Animal models of hypertension - revisited

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ABSTRACT

Nowadays, civilization diseases, such as hypertension, are one of the biggest global health problems. In 2017 the threshold for hypertension diagnosis was set at 130/80 mmHg, which resulted in its increased prevalence, reaching nearly 50% of the human population. Therefore, strategies for hypertension prevention and treatment have been recently extensively developing. Nonetheless, growing body of factors which can affect blood pressure and induce hypertension is constantly prompting researchers to conduct experiments in this field. For this purpose, animal models seem to be appropriate and necessary. The present report reviews current findings related to hypertension types and causes. It also presents the main guidelines for high blood pressure prevention and describes different experimental models introduced to be carried out in such studies.

Keywords: Dahl salt-sensitive rat, Deoxycorticosterone acetate-salt rat, Hypertension, Spontaneously hypertensive rat, Two-kidney one-clip model

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INTRODUCTION

Hypertension is one of the risk factors for the development of cardiovascular diseases, which are responsible for more than 50% of the deaths globally [1]. The year 2017 brought changes in the scope of recommended threshold for hypertension diagnosis (Table 1). According to the latest American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, high blood pressure should be treated at 130/80 mmHg rather than 140/90 mmHg [2]. Thereby, hypertension prevalence reaches half of the human population worldwide [2]. Therefore, it is not surprising that many of the recent experimental approaches are concentrated around this issue.

Table 1. New classification of blood pressure categories and hypertension stages recommended by the American College of Cardiology (ACC) and American Heart Association (AHA). SBP – systolic blood pressure, DBP – diastolic blood pressure

	Blood Pressure Categories			
	Normal	**Elevated**	**Hypertension**	
			Stage I	**Stage II**
SBP (mm Hg)	< 120	120-129	130-139	≥ 140
DBP (mm Hg)	< 80	< 80	80-89	≥ 90

CAUSES OF HYPERTENSION

I. Genetic predisposition

It is well known that many genes or gene variants may affect blood pressure (BP) [3]. To date, there are only several described single-gene mutations (e.g. in glucocorticoid-remediable aldosteronism, Gordon`s or Liddle syndromes), which contribute to the development of hypertension [4]. However, these disorders are rarely observed. Usually, hypertension results from complex, polygenetic mutations as well as multiple single-nucleotide polymorphisms (SNPs) [3].

Genetic predisposition to elevation of BP is especially pronounced in primary hypertension, in which chronically increased BP has no identifiable cause. On the basis of studies carried out on twins, it has been proven that the heredity of hypertension reaches approximately 30-60% [5]. Moreover, family history of the hypertensive individuals also confirms relevant role of the genetic background in the etiology of hypertension [6].

II. Secondary hypertension

In contrast to the genetic basis of increased BP, secondary hypertension is caused by identifiable factors, which can explain occurrence of the elevated BP. However, this hypertension type affects only 10% of the adult patients [7]. Nevertheless, correct diagnosis and treatment may effectively decrease BP and prevent further organ damage.

1.Lifestyle factors

Environmental factors as well as an unhealthy lifestyle are often indicated as the major causes of hypertension. Interestingly, appropriate and balanced diet might play a crucial role in maintaining physiological BP values. Experimental researches have shown that among all dietary components, sodium and potassium consumption has the most pronounced influence on BP value [8-10]. It was demonstrated that excessive sodium intake positively correlates with increased BP [8,9] and this relationship enhances with age [9,11]. On the other hand, it was shown that reduction of salt intake decreases BP in the normotensive as well as hypertensive persons [8]. Although, there were minor differences between races in the aforementioned BP lowering effect, since Asian and black populations were more sensitive to low sodium diet compared to Caucasians. In contrast, increased potassium intake is linked to reduce BP value [12]. Moreover, there is evidence that high potassium consumption neutralizes sodium`s influence on BP [10], which may be important in the prevention of hypertension.

Currently, there is discussion upon advantages and disadvantages of alcohol drinking and its connection with increased BP. A growing body of evidence indicates that chronic and high (i.e. >30g of ethanol/day) alcohol consumption is associated with hypertension [13]. Whereas, moderate alcohol consumption reduces BP and exhibits beneficial effects on the cardiovascular system [14-16]. Recommended “safe” ethanol amount for healthy man and nonpregnant women was set up to 20g/day and 10g/day, respectively

[17]. Therefore, alcohol should be drunk in small doses in order to sustain its positive properties.

It is widely accepted that sedentary lifestyle and lack of adequate levels of physical activity may promote hypertension. Importantly, numerous studies indicate on the existence of a direct link between physical activity and the reduction of BP, which is most prominent in Caucasians [18-20]. Accordingly, even moderate activity, such as 20-minutes walk a day, can successfully prevent the development of hypertension [20]. Moreover, hypotensive benefits have been already noted for three 30-60-minutes exercise sessions per week at the intensity of 50-87% of maximal oxygen consumption [21]. Additionally, exercises diminish the elevation of BP with age, what provides the evidence that regular physical activity may reduce the risk of developing hypertension in the aging population [22].

