ISSN 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

Animal models in antihypertensive drug development research

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https://doi.org/10.22146/ijpther.585

Submitted: 16/12/2020
Accepted : 17/08/2020

Keywords:
hypertension,
animal model,
drug development research,
pathogenesis,

ABSTRACT

Hypertension is one of the most common diseases in the world. However, its pathogenesis is not fully understood and its treatment is not yet satisfying. Animal models of hypertension have been useful to understand the pathogenesis of hypertension and to test novel therapeutic agents. There are several kinds of hypertension animal models. Each model has different characteristics. Knowing the characteristic of each model is important to obtain valid research. This review will describe several available methods to develop animal model for hypertension.

ABSTRAK

Hipertensi adalah salah satu penyakit paling umum di dunia. Namun, patogenesisnya belum sepenuhnya dipahami dan pengobatannya belum memuaskan. Model hewan hipertensi telah berguna untuk memahami pathogenesis hipertensi dan untukmenguji agen terapeutik baru. Ada beberapa jenis model hewan hipertensi. Setiap model memiliki karakteristik yang berbeda. Mengetahui karakteristik masing-masing model penting untuk mendapatkan penelitian yang valid. Review ini akan menjelaskan beberapa metode yang tersedi auntuk mengembangkan model hewan untuk hipertensi.

INTRODUCTION

Hypertension is a condition where the systolic blood pressure values(SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) values ≥90 mmHg.[1] In 2015, the global prevalence of hypertension was estimated around 1.13 billion in 2015.[2] The high prevalence of hypertension is consistent accross the globe.[3] In Indonesia, based on *Riset Kesehatan Dasar* 2018 (Riskesdas 2018), the prevalence of hypertension in adult is 9.4-9.5%.[4] The prevalence of hypertension is higher in older age. Among people aged >60 years, the prevalence of hypertension is > 60%.[3] Therefore, as the life expectancy is increase, the prevalence of hypertension worldwide is rising. It is estimated that by 2025 the number of people with hypertension will increase by 15–20%.[5]

Hypertension or high blood pressure is often called as silent killer since the only way to detect it is by measuring the blood pressure. Based on previous study, 20 mmHg increase of SBP or 10 mmHg increase of DBP is observed to be associated with cardiovascular death.[6] Hypertension is also a well-known independent risk factor for other chronic diseases including diabetes and cardiovascular diseases which consequently becomes a burden to the society and families.[7] Therefore controlling blood pressure is important to decrease the burden of hypertension.

There are many kinds of drugs used to treat hypertension i.e.diuretics, angiotensin converting enzyme inhibitor (ACEI), renin inhibitor, angiotensin receptors blockers

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(ARBs), calcium channel blockers, beta blockers and vasodilators.[8,9] Despite abundance of available treatment for hypertension, only 34% of hypertensive patients was managed by the current available treatment.[10-11] There are several possible factors affecting the result of antihypertensive treatment such as high costs of antihypertensive drugs,[9] unbearable side effects of antihypertensive drugs[9,11] and low compliance to routine drug administration.[10] Therefore, hypertensive patients are looking for alternatives approach to control their blood pressure. One of the most popular alternatives is taking herbal medicine known to have blood pressure lowering effect.

Herbal medicine has been long be a part of Indonesian people. There are many herbs used to treat hypertension. However, their use in conventional health care is limited since its lack of scientific evidence regarding their safety and efficacy. Therefore, many researches have been done to develop antihypertensive drugs. The drug development research is divided into two consecutive parts which are preclinical and clinical research. The most part of preclinical research is an *in vivo* study using animal model. The right animal model is an important-factor that enables the researcher to get valid study result. There are many kinds of animal model of hypertension which can be divided into non-genetics and genetics model. Choosing the suitable animal model for antihypertension study should be based on the predicted drug candidate mechanism of action and also the understanding of the mechanism of hypertension in the animal model used. Thus, this review discussed about different kinds of animal model of hypertension including non-genetics and genetics animal models of hypertension.

