heal after surgery. Six weeks after surgery, blood pressure is monitored. Blood pressure is measured usingan indirect tail cuff process. Test drugs will be given over a duration of five days.On the first day, readings are taken every two hours immediately before oral medication and again two and four hours later. On days three and five, blood pressure is measured prior to, during, and after drug therapy. The average of both readings obtained before the medication was administered is the starting value. By subtracting this value from the prior data, the subsequent values are recorded as a drop in blood pressure at the various measures [44, 45].

XIV. Angiotensin II-Induced Hypertension

Evidence suggests that the SNS plays a significant role in activating vascular and renal Ang II, especially at lower dosages in rats and mice, despite the fact that many would contend that the Ang II AT1 receptor is the mechanism of activation [46,47]. Neuronal NOS and IL-1β are down-regulated in the SNS, same like in the SHR. Superoxide dismutase overexpression, however, reduced Ang II-induced hypertension, suggesting that the superoxide anion also plays a significant function in the subfornical organ [48]. Furthermore, a neurogenic form of hypertension in rats caused by prolonged infusion of Ang II is inhibited by ganglion blocking with hexamethonium and is related to enhanced expression of AT1 receptors in the rostral ventrolateral medulla and sub fornical organ[49]. A significant function of the SNS in this hypertension model is supported by the finding that the full development of angiotensin-dependent hypertension requires activation of AT1 receptors on catecholaminergic cells. the several systems that control the blood pressure that Ang II raises[50].

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