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Experimental control for the spontaneously hypertensive rat: Wistar or Wistar Kyoto? A systematic review and meta-analysis

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Abstract This study aimed to carry out a systematic review and meta-analysis of studies that measured the blood pressure (BP) and body mass (BM) of the Wistar (WIS), Wistar Kyoto (WKY) and spontaneously hypertensive rat (SHR) strains. The methods followed the criteria established by the PRISMA guidelines. A systematic search in PubMed, Web of Science and EMBASE was performed. After analysis, 83 studies were included for systematic review, and of those, 74 were applicable for BP meta-analysis and 39 for BM meta-analysis. The SHR had higher BP compared to control strains, while WKY had higher systolic BP compared to WIS. The WIS are heavier, followed by the WKY and the SHR. The WIS and WKY strains exhibit similarities and differences, and the choice of the strain to be used as the SHR control requires a deep analysis. However, our results support this theory that both strains can be used as SHR controls.

Keywords: hypertension, experimental models, experimental control, spontaneously hypertensive rat, Wistar, Wistar Kyoto

1. Introduction

Science consists of a set of knowledge to be studied, tested, discussed, replicated, and disseminated. It should be objective, generating tested and proven information from experimental methods that are carefully planned and executed. It is a continuous pathway, since from the established data, new theories are formed aiming for progress and information addition (Borko, 1968).

To promote scientific advancement, animals are commonly used as experimental models in all research fields (Ferreira, Hochman, and Barbosa, 2005). For this, methodological and ethical standards are established to preserve the scientific quality, as well as the welfare of the species used (Fagundes and Taha, 2004). Thus, such models need to mimic the studied phenomenon as closely as possible to the real situation. Consequently, the selection of the experimental model represents a crucial step in scientific planning since the use of the appropriate model for the study objectives is decisive to obtain reliable results (Fagundes and Taha, 2004).

The spontaneously hypertensive rat (SHR) has been widely used as a model in studies on essential arterial hypertension (EAH). In the 1950s, hypertension expanded as a high-incidence disease, which made it necessary to develop scientific studies to better understand this phenomenon. However, at that time, there was no adequate experimental model for studying the disease. Thus, several research groups have focused on this issue (N. Alexander, Hinshaw, and Drury, 1954; Okamoto and Aoki, 1963; Smirk and Hall, 1958). In 1954, Alexander et al. developed a strain of hypertensive rabbits in which 86% of males and 53% of females manifested the disease (N. Alexander, et al 1954). In 1958, in Otago, Smirk and Hall developed a strain of hypertensive rats by mating siblings; however, only 30% of descendants developed the disease (Smirk and Hall, 1958). In 1962, the same group reported that 50% of offspring manifested the disease, and the mean systolic blood pressure (SBP) obtained was 147.2 mmHg (E. L.; Phelan and Smirk, 1962). It is important to note that for rodents, EAH is classified as sustained SBP above 150 mmHg (Okamoto and Aoki, 1963; I. H. Page, 1939; E. L. Phelan, Eryetishir, and Smirk, 1962; E. L.; Phelan and Smirk, 1962).

In 1963, Okamoto and Aoki developed the SHR strain from Wistar Kyoto (WKY), a normotensive rat from Kyoto, Japan (Okamoto and Aoki, 1963). The researchers performed a screening among the WKY rats, selecting those who had sustained high blood pressure for approximately one month, subjecting them to consanguineous mating for several generations, and until after the 6th generation, all descendants (100%) developed EAH (SBP > 150 mmHg) (Okamoto and Aoki, 1963; Okamoto, Tabei, Fukushima, Nosaka, and Yamori, 1966). Thereafter, the SHR strain was established as the appropriate model to study EAH, using normotensive WKY as controls (Doggrell and Brown, 1998). However, several studies have pointed out limitations

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in the use of WKY as an SHR control, indicating that such a strain may have characteristics inherent to the disease, such as high SBP, sympathetic hyperactivity and left ventricle pathological concentric hypertrophy (Collins, Loka, and DiCarlo, 2005; Deschepper, Picard, Thibault, Touyz, and Rouleau, 2002; Kurtz, Montano, Chan, and Kabra, 1989; Kurtz and Morris, 1987; Okamoto, et al 1966).