DISCUSSION

Ideally animal models of hypertension should mimics hypertension in human. However, hypertension is complicated condition resulted from coordination of many factors. Thus, understanding the hypertension mechanism of action of each animal model used is very important in selecting the suitable animal model for research.

There are many kinds of animal model of hypertension. Based on the etiology of hypertension, animal models of hypertension could be divided into animal model for primary hypertension and animal model for secondary hypertension. Primary hypertension or also called as essential hypertension is a hypertension caused by interaction of many factors both internal and external or environmental factors. There are several causes of secondary hypertension. Some of the causes of secondary hypertension are renovascular hypertension, kidney diseases, hormonal related disorder and other diseases.[12] Based on the approach, animal model for hypertension could also be divided into two categories that are genetics and non-genetics models. TABLE 1 shows several methods to develop animal model of hypertension.[13]

TABLE 1. Various kind of animal model for hypertension[12-13]

Model categories	Animal model	Hypertension in human
Genetics model	• Spontaneous hypertension rat (SHR)	• Primary hypertension
	• Stroke prone Spontaneous hypertension rat (SP-SHR)	• Primary hypertension
	• Dahl salt sensitive rats	• Primary hypertension
	• Transgenic mice/rat, etc	• Primary hypertension
	• Cryptochrome 1, 2 double knocked out (Cry1,2 DKO) mice[14]	• Primary hyperaldosteronism
Non-genetics model	• Goldblatt (2K-1C/1K-1C)	• Renovascular hypertension
	• Deoxy-corticosterosteroid acetate (DOCA)-salt	• Primary hyperaldosteronism
	• Fructose-fed rat	• Metabolic syndrome related hypertension

Genetics Model of Hypertension

Most of genetics models of hypertension represents essential hypertension in human which is the most common form of hypertension in human. Genetics model of hypertension basically can be divided into two models which are phenotype driven and genotype driven. Phenotype driven model shows spontaneous hypertension i.e. SHR. Genotype-driven models is made by selective modification of specific genes i.e. mice with modification in renin angiotensin aldosterone system related genes.[13]

Spontaneous hypertensive rats (SHR)

SHR is an inbred rat strain developed by selective breeding of the Wistar-Kyoto (WKY) population.[15] The SHR strain shows moderate-to-severe hypertension on the age 7-15 weeks.[16,17] Previous studies showed that hypertension development in SHR is stress responsive. Interestingly, SHR is resistant to high sodium diet challenge without stress induction.[18-20] Even SHR is one of the most popular animal models for hypertension used until now, the mechanism of hypertension especially its relation with genetics causes in the SHR model is not fully understood yet. Nevertheless, its spontaneous hypertension phenotype is closely mimicking human hypertension. Thus many studies related to hypertension have been done using SHR.

Many herbal has been found to have anti-hypertensive effect based on the study using SHR. Azuki beans (*Vigna angularis*) treatment on SHR with SBP approximately 200 mmHg showed that azuki beans treatment could reduce the SBP which suggested to be the result of endothelial nitric oxide synthetase (eNOS) and inducible nitric oxide synthetase (iNOS) expression in the vascular and kidney of SHR.[21] Dose dependent antihypertensive effects in SHR also shown by Xinjian red raspberry fruit extract. Treatment of SHR with Xinjian red raspberry fruit extract results in the decrease of blood pressure, increase of nitric oxide (NO) and superoxide dismutase (SOD) and decrease of endothelin (ET) level.[22] Another study using SHR was study of jamblang or dhuwet (*Syzygium cumini*). Treatment of *Syzygium cumini* in SHR results in blood pressure and heart rate reduction. It was suggested that the antihypertensive effect of *Syzygium cumini* is due to inhibition of vascular constriction and extracellular calcium influx.[23]