What is interesting, it was found that BMI above 25 kg/m^2, which occurs in overweight and obese humans, is also related with increased risk for high BP [23,24]. Thus, maintaining a normal body weight, except for balanced diet and workout, is the main guideline of lifestyle modifications for prevention and treatment of hypertension [2].

2.Hypertension secondary to diseases

To date, obstructive sleep apnea, renovascular diseases, and primary aldosteronism seem to be the most common disorders, in which hypertension may coexist [2]. Obstructive sleep apnea is a chronic malfunction caused by complete or partial obstructions of the upper airways during sleeping, which induces episodes of apnea or hypopnea and results in hypoxemia and sleep disruptions [25]. Moreover, there is a positive correlation between an increased risk of hypertension and obstructive sleep apnea [26]. It is suggested that more than 80% of the adult patients with resistant hypertension are also affected by this disorder [27]. The exact mechanism underlying obstructive sleep apnea-related hypertension is still unknown. Nonetheless, there is a conception that the increased activity of the sympathetic nervous system and the renin-angiotensin system (RAS) is responsible for alternations in structure and functioning of blood vessels as well as blood pressure elevation [28].

Renovascular hypertension is caused by narrowing or blockage of the arteries supplying the kidneys [29]. For this reason renal perfusion pressure decreases and the juxtaglomerular cells secrete renin. Consequently, the activated RAS elevates retention of sodium and water causing an increase in BP [29]. Renal artery stenosis results mainly from atherosclerotic disease (90%) [30], however, nonatherosclerotic disorders (such as fibromuscular dysplasia) can also induce development of renal hypertension [30,31].

Primary aldosteronism (also known as primary hyperaldosteronism or Conn`s syndrome) is commonly caused by adrenal hyperplasia, adrenal carcinoma [32] and rarely may be inherited [33]. In primary aldosteronism production of aldosterone is too high in comparison with plasma sodium concentration and is not suppressed by sodium loading [34]. Moreover, this excessive aldosterone production is not sensitive to the major regulators of its secretion, such as renin-angiotensin system or plasma potassium concentration [34]. Since primary aldosteronism causes increased renal sodium reabsorption and concomitant potassium excretion, 9-37% of patients with this disorder may also develop hypokalemia apart from hypertension [35].

ANIMAL MODELS OF HYPERTENSION

The animal models provide possibility not only to investigate the mechanisms involved in the pathogenesis of certain diseases, but also to screen potential therapies. Among several experimental models, rats are the most commonly used animals [36]. Moreover, since the etiology of human hypertension is heterogeneous, several types of animal models for hypertension assessment are introduced.

I. Animal models of primary hypertension

Interestingly, spontaneous development of high BP without any pharmacological or surgical intervention may occur in individual animals. This observation has contributed to the creation of genetic animal model of hypertension and enabled investigation of the genetic background of the disease. In 1963, Okamoto and Aoki introduced the first experimental model of primary hypertension, known as spontaneously hypertensive rat (SHR) [37]. The above researchers obtained a strain of rats with spontaneous hypertension by inbreeding Wistar-Kyoto rats with “naturally” abnormal high BP [37]. In this model, BP starts rising around 5-6th week of age and systolic blood pressure (SBP) reaches level of 180-200 mmHg in the mature rats [37]. It is suggested that at least 3 loci (on chromosomes 1, 3 and 4) are responsible for early development of hypertension in SHR. While gene detected on chromosome 10 promotes maintenance of higher BP values during aging in these animals [38]. Similarly to hypertensive patients, the SHRs develop cardiac hypertrophy and failure together with renal dysfunction. In spite of depressed endothelial-dependent relaxation response, these

animals do not exert major vascular problems, such as stroke, atherosclerosis or vascular thrombosis [37]. Interestingly, further-developed substrain named stroke-prone SHR [SHR-SP], apart from higher BP [SBP of about ~240 mmHg], exhibits severe vascular damages and increased incidences of deaths from a stroke compared to SHRs [39]. However, noteworthy advantage of this model is similarity of stroke course in SHR-SP and humans. This in turn, enables application of these animals in stroke studies, which is a common complication of hypertension in humans. On the other hand, there are experimental models, which manifest their predisposition to high BP under certain conditions. For example, in Dahl salt-sensitive strain, increased dietary sodium intake leads to severe (average SBP is over 200 mmHg) and fatal hypertension [40]. It has been proven that in this strain the above mentioned phenomenon is regulated by angiotensin-converting enzyme and atrial natriuretic peptide receptor genes [40]. Interestingly, even though BP values in Dahl salt-sensitive rats are higher compared to SHRs, the stage of cardiac hypertrophy is comparable in these two hypertension models [41,42]. However, it should be underlined that cardiac failure occurs earlier in Dahl salt-sensitive rats than in SHRs (4-5 vs 18 months of age) [41,42]. Moreover, renal changes in this strain are more severe and appear quicker in contrast to SHRs [43]. Recent knowledge progress and development of genetic engineering enable introduction of animals with overexpression or deletion of genes, which are involved in the regulation of BP. One of the first transgenic rat model was TGR(mRen2)27, in which overexpression of the mouse Ren2 renin gene led to hypertension [44]. Nonetheless, commonly used in the studies "knockout" animals, such as mice lacking the genes, which code ACE [45], angiotensin II type 1a receptor [46], endothelial synthase [47] or natriuretic peptide [48] also enable determining the function of particular genes by evaluating effects of their absence.