The normotensive Wistar rat (WIS) emerged as an alternative control for SHRs since they do not exhibit the characteristics inherent to hypertension. These animals came out in Philadelphia, USA, in the early 20th century at the Wistar Institute of Anatomy and Biology, and this experimental strain served as the basis for the development of many others, such as WKY (Atanur et al 2013; Bailey, 1971). A group of WIS rats was transported from Philadelphia to the University of Tokyo, Japan, in 1938 and later to the University of Hokkaido in 1944. Then, this strain arrived at the Kyoto University Faculty of Medicine in 1951, where they were used as progenitors of the WKY and, consequently, of the SHR (Doris, 2017; Yosida and Amano, 1965). Thus, there is a genetic relationship between these three strains, and the WIS represents the matrix for WKY and SHR (Doris, 2017). Therefore, the strain supposed to be used as SHR control represents an issue of wide debate in the literature.

Despite being used instinctively by intellectuals in the 17th century—as in Pascal's atmospheric pressure experiment—the idea of experimental control had its first registration at the end of the 19th century, being understood as a method of standardization to check the inferences deduced from an experiment (Boring, 1954). The first randomized study using an experimental control group was carried out by Thorndike and Woodworth (Thorndike and Woodworth, 1901) in 1901. From that moment, the universe of science comprehended that the use of experimental control is inherent to the nature of research. The use of the term control in scientific research comes from the concept of "*contre-rolle*", which means a duplicate and parallel record made to compare the facts between then (Boring, 1954). Thus, the experimental control is applied to maintain the constancy of the experimental conditions between different groups, except the variable to be studied. For example, experimental control for the hypertensive rat must invariably be normotensive (Doggrell and Brown, 1998).

Currently, it is recommended that all experimental work has a control group, which allows the suitable interpretation of the results (Doggrell and Brown, 1998; Fagundes and Taha, 2004). The selection of the control group represents a step as important as the selection of the experimental group. Research groups have been showing concerns over time about which strain should be used as an SHR control. In this sense, multiple studies have compared different variables between SHR, WIS and WKY, aiming to provide a background when selecting rat strains for scientific research (Bizot et al 2007; Eichelman, Dejong, and Williams, 1973; Felten, Weyhenmeyer, and Felten, 1984; Gattone, 1986; Gordon, Phillips, and Johnstone, 2016; Hard et al 1985; Herlitz et al 1982; Langen and Dost, 2011; Lundin et al 1982; Nishiyama, Nishiyama, and Frohlich, 1976; Sagvolden, Pettersen, and Larsen, 1993; Sanada, Tavares, Neubern, Salgado, and Fazan, 2011; Soderpalm, 1989). Therefore, this study aimed to carry out a systematic review and meta-analysis of studies that measured the blood pressure and body mass of the WIS, WKY and SHR strains, since these variables are determinants for selecting the SHR control.

2. Material and methods

2.1. Search strategy

The elaboration of this systematic review and meta-analysis followed the criteria established by the *Preferred Reporting Items for Systematic Reviews and Meta-analysis* (PRISMA) (M. J. Page et al 2021), and the methodological protocol was prospectively registered in the *Open Science Framework* (DOI: 10.17605/OSF.IO/57XT3).

A systematic search in electronic databases, including PubMed, Web of Sciences and EMBASE, was performed in February 2023, and an additional search in the references of the selected articles was carried out. The following descriptors were defined and applied in the search: "*Spontaneously hypertensive rat OR SHR AND Wistar Kyoto OR Normotensive Wistar Kyoto Rat OR WKY AND Wistar OR Normotensive Wistar Rat OR WIS OR NWR*".

Major disputes regarding regionalization are sparked by problems on the boundaries of various natural complexes. The question in dispute is whether it is possible to consider them concise and real. To understand in detail the essence of the discrepancy, one should turn to the issue of natural territorial complexes, which are more often called landscapes and form the basis of regionalism in geography (Isachnko 1965).