Dahl salt sensitive resistant rats

Study on the effects of high salt diet on blood pressure of Sprague-Dawley rat have led to the discovery of a group of rats with response to high salt diet. Dr Lewis K. Dahl who have been studied of the salt effects on blood pressure were able to breed salt sensitive (S) and salt resistance (R) hypertensive rats. The S and R line were able to be separated into 2 different group only after three generation of selective breeding. The blood pressure increases in response to high salt (NaCl 8%) administration in Dahl salt-susceptible (S) rats is inherited as a polygenic trait. The blood pressure increases to > 200 mmHg within six weeks when given high salt at weaning. Previous studies indicate that the kidney, adrenal cortex, nervous system, and unidentified humoral are important factors in regulating blood pressure in S rats.[24]

Many studies on anti-hypertensive effect of herbal were conducted using Dahl salt sensitive hypertensive rats. *Ginkgo biloba* extract administration on high-salt treated Dahl Salt sensitive hypertensive rats result in the reduction of SBP without changing the heart rate.[25] study on Chinese herbal remedy, Hachimi-Jio-gan extract showed that the extract could reduce the systolic blood pressure in Dahl S rats treated with 2% NaCl. The SBP reduction was associated with improvement of cardiac mass, aortic wall thickness, glomerular filtration rate, glomerulosclerosis and kidney arterial injury.[26] Therefore, this model also could be used for studying organ damage in high salt intake associated hypertension.

Cryptochrome 1,2 double knocked out mice (CRY 1,2 DKO mice)

One example of genotype driven animal model of hypertension is Cry 1,2 DKO mice. Cry 1,2 DKO mice exhibit salt sensitive hypertension with primary hyperaldosteronism. Based on the microanalysis of the adrenal gland and biochemical analyses, it was found that a subtype of 3β-hydroxysteroid dehydrogenase (HSD), an enzyme involves in the synthesis of aldosterone, is highly overexpressed in Cry 1,2 DKO adrenal cortex.[27] The enzyme is controlled by clock gene. Therefore, this model is suitable for studying hypertension related to irregular lifestyle that might disrupt circadian rhythms leading to deterioration of body physiologic.

The Cry 1,2 DKO mice showed high blood aldosterone levels and low plasma renin activity. Interestingly the mice also showed signs of renal disturbance and increased reactive oxygen species production even when hypertension is absent. High salt exposure aggravates the renal disturbance observed in these mice. Interestingly, lowering the blood pressure without blocking aldosterone in the mice did not improve the renal disturbance in high-salt-treated Cry 1,2 DKO mice. Therefore, this model could be a suitable model for research on primary hyperaldosteronism.[14]

Non-Genetics Model of Hypertension

Non-genetics model of hypertension basically can be divided into two large groups namely pharmacologically induced model and non-pharmacologically induced model. There are several substances used to induce hypertension i.e. L-NAME and DOCA. Each of the substance has their own mechanism of action to induce hypertension. Non genetics animal model of hypertension can be divided into surgical and non-surgical model (FIGURE1).

