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EXPERIMENTAL MODELS OF HYPERTENSION REVIEW: A TAILORED APPROACH

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Abstract: Hypertension is a multifactorial disease with complex etiology. Either hypertension itself or its consequences are leading causes of death in many countries because of its multipart nature it's difficult to find single culprit for it. So, laboratory animals are used to mimic those conditions artificially. Animal models of hypertension are proven useful in knowing etiology, pathophysiology, complications, treatment and testing of new compounds. Selection of model should be made wisely according to research aim, available finances and technical experts. The aim of this review is to present a tailored approach of current available models and brief information to reproduce those models.

Keywords: Animal models, hypertension (HT), experimental hypertension, RAAS, blood pressure (BP).

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INTRODUCTION

Hypertension is defined as repeatedly elevated blood pressure exceeding 140 over 90 mm Hg. It is one of the most common cardiovascular diseases which itself is not that much dangerous as their secondary complications if ignored or left untreated. Due to its high incidence and related morbidity many groups and regimens of drugs have been proposed to control the hypertension, but still research is continuing to developing more suitable drugs for hypertension of various etiologies from the last couple of decades. With the aid of both advancement in research tools and elucidated molecular pathways had broaden our view regarding mechanisms involved in the pathogenesis of hypertension.

Various animal models are present today those exhibit similar features which are common to human hypertension. So, many of these models have been developed by utilizing the etiological factors that are presumed to be responsible for human hypertension such as excessive salt intake, hyperactivity of renin angiotensin- aldosterone system (RAAS), social factors like stress, genetic factors and many more. The animal models are used in the pharmacological screening of potential antihypertensive agents.

As the new drugs are developing with their respective actions, the utility of animal's models had also increased with the passage of time. New animal models of hypertension are being developed as new insights in to the pathogenesis of hypertension are revealed.

MATERIALS AND METHODS

Various animals species had been already used to produced various models of hypertension in the scientific literature those models are based on the various mechanisms. By altering those physiological mechanisms mechanically result in production of hypertension, majority of them are briefly discussed in figure-1 and details of the outcome models of hypertension are enlisted in table-1

Figure 1: This figure represent the RAAS and other possible mechanisms involved in the induction of hypertension in various animal models

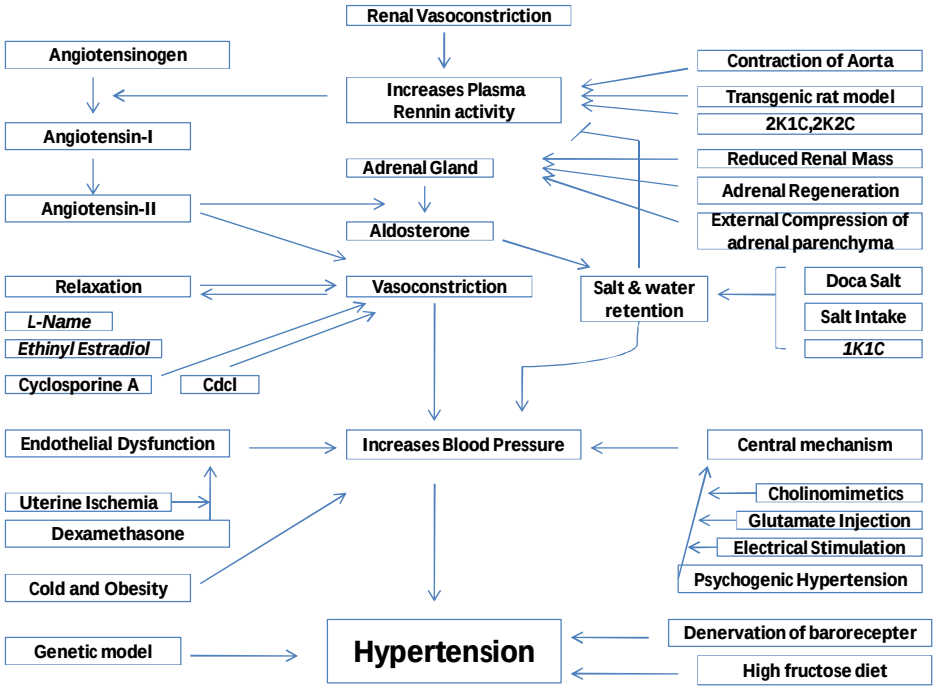

Table 1: Different models of hypertension.