2.2. Study selection

This review included original studies that measured and compared the blood pressure and body mass of WIS, WKY and SHR. Therefore, the excluded studies were those a) qualitative; b) duplicated; c) that did not use the three strains, i.e., only WIS or WKY as control; d) that did not measure blood pressure or body mass; e) that used the SHR as control; f) that used another strain as control; and g) review or meta-analysis.

The selected studies were transferred to *Mendeley* version 1.17.13 (Elsevier), which automatically promoted the exclusion of duplicate papers. The screening of titles (phase 1) and abstracts (phase 2) of all studies identified was performed by two reviewers independently. The complete studies (phase 3) considered potentially relevant after discussion between the

reviewers were then obtained and evaluated for eligibility. Any discrepancies were discussed with a third reviewer. This process was performed using *Rayyan*, a Web application designed to assist in this step of the review studies.

2.3. Data extraction

The data were extracted from the studies by using a standard form previously established, in which information was obtained approximately 1) study/year; 2) country in which the research was carried out; 3) source of the experimental strains; 4) age of the animals; 5) sex of the animals; 6) body mass of the animals; 7) blood pressure of the animals and the method of measurement; and 8) the statistical results for blood pressure.

2.4. Data grouping

The studies selected for inclusion in the meta-analysis were divided into studies that compared systolic blood pressure, mean arterial pressure and body mass between the three strains. The meta-analysis between the three strains was performed using the following comparisons: WIS *vs.* WKY, WIS *vs.* SHR and WKY *vs.* SHR.

2.5. Statistical analysis

The mean and standard deviation values of the blood pressure and body mass were obtained from the included papers. Heterogeneity was evaluated using the χ2 test for homogeneity and the I^2 statistic. The effect size (Cohen's d or Hedges' g) was calculated for blood pressure and body mass. Then, a weighted-mean estimate of the effect size was calculated to account for differences in the sample sizes. The mean unweighted effect size and associated 95% CI were also calculated. We used Cohen's classification of the effect size magnitude, where d < 0.20 for a negligible effect; d = 0.20 - 0.49 for a small effect; d = 0.50 - 0.79 for a moderate effect; and d > 0.80 for a large effect (Cohen, 1988).

3. Results

3.1. Systematic review

The stages of the article search process are shown in the flowchart (Fig. 1). The search identified 28,913 studies. Duplicates were excluded (n = 5613), leaving 23300 articles. The exclusion criteria were applied, and 194 papers were read in full. After reading the full papers, 29 studies were excluded because they did not perform a comparative analysis between the three strains, and the other 82 studies were excluded because they did not perform blood pressure or body mass measurements. Finally, 83 articles were included in the systematic review. Of these, 74 were applicable for blood pressure meta-analysis - where 52 were applicable for SBP and 25 for MAP meta-analysis - and 39 for body mass meta-analysis.