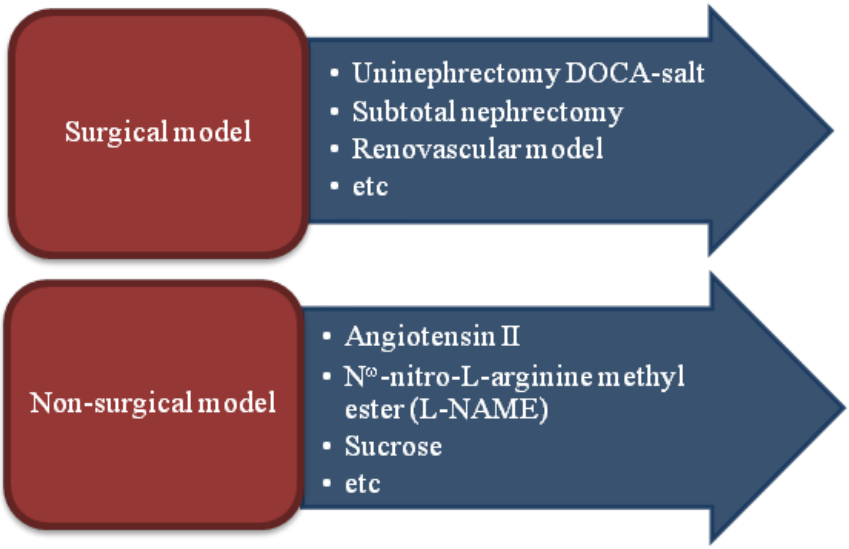

FIGURE 1. Non genetics animal model of hypertension

Uni - nephrectomy - salt - deoxycorticosteroneacetat induced model

Uni-nephrectomy followed with deoxycorticosterone acetate (DOCA) administration in combination with salt loading to young adult Wistar rats can induces hypertension. Our previous study showed that Left unilateral nephrectomy followed by DOCA-NaCl 0.9%-KCl 0.2% administration in 12-16 weeks old male Wistar rat induced the increase of the blood pressure. The DOCA-NaCl 0.9%-KCl 0.2% was given to the uni-nephrectomized rat at 1 week after the operation. Based on the previous study on 12-16 weeks

old male Wistar rat, the SBP increased to above 150 mmHg at nine weeks after DOCA administration.[28] DOCA is a synthetic of mineralocorticoid which has the same function as endogenous mineralocorticoid. Mineralocorticoid increase water retention and blood pressure. Thus, SBP increase in this model is assumed to be the result of water retention.[29] Treatment with polyherbal preparation contains garlic (*Allium sativum*), jelawe (*Belericae fructus*), temuhitam (*Curcuma aeruginosa*), and *Amomi fructus* could decrease the SBP after three weeks of treatment. It was suggested that antioxidant effect of the polyherbal has an important role in the reduction of blood pressure in this model.[28]

Uni-nephrectomy DOCA-salt model is also a good model for cardiovascular problem related high blood pressure. Previous studies showed that the cardiovascular changes in this model is similar with thosein human volume-overloadi,e. hypertrophy, fibrosis, conduction abnormalities and endothelial dysfunction.[30,31] Therefore, this model also could be used to study hypertension related to cardiovascular disease.

Sucrose induced model

High-sucrose or high-fructose diet-induced hypertension model often used for metabolic syndrome models. Fructose is a monosaccharide that is usually found in fruits. While sucrose is a disaccharide consisting of one molecule of fructose and one molecule of glucose.[32] The high-sucrose diet is usually given in the form of a liquid that is mixed together with drinking water with a concentration of 30-35%.[33-35] Sucrose can increase blood pressure in male Wistar rats after administration for 16-20 weeks.[34,35] In the Wistar Kyoto Rat, systolic blood pressure had increased significantly in the administration of a high-sucrose diet for 23 weeks meanwhile diastolic blood pressure had increased at week ninth.[33] The combination of animal models of hypertension can accelerate the onset of increased blood pressure. A high-fat high-sucrose diet for four weeks can significantly increase blood pressure compared to controls.[36] The administration of a high-sucrose diet in spontaneous hypertensive rats can significantly increase blood pressure during control for 3-4 weeks.[37,38] Besides increasing blood pressure, sucrose also increases the other components of the metabolic syndrome parameter, that is increasing insulin concentration, increasing blood glucose levels and increasing triglyceride levels without increasing body weight.[34,39]

High-fructose diet-induced hypertension animal models are carried out by providing a high-fructose diet in the form of food [40,41] or mixed with drinking water.[42,43] This model can lead to a significant increase in blood pressure compared to controls at 4-8 weeks on a high-fructose diet.[40-44] Besides increased blood pressure parameters, cholesterol levels, triglycerides and insulin levels are also increasing.[41,42,45] Body weight parameters do not increase in the fructose-induced animal model. Combination of high-fat high-fructose diets can increase the body weight.[46]