II. Animal models of secondary hypertension

1.Environmental models of hypertension

Apart from studies upon genetic factors, the growing body of research is focused on the influence of environment on BP. Interestingly, it was demonstrated that low temperature (around 5°C) may cause nearly 40% elevation of BP in animals within 3 weeks [49]. The above mentioned report is consistent with findings in humans, since people who chronically work in cold areas also develop hypertension [50]. Moreover, it was noticed that BP values in humans are higher in winter than in summer [51]. Furthermore, there are models, in which hypertension is generated by provoking stress in animals (e.g. using flash lights, loud noises or shaking) [52,53]. Additionally, high fat, sugar or salt diet can increase BP in animals and may be implemented as a method of hypertension induction [54,55]. Importantly, it is suggested that increased activity of the RAS, as well as the sympathetic nervous system, plays a pivotal role in the pathogenesis of described above environmental models of hypertension [55-58].

2. Renal hypertension

It is well known that renovascular disorders can cause an elevation of BP. Similar conditions may be triggered in animals by applying surgical procedures. There are two main methods, which are widely used for this purpose.

The first one, created in 1934 by Goldblatt et al. [59], is performed by a constriction of one or both renal arteries using a small clamp. To date, there are following Goldblatt`s technique variants: one-kidney one-clip (1K1C; one renal artery is constricted and concomitantly the contralateral kidney is removed), two-kidney one-clip (2K1C; one renal artery is constricted and the contralateral kidney is left intact) and two-kidney two-clip (2K2C; aorta or both renal arteries are constricted) [60]. In contrast to other Goldblatt's models, in 1K1C hypertension only initial increase of BP is due to RAS activation. As a result of disruption in the functioning of the remaining kidney, no compensatory excretion of sodium and water is observed and greater volume of fluid is retained. Taking into consideration the mechanism of BP elevation, the 1K1C model represents volume- rather than RAS-dependent type of hypertension [61]. Increased BP in the 2K1C model results from chronic hyperactivity of RAS, which is caused by artery constriction. Since one kidney is intact, it compensates impaired function of the second kidney and help sustain fluid and electrolyte balance in this model. Therefore, 2K1C model of hypertension is sensitive to RAS inhibition, but not to diuretics action [43]. In turn, the mechanism involved in the induction of the 2K2C hypertension is similar to the 2K1C model. However, more severe renal damages are observed in 2K1C rats, including acute renal failure and a high incidence of spontaneous stroke [62].

The second method of renovascular hypertension generation is based on procedures, which provoke renal parenchyma damages. It can be performed for instance by a renal mass reduction, which mimics chronic renal disease [63]. On the other hand, the external compression of the kidney e.g. by wrapping the kidney in cellophane, is often applied to obtain perinephritic fibrosis, which is formed after kidney transplantation [64].

Furthermore, microembolization-induced ischemia may be used to generate nephrosclerosis [65]. As high salt diet remarkably accelerates hypertension progression in the above mentioned animal models, it may be used in combination with surgical procedures to save time and costs of experiments [66].

3. Endocrinal hypertension

Pharmacological approaches for the induction of hypertension are also extensively used, e.g. in models of endocrine-related hypertension, such as deoxycorticosterone acetate (DOCA)-salt rats. In this model of secondary hypertension synthetic mineralocorticoid derivate - DOCA, combined with sodium chloride in unilateral nephrectomised rats produce volume overload hypertension [67]. The most important advantage of DOCA-salt hypertension is markedly depressed RAS activity, which enables its use in studies as an angiotensin-independent model [68]. It was found that DOCA-salt hypertension causes an elevation in the sympathetic nervous system activity [69]. Moreover, there is enhanced vasopressin secretion, which additionally increases renal water retention and leads to vasoconstriction [70]. Furthermore, DOCA-salt hypertension immediately progresses to severe hypertension (SBP < 200 mmHg) and cardiac hypertrophy. Therefore, it is useful model for experimental investigation of all its complications, especially those in the cardiovascular system [67]. It should be mentioned that other mineralocorticoids, such as aldosterone or glucocorticoids e.g. cortisol, can also initiate this type of hypertension [71,72].