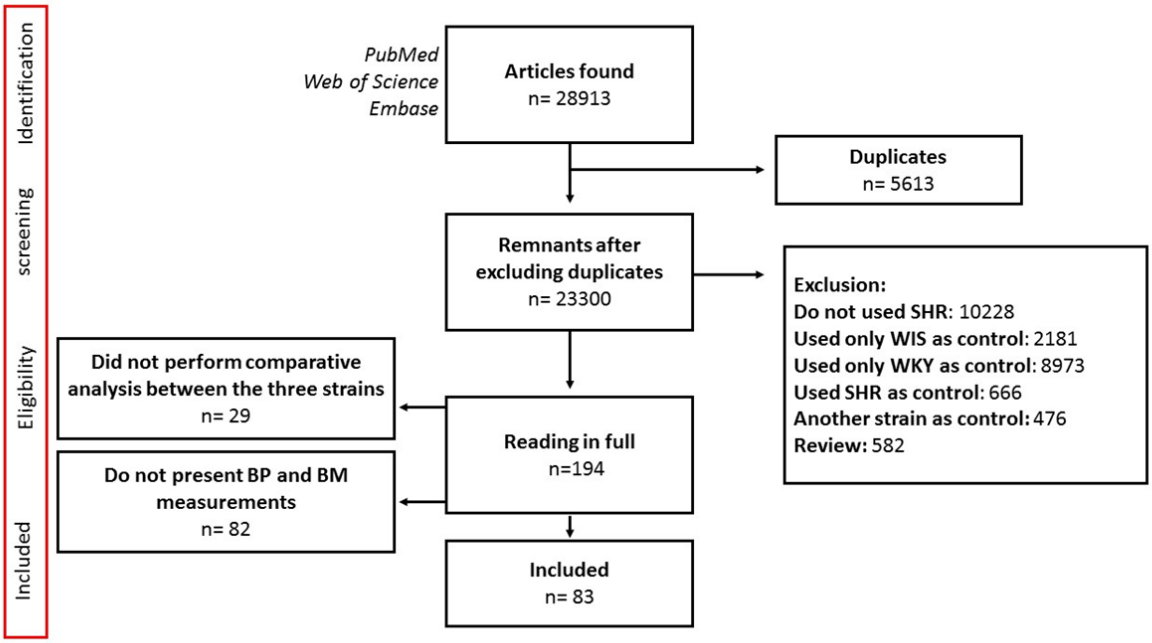

Figure 1 Flowchart of the study selection process.

Figure 2 shows the annual frequency of articles identified in the search (n = 28913; fig. 2A), in which we highlight the year of development of the SHR (1963) (Okamoto and Aoki, 1963). Figure 2B presents the starting point at which the researchers compared the three experimental models (1974), as well as the annual frequency of studies on this issue.

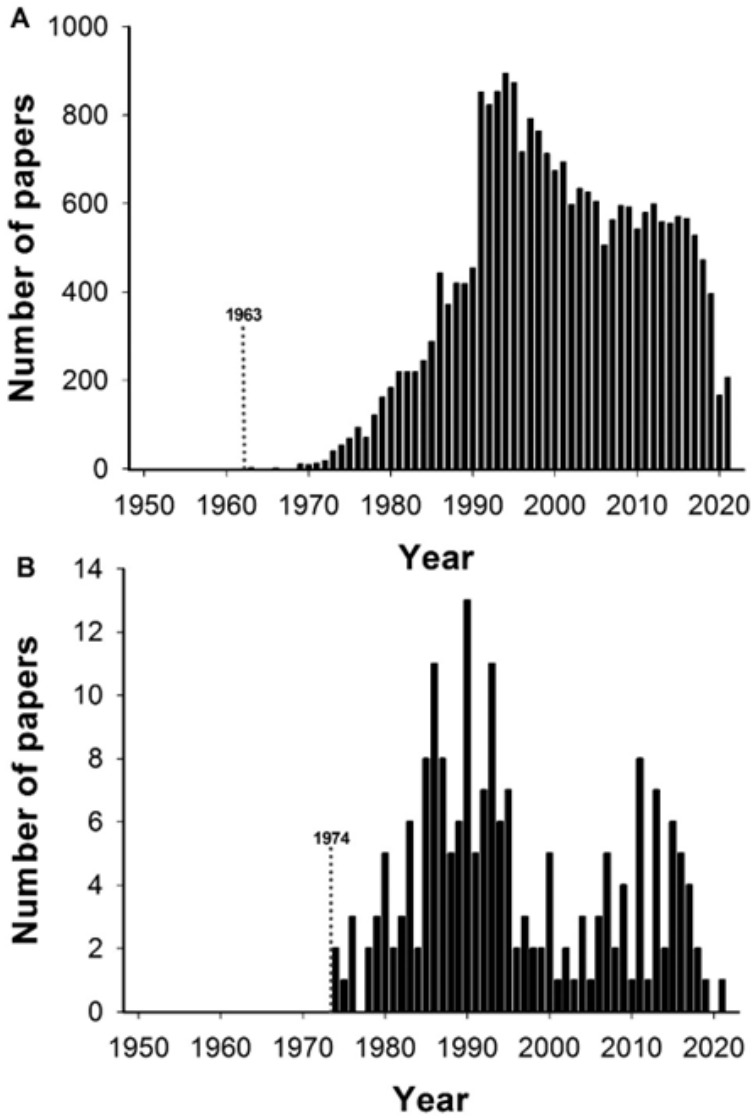

Figure 2 Number of published works/year on blood pressure found in the databases (A). Number of published works/year that studied hypertension using the SHR, WKY and WIS models (B).