The mechanism of the occurrence of hypertension in high-sucrose or high-fructose diet-induced hypertension model is estimated in several ways. Sucrose will be broken down into one fructose molecule and one fructose molecule. Fructose will increase the absorption of Na^+ in the intestine, causing Na retention so that blood pressure will increase.[32] Fructose also increases the expression of potent vasoconstrictors such as endothelin-1 and angiotensin, and decreases vasodilator levels such as NO so that hypertension can occur.[32,47] Another mechanism that is expected to occur is fructose will result in insulin resistance which will ultimately increase the activity of the sympathetic nervous system.[48]

Subtotal nephrectomy model

Subtotal nephrectomy or 5/6 nephrectomy is a method to develop

chronic kidney disease model. Subtotal nephrectomy is performed by taking the 2/3 part of one kidney followed by uni-nephrectomy of the contralateral kidney.[49] Initially, this animal model will present hypertrophy of the remaining glomerular. The model also presents some biochemical signs of kidney failure i.e. increased of serum creatinine levels and decreased of urine urea levels, decrease of creatinine clearance, polyuria and alteration remnant kidney tissue.[50,51] Besides some changes in the kidney, subtotal nephrectomy also results in a significant increase of systolic and diastolic blood pressure.Previous study showed that the resting heart rate also increases significantly in the 10th week after surgery. In addition, this model also indicates some changes in cardiovascular system i.e. reduced parasympathetic cardiac tone, heart fibrosis and left ventricle hypertrophy.[51,52] Therefore, this model can be used to study hypertension and cardiovascular diseases related to chronic kidney disease.

Developing animal model using subtotal nephrectomy methodscan be tricky. It sounds easy to take 2/3 part of one kidney followed by uni-nephrectomy but proper training is needed to develop the animal model with similar grade of CKD. Moreover, since this method is mainly relied on operation, standard care for operation is needed. Subtotal nephrectomy method correlated to a high risk of infection and death in experimental animals due tobleeding that often happen after cutting the upper and lower poles of the kidney which.[53]

L-NAME induced hypertension

N$^{\omega}$-nitro-L-arginine methyl ester (L-NAME) is a nitric oxide synthetase inhibitor that induces blood pressure increase by inhibiting the mechanism of NO. The increase of the blood pressure is the result oflocal and systemic vasoconstriction.[54] L-NAME administration also results inthe decrease of heart, kidney, and brain function by causing systolic blood pressure increase, left ventricular hypertrophy, aortic fibrosis, and left ventricular fibrosis.[55]

L-NAME administration will cause restriction of NO production in the sympathetic nerve center, activation of the sympathetic nervous system and alteration of the renin angiotensin system.[56] Lack of NO in the kidneys can cause vasoconstriction of the renal arteries, causing stimulation of rennin and angiotensin II production which results in general vasoconstriction and hypertension.Inhibition of NO synthesis in the rat brain causes an increase in blood pressure.[55]

There are several methods to develop hypertension animal model using L-NAME. Studies showed that L-NAME administration in Wistar rat to develop hypertension could be done by oral administration for 4-6 weeks using oral gavage or diluted in the drinking water.[55-57] L-NAME dose applied were varied, from 20, 40, and 50 mg/kg/day.[56,57] L-NAME administration at a dose of 20 mg/kg/day for 4 weeks, the animal showed an increase in blood pressure up to 146% and a decrease of NO synthesis up to 86%. L-NAME administration at a dose of 40 mg/kg/day for 4 weeks results in the increase of blood pressure up to 149%, decreases NO of synthesis up to 65%, and increase of aortic wall thickness. L-NAME administration at a dose of 50 mg/kg/day for 6 weeks causes persistent severe hypertension characterized by increased blood pressure, and weight loss.[57]

CONCLUSION

Using animal models to understand pathogenesisand develop treatment of hypertension relies on the methods validity to represent hypertension in human. There are several available methods to develop animal model of hypertension. Each method has their own advantages and disadvantages. Understanding the pathogenesis of hypertension in each method and suitability of the methods with the research objectives are clearly important to conduct an scientifically sound research.

ACKNOWLEDGEMENT

We would like to thanks Allah SWT so this review can be finished in time and also all the parties who give author(s) support to write down this review.

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