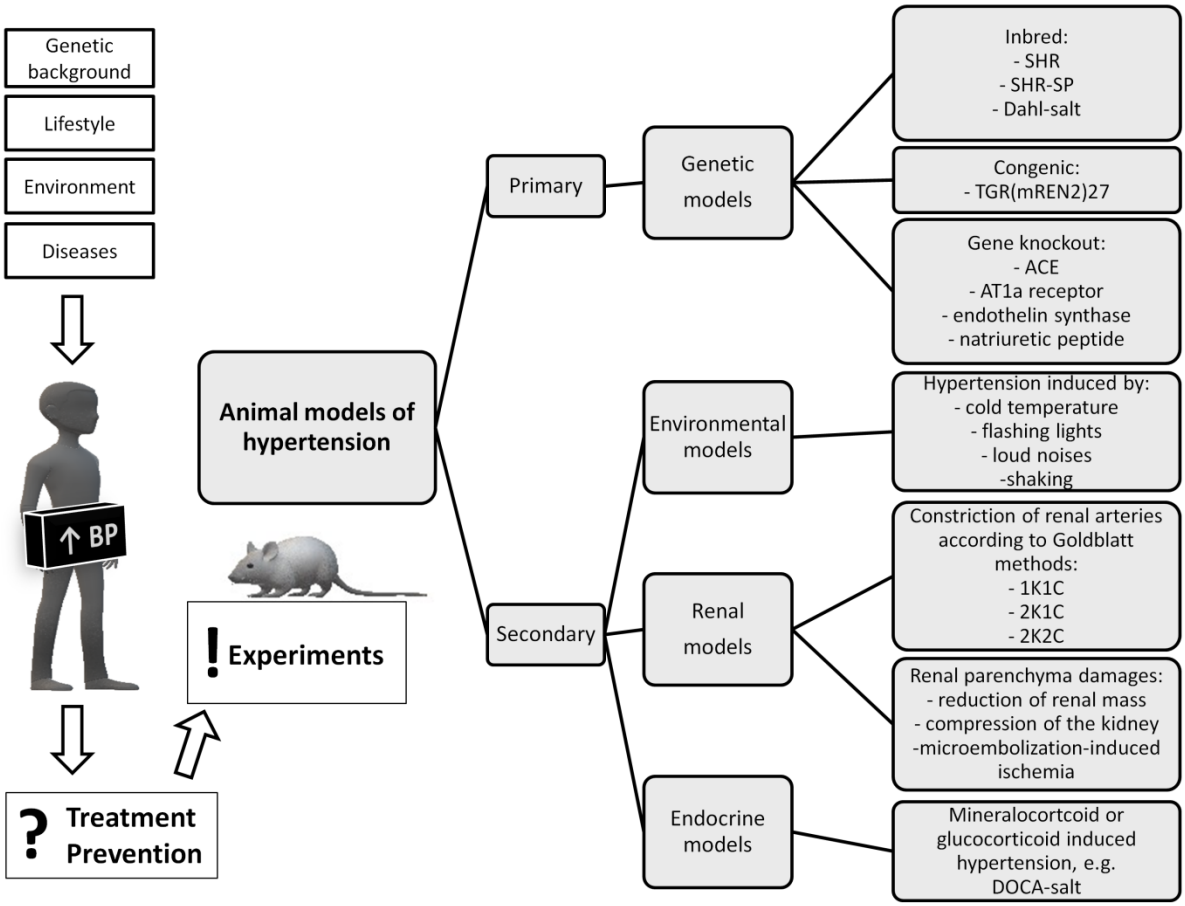

Figure 1. Animal models of hypertension in experimental research. 1K1C – one-kidney one-clip, 2K1C – two-kidney one-clip, 2K2C – two-kidney two-clip, AT1a receptor – angiotensin II type 1a receptor, ACE – angiotensin-converting enzyme, DOCA- deoxycorticosterone acetate, SHR – spontaneously hypertensive rat, SHR-SP – stroke-prone spontaneously hypertensive rat, TGR(mREN2)27 – rats overexpressing the mouse Ren2 gene.

CONCLUSIONS

According to new guidelines for hypertension detection, nearly half of the human population may suffer from this disorder. Since cardiovascular diseases are the major cause of death globally, it is not surprising that strategies for treatment and prevention of hypertension are currently one of the most common area of research.

The present report describes the most popular animal models of hypertension as well as provides the information concerning novelties in the field of high blood pressure. We believe that this review will help understanding how important issue is hypertension. Moreover, we present comprehensive scope of experimental animal models, which are used for hypertension evaluation (Figure 1).

Conflicts of interest: None declared

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