Table 1 shows the laboratories and the number of times that each laboratory provided rats for research. It is important to note that 21 studies did not indicate the source of the experimental animals used.

Table 2 presents the data from the systematic review. The first study to use the three strains was developed in 1974, i.e., 11 years after SHR creation. Regarding the sex of the animals used in the studies, 55 used males, 6 females and 5 used both. The age of the animals varied between studies (e.g., from newborns to 72 weeks).

Table 1 Laboratories that provide rats for studies.

Source	WIS	WKY	SHR
Charles-River Breeding Laboratories, Wilmington massachusett- USA	7	11	11
Charles-River Breeding Laboratories, Burlington, Massachusetts, USA	2	2	2
Charles River Breeding Laboratories, Margate- USA	1	1	1
Charles River Laboratories, Kingston, New York- USA	1	1	1
Charles River Laboratories, St-Constant, Quebek, Canada	5	1	1
Charles River Wiga GmbH, Sulzfeld, Germany	1	1	1
Charles River Laboratories, Kisslegg, Germany	1	1	1
Charles River Laboratories. Yokohama, Japan	x	1	1

Charles River Laboratories, Shizuoka, Japan	1	1	1
Charles River Breeding Laboratories, United Kingdom	1	x	1
Charles River Breeding Laboratories, Spain	1	1	1
Charles-River Breeding Laboratories (not indicated the local)	8	7	7
Harlan Laboratories, Frederick, USA	1	x	x
Harlan Laboratories, Bicester, England	1	1	1
Harlan Sprague Dawley, Indianapolis- USA	2	1	1
Harlan Laboratories, Netherlands	x	x	x
Harlan Laboratories, Mexico City, Mexico	2	x	x
Harlan Laboratories, United Kingdom	x	1	x
Wistar Institute, Philadelphia- USA	2	1	1
Mollegaard Breeding Farm, Skensved, Denmark	3	4	4
Clinical Research Institute of Montreal- Canada	x	1	1
Iffa Credo, Lyon, France	2	2	2
National institutes of Health stock- USA	x	1	1
University of Connecticut School of Medicine, Farmington, USA	1	1	1
Madörin ag, Füllinsdorf, Switzerland	1	1	1
National Heart and Lung Institute, England	x	1	x
Carworth farm, Missouri- USA	1	x	1
Health Sciences Center from animals, University of Oklahoma- USA	2	2	3
National Institutes of Health, Bethesda, Maryland, USA	x	3	2
Laboratory Supply Coompany- Indianapolis- USA	2	3	1
West Jersey Biological Supply, New Jersey-USA	1	x	x
Merrell National Laboratories, Cincinnati, Ohio-USA	x	x	1
Taconic Farms, Germantown, New York- USA	3	8	8
Savo-Ivanovas, Kiss Leg, Germany	x	x	1
Dr Karl Thomae GmbH- Germany	1	x	x
Shizuoka Laboratory Center, Hamamatsu, Japan	1	x	x
school of medical sciences, Argentina	1	x	x
Disease Model Cooperative Research Association, Kyoto, Japan	x	1	1
Centre d'Elevage René Janvier, France	1	1	1
animal care facility of the Department of Neurology, School of Medicine of Ribeirao Preto- Brazil	1	1	1
Central Institute for the breeding of Laboratory Animals, Zeist. Netherlands	1	1	1
Chapel Hill Breeding Colonies, North Carolina- USA	1	x	x
University of Antwerp, Belgium	x	x	1

Table 2 Systematic review of body mass and blood pressure of experimental models.