Major Categories	Animal models		References
Surgical models of hypertension	Goldblatt method	2K1C	[1][2][3]
		1K1C	[1][2][3]
		2K2C	[2]
	Hypertension induced by external compression of renal parenchyma	Page hypertension	[3][4][5]
		Grollman Hypertension	[6]
	Uterine ischemia		[7][8][9]
	Coarctation of aorta		[10][11][12]
	Reduced renal mass		[13]
	Adrenal regeneration hypertension		[14][15][16]
	Electrical stimulation of hypothalamus		[17]
	Denervation of sinoaortic barorecepters		[2][14][18][19]
Non Surgical model of hypertension	Diet induce hypertension	Increase salt intake	[20][21]
		Fructose administration	[22][23][24][25] [26]
	Transgenic rat model of hypertension		[27]
	Psychogenic hypertension		[28][29][30]
	Genetic hypertension		[31][32][33][34][35][36]
	Obesity related hypertension		[37]
	Environmentally induced hypertension	Cold induce hypertension	[38][39]
Chemically induced models of hypertension	Mineralocorticoid induce hypertension	DOCA salt induce hypertension	[20][40][41][42][43][44] [45][46]
	Glutamate injection in rostral ventrolateral medulla(RVM)		[47]
	Cholinomimetic agents induce hypertension		[48][49][50]
	Angiotensin-II induce hypertension		[51][52]
	Cadmium induce hypertension		[44][52]
	Chronic nitric oxide inhibition induce hypertension		[53][54]
	Ethinyl estradiol induced hypertension		[55]
	Cyclosporine induced hypertension		[56][57]
	Dexamethasone induced hypertension		[58][59][60][61]

I. Surgical models of hypertension

1. **Goldblatt method:**

(a) **Two kidneys one clip hypertension (2K1C)**: H. Gloldblatt in 1960 proposed method to produced hypertension in rabbit by constricting one renal artery at a time while other remained as such which result into sustained increase in blood pressure (BP) due to increased plasma rennin activity, it further cause increased availability of angiotensin-II (a potent vasoconstrictor) which leads to hypertension. Resultant hypertension occurred at this stage was only rennin angiotensin dependent because there is no salt and water retention. However, salt and water retention may occur after about 6 weeks of this procedure due to release of aldosterone from adrenal cortex, where adrenal cortex is stimulated via increased level of angiotensin–II. Enhanced salt and water retention leads to decreased rennin production and hence hypertension from this stage on wards is become volume dependent [1,2,3]. So, water and salt are critically involved in the pathogenesis of hypertension of renovascular origin. Unclipping or removal of affected kidney normalize the both BP and rennin activity [3].

(b) **One kidney one clip hypertension (1K1C)**: In this procedure constriction of one renal artery is done while other kidney is removed, which leads to increase in BP in few hours because of no other kidney to produce diuresis and natriuresis. So in this case rapid water and salt retention take place which result into volume dependent hypertension soon. Plasma rennin activity usually remains normal in this procedure [1,2,3].

(c) **Two kidneys two clip hypertension (2K2C):** In this model constriction of both renal arteries is done which result's into formation of patchy ischemic tissue due to lack of proper blood circulation. This ischemic renal tissue secretes rennin which leads to increased BP and the remaining tissue of the kidney retains salt and water. This type of renal hypertension is one of the common causes of patch ischemic diseases in human beings [2].

2. Hypertension induced by external compression of renal parenchyma:

(a) **Page hypertension:** This type of hypertension was first produce successfully by I. H. Page. In this procedure a cellophane sheet is tied with the help of silk suture so that it remains in close touch with kidney, consequently fibrocollagenous shell is formed around the kidney within 3-5 days due to reaction with foreign material. Formation of this shell compresses renal parenchyma leading to decreased renal vascular pressure. This expands extracellular volume which further lead to increased peripheral resistance and then increase BP. In this case either both the kidneys are covered or one is covered and other is removed [3,4,5].

(b) **Grollman hypertension:** According to this method also kidney tissue are compressed to produce hypertension but by means of securing figure 8 around the kidney with the help of

a ligature. This type of hypertension can be produce in different animals like dogs, rabbits and rats[6] Its of two types:

(1) Two kidneys one ligature (2K1L): In this, ligature is applied to one kidney and other remained untouched.

(2) One kidney one ligature (1K1L): In this, ligature is applied to one kidney but other kidney is removed.[6]

3. Uterine Ischaemia: Uterine ischaemia can produce hypertension as seen in clinical condition of preeclampsia [7,8]. It was found that in monkeys at 116±7day of gestation, lower aortic pressure was reduced by 24±11 mm Hg by a stricture on the aorta just below the renal arteries and due to reduction in the BP animals developed sustained hypertension [9].

4. Coarctation of aorta: By compressing the aorta renal blood flow can be decreased. Coarctation can be done just above the renal arteries i.e. between renal arteries and superior mesenteric arteries or between two renal arteries with the right artery above and the left artery below the site of coarctation [10]. If rubber band is applied to abdominal aorta along with constriction of right renal artery for 8 weeks then it results to increase in BP similar to 2K1C model [11]. Coarctation can be followed by unilateral nephrectomy to produce this type of hypertension [12].

5. Reduced renal mass: Surgically reducing renal tissue to five-sixth (5/6th) by renal mass ablation produces hypertension. In this method, the right kidney is removed completely and 2 or 3 branches of left renal artery are ligated to produce infarction of approximately 2/3rd of the left kidney [13]. Removal of this 5/6th of renal mass result into sustained systemic hypertension. While the mechanism of hypertension associated with renal mass ablation remains unclear [13].

6. Adrenal regeneration hypertension: Unilateral nephrectomy followed by removal of right adrenal gland and enucleation of left adrenal gland in rats produced hypertension. Enucleation is carried out by making a small incision in adrenal gland through which the bulk of glandular tissue is extruded from the capsule by gentle application of pressure and drinking water is replaced with 1% saline. Hypertension develops during regeneration of adrenal gland in about 2 weeks [14]. Once hypertension had been established then it's difficult for BP to come to normal even after removal of the regenerated adrenal tissue or substitution of saline with drinking water [15]. This type of hypertension readily develops in female rats and young rats [16].

7. Electrical stimulation of hypothalamus: Electrical stimulation of posterior hypothalamus (PH) of brain results in development of hypertension in animals. During the reproduction of this model, a bipolar concentric electrode was stereotaxically placed in the PH and electrical

stimulation was delivered at 20, 60 and 100 Hz (3-seconds duration, 0.1 milliseconds pulse width) result in increase in blood pressure. Spontaneous hypertensive (SHR) rats respond with significant greater increase in BP than other strains [17].

8. Denervation of sinoaortic barorecepters: This type of model can be reproduced on various animals like dogs, rabbits and rat. In dogs cardioaortic nerve runs in the form of several fine strands and can be easily detected at the junction of superior laryngeal and vagus nerve. These strands unite and may be traced back as a white band lying within the vagal sheath alongside the cervical sympathetic nerve [14]. After bilateral vagotomy and carotid sinus denervation to ensure complete denervation of the carotid sinus 5% phenol and then alcohol is used at surgical site this denervation procedure results in sudden increase in BP [18]. Then the dog is allowed to equilibrate for approximately 30 minutes and a bolus of the test compound which is to be tested for its action can be given by IV route. BP returns to normal within about 2 days because the response of vasomotor centre in the absence of baroreceptor signals fades away, which is called "resetting of baroreceptors". Thus, this is only an acute type of hypertension [2].

In case of rabbit, right carotid sinus can be removed together with the right cervical sympathetic and depressor nerves while the left carotid sinus can be removed later on [19].

In case of rats, only sinoaortic denervation leads to marked and sustained increase in BP, which is comparable to renovascular hypertension or DOCA-induced hypertension [19].

II. **Non surgical model of hypertension**

1. Diet induce hypertension

(a) **Increased salt intake:** In physiological conditions kidneys are able to excrete normal daily intake of salts efficiently without marked rise in extra cellular volume but chronic ingestion of excess salts produce hypertension in rats which is similar to human hypertension up to major extent. This type of hypertension has been produced in both chicks and rabbits by replacing drinking water with 1-2% sodium chloride for 9-12 months [20,21].

(b) **Fructose administration:** Several studies have shown that chronic fructose feeding in normal rat result into insulin resistance, hyperinsulinemia and hypertriglyceridemia in short time [22,23,24]. In this model a fructose rich diet consist of 21% protein, 5% fat, 60% carbohydrate, 0.49% sodium and 0.49% potassium is given to male Spraque Dawley rats for 5 weeks which produced hyperinsulinemia, hypertriglyceridemia and hypertension. If same diet will continued for 7 weeks then animals developed high systolic blood pressure [25,26].

2. Transgenic rat model of Hypertension: Transgenic animals are very useful as a tool in experimental work. Many transgenic cell lines have been produced having candidate gene for

hypertension and those revolutionized the experimental work. Transgenic hypertensive strain like TGR 27 is already produced with introduction of additional rennin gene rennin 2 into the germ lines of rats that have over expression of rennin. Such models may be useful in studying the role of the local RAAS system of hypertension [27].

3. Psychogenic Hypertension: It has been reported that when borderline hypertensive rats are exposed to stressful situation daily in sessions of either short (20 min) or long (120 min) duration of time with air-jet stimulation developed hypertension within 2 weeks in comparison to controls. It was noticed that animals exposed to 120 min stress sessions had significantly higher systolic BP relative to the 20 minutes group [28].

Other types of stress full situations have also been applied, such as emotional stimuli, psychosocial stress, immobilization stress and electric stimuli, but in all cases the results were similar as above [29,30].

4. Genetic hypertension: In 1963; Okamoto and Aoki developed a spontaneous hypertensive rat (SHR) model for experimental hypertension which required no physiological, pharmacological and surgical interventions. SHR was developed by selective inbreeding on genetic bases which result in 100 % progeny of naturally occurring hypertension [31]. After the pioneer of Okamoto and Aoki, many authors had introduced new strains of genetic origin like New Zealand strain, Japanese SHR [32], Milan strain [33], S strain, R strain [34], Sabra strain and Lyon strain [35,36].

5. Obesity related hypertension: Cross breeding between Wistar Kyoto and Obese Zucker rat's result into Wistar fatty rat (WFR) which shows persistent hyperinsulinemia and hypertension after 16 weeks of age and this model is may be a good model to elucidate the relationship between hyperinsulinemia and hypertension [37].

6. Environmentally induced hypertension:

Cold induce hypertension: Fregly M.J. et al. found that chronic exposure of rats to mild cold temperature (6°C) induced hypertension including cardiac hypertrophy within 4 weeks [38].

It is interesting that the elevated blood pressure of rats exposed to cold for 7 weeks does not return to pre-cold exposure level even in 4 weeks after removal from cold atmosphere. Thus, an induced elevated blood pressure by a longer period of cold exposure might not be reversible after return to thermoneutral temperature [39].

III. Chemically induced models of hypertension

1. Mineralocorticoid induced hypertension:

DOCA salt induce hypertension: Selye et al. were the first to demonstrate that deoxycorticosterone acetate (DOCA) produces hypertension in rats [40]. DOCA induce increased reabsorption of water and salt in animal which lead to increased blood volume and hence increased BP. There is also increased secretion of vasopressin leading to water retention and vasoconstriction. In addition RAAS activity is also altered which enhanced sympathetic activity [20,41]. This type of hypertension can also be produced in dogs and pigs [42]. DOCA induced hypertension is salt dependent. Neither there is an administration of DOCA alone nor is partial removal of renal mass effective in increasing BP when applied without salt administration [20]. To produce hypertension in rats, weighing 100 g of rats are kept on a diet rich in sodium chloride and drinking water is replaced by 2% sodium chloride solution ad libitum. After they attain a weight of about 250 g, they are given DOCA dissolved in sesame seed oil at a dose of 10 mg/kg, twice weekly for 43 days [43,44]. In another method, unilateral nephrectomy is performed followed by DOCA administration [45,46].

2. Glutamate injection in rostral ventrolateral medulla [RVM]:

In a study Machado B. H and Brody M. J were found an increased in arterial pressure and heart rate with an injection of glutamate in nucleus ambiguus via cannula placed steriotaxically. Glutamate was injected bilaterally using a 33-gauge injector through 23-gauge guide cannula while rat was under urethane anesthesia. At low dose of 20 nmol/100 nl they found increased in arterial pressure and heart rate while decreased heart rate at 50 nmol/100 nl [47].

3. Cholinomimetic agents induced HT: The cholinomimetics cause activation of central cholinergic mechanism and mediated peripherally through sympathetic nervous system thus induced hypertension in animal [48]. Physostigmine (10-80 µg/kg, i.v) which is a cholinesterase inhibitor and oxotremorine (20-40 µg/kg, i.v) is a direct muscarinic cholinergic agonist cause a dose-dependent increase in BP [49]. Pre-treatment with methyl scopolamine (1 mg/kg) 5-10 minutes before giving oxotremorine prevents initial hypotension in this model [50].

4. Angiotensin-II induced hypertension: Angiotensin-II a potent vasoconstrictor when infused subcutaneously at dose of 0.7 mg/kg/day using minipump it induces increase in BP thus elicits hypertension in 4-8 weeks in rats and mice [51,52].

5. Cadmium induced hypertension: Heavy metal cadmium produce hypertension when chronic administration of CdCI at dose of 1 mg/kg/day, i.p for 2 wks is administered. CdCI induced hypertension might be due to the fact that the metal ion might mimic Ca^{2+} ion as a partial agonist and produce a direct contractile effect on vascular smooth muscle [44,52].

6. Chronic NO inhibition induced HT: Administration of L –NAME by oral route at dose of 40mg/kg at corresponding volume 1ml/kg body weight for 4 weeks induce hypertension. Blood pressure start rising after 2 weeks and significant increased up to 4 weeks [53,54].

7. Ethinyl estradiol induced hypertension: Ethinyl estradiol when given at high doses it decrease the release of nitric oxide. It also shows significant impairment of Ach and nitroprusside induced relaxation in rats and hence produce hypertension [55].

8. Cyclosporine induced hypertension: Cyclosporine induces vasoconstriction of systemic circulation and increases arterial blood pressure [56]. If cyclosporine A (CsA) at dose of 25 mg/kg in 1 ml of olive oil is injected intraperitoneally in Sprague Dawley rats daily for 7 days then it cause hypertension [57].

9. Dexamethasone induced hypertension: It has been noticed that a synthetic glucocorticoid like dexamethasone on infusion increases blood pressure in rats [58] and in human beings [59]. Chronic dexamethasone treatment increases reactive oxygen species (ROS) production in human umbilical vein endothelial cells and elicit endothelial dysfunction [60]. However in rats dexamethasone at dose of 20µg/kg/day, in a volume of 1 ml/kg if administered subcutaneously every day up to 13 days then it increased systolic blood pressure in rats [61].

RESULT AND DISCUSSION

Animal models provide best possible clear view of mechanisms or factors involved in the hypertension. Many of above mention models are created time to time with consideration of etiological factors involved in human hypertension. But there is no evidence that any of model mimic 100% similarity of symptoms of human hypertension that may be because of different variables like age, species, time, course and dose of drugs administered to them. However, these animal models are very useful in understanding the pathogenesis of hypertension and to check the action of new leading antihypertensive agents during preclinical studies.

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