Study	Country	Sex	Age	Origin	Body mass	Blood pressure	Results (blood pressure)
Tobia, Lee and Walsh (1974)	USA	Male	5 to 8 months	WIS and SHR- Carworth farm, Missouri- USA WKY-National Institutes of Health, Bethesda, Maryland, USA	NI	Direct registration of MAP from catheter in carotid artery WIS: 99 ± 4 mmHg WKY: 114 ± 7 mmHg SHR: 183 ± 12 mmHg	SHR > WIS = WKY
Frohlich and Pfeffer (1975)	USA	NI	8 to 11 weeks	WIS and SHR- University of Oklahoma, Health Sciences Center from animals, USA WKY- National Heart and Lung Institute, England	WIS: 225 ± 4 g WKY: 221 ± 7 g SHR: 210 ± 9 g	Direct registration of SBP from catheter in carotid artery WIS: 143 mmHg WKY: 134 mmHg SHR: 185 mmHg	SHR > WIS = WKY
Nickerson (1976)	USA	Male	21 weeks	WIS and SHR - Charles-River	WIS: 467 ± 9 g WKY: 344 ± 8 g	SBP: method was not indicated	SHR > WIS = WKY

				Breeding Laboratories, Wilmington, Massachusetts-USA WKY- Laboratory Supply Company, Indianapolis, IN, USA	SHR: 286 ± 6 g	WIS: 113 ± 2 mmHg WKY: 105 ± 4 mmHg SHR: 172 ± 6 mmHg	
Nishiyama, Nishiyama and Frohlich (1976)	USA	Male	18 to 25 weeks	WIS- West Jersey Biological Supply, New Jersey-USA WKY and SHR- University of Oklahoma, Health Sciences Center from animals, USA	WIS: 458 ± 15 g WKY: 347 ± 7 g SHR: 326 ± 6 g	Direct registration of MAP from catheter in carotid artery WIS: 111 ± 6 mmHg WKY: 102 ± 4 mmHg SHR: 154 ± 5 mmHg	SHR > WIS = WKY
Mullins and Banks (1976)	USA	Female	6 weeks 12 weeks 16 weeks	WIS and WKY- Laboratory Supply Company, Indianapolis, IN, USA SHR- Merrell National Laboratories, Cincinnati, Ohio-USA	6-7 weeks WIS: 155.0 ± 11.2 g WKY: 132.6 ± 10.7 g SHR-L: 121.0 ± 9.8 g SHR-M: 92.1 ± 10.3 g 12-13 weeks WIS: 261.4 ± 9.8 g WKY: 197.8 ± 7.0 g SHR-L: 178.4 ± 5.6 g SHR-M: 157.4 ± 6.5 g 16-17 weeks WIS: 295.5 ± 8.4 g WKY: 216.6 ± 8.9 g SHR-L: 204.5 ± 6.1 g SHR-M : 192.4 ± 6.5 g	Direct registration of SBP from catheter in femoral artery; and SBP were estimated using the tail-cuff occlusion and plethysmography method Tail WIS: 131 ± 3 mmHg WKY: 102 ± 1.5 mmHg SHR: 148.3 ± 4.1 mmHg Artery WIS: 127.5 ± 4.6 mmHg WKY: 107 ± 2.5 mmHg SHR: 153.8 ± 3.8 mmHg	SHR = WIS = WKY
Hodgins and Frohlich (1978)	USA	NI	4 and 16 weeks	NI	WIS: 364 ± 34.6 g WKY: 257 ± 28.3 g SHR: 219 ± 23.5 g	NI	X
Cox (1979)	USA	NI	10 weeks	Charles-River Breeding Laboratories	WIS: 305 ± 9 g WKY: 269 ± 13 g SHR: 245 ± 5 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 121 ± 3 mmHg WKY: 124 ± 4 mmHg SHR: 187 ± 5 mmHg	SHR >WKY SHR = WIS WIS = WKY
Johnson and Macia (1979)	USA	NI	10 to 12 weeks	WIS: Charles-River Breeding Laboratories WKY and SHR- National Institutes of Health, Bethesda, Maryland, USA	NI	Direct registration of MAP from catheter in carotid artery WIS: 166 ± 2 mmHg WKY: 107 ± 9 mmHg SHR: 201 ± 2 mmHg	X
Collis, Mey and Vanhoutte (1979)	Belgium	NI	6 weeks	NI	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS and WKY: 119.5 ±1.1 mmHg SHR: 158.3 ± 2.6 mmHg	SHR > WIS = WKY
Haack, Schaffer e Simpson (1980)	USA	Male	5 to 10 weeks	Charles-River Breeding Laboratories, Wilmington	WIS: 212 ± 11 g WKY: 176 ± 8 g SHR: 190 ± 9 g	SBP were estimated using the tail-cuff occlusion and plethysmography	SHR > WIS = WKY

				Massachusetts, EUA		method WIS: 124 ± 3 mmHg WKY: 115 ± 5 mmHg SHR: 149 ± 4 mmHg	
Lukacsko, Messina and Kaley (1980)	USA	Male	210 to 225 days	Charles-River Breeding Laboratories	NI	Direct registration of MAP from catheter in carotid artery WIS: 107 ± 3 mmHg WKY: 114 ± 4 mmHg SHR: 143 ± 2 mmHg	SHR > WIS = WKY
Webb, Vanhoutte and Bohr (1980)	Belgium	Male and female	3.5 to 6 months	WIS and WKY- Charles-River Breeding Laboratories, Wilmington Massachusetts, EUA SHR- University of Antwerp, Belgium	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS and WKY: 124 ± 2 mmHg SHR: 183 ± 3 mmHg	SHR > WIS = WKY
O'donnel and Volicer (1981)	USA	Male	12 weeks	Charles-River Breeding Laboratories, Burlington, Massachusetts, EUA	NI	SBP were estimated using the tail-cuff occlusion and physiograph method WIS: 111 ± 7 mmHg WKY: 115 ± 7 mmHg SHR: 185 ± 4 mmHg	X
Kitamura et al. (1981)	USA	Female	WIS and WKY: 8 ± 0.2 weeks SHR: 33 ± 1 weeks	NI	NI	MAP was recorded on multichannel polygraph WIS: 112 ± 3 mmHg WKY: 107 ± 4 mmHg SHR: 162 ± 4 mmHg	SHR > WIS = WKY
Piccoti et al. (1982)	Italy	Male	SHR and WKY: 13 to 14 weeks	University of Oklahoma, Health Sciences Center from animals, USA	220 - 300 g	Direct registration of MAP from catheter in carotid artery WIS: 111 ± 2 mmHg WKY: 125 ± 4 mmHg SHR: 183 ± 4 mmHg	SHR > WIS = WKY
Borkowski and Quinn (1983)	England	Male	NI	NI	250-300 g	Direct registration of SBP from catheter in femoral artery; and SBP were estimated using the tail-cuff occlusion and oscillograph method Tail WIS: 111 ± 6 mmHg WKY: 151 ± 5 mmHg SHR: 174 ± 10 mmHg Artery WIS: 119 ± 3 mmHg WKY: 157 ± 5 mmHg SHR: l78 ± 5 mmHg	SHR = WIS = WKY
Häusler et al. (1983)	Switzerland	Male	NI	Madörin ag, Füllinsdorf, Switzerland	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 133.7 ± 1.9 mmHg WKY: 134.4 ± 3.9 mmHg SHR: 181.2 ± 4.4 mmHg	SHR = WIS = WKY
Takahashi et al. (1983)	Japan	Male	16 weeks	NI	WIS: 250 ± 5 g WKY: 289 ± 7 g SHR: 244 ± 4 g	Direct registration of MAP from catheter in femoral artery WIS: 115 ± 6 mmHg WKY: 123 ± 6 mmHg	X

						SHR: 156 ± 6 mmHg	
Krukoff and Calaresu (1984)	Canada	Male	NI	Charles-River Breeding Laboratories	300 ± 30 g	Direct registration of MAP from catheter in femoral artery WIS: 112 ± 3 mmHg WKY: 104 ± 3 mmHg SHR: 156 ± 2 mmHg	SHR = WIS = WKY
Hard et al. (1985)	Sweden	Male and female	87 - 180 days	Mollegaard Breeding Farm, Skensved, Denmark	NI	Direct registration of MAP from catheter in tail artery WIS: 124.7 ± 11.0 mmHg WKY: 178.5 ± 10.2 mmHg SHR: 115.9 ± 8.8 mmHg	SHR > WIS = WKY
Kino et al. (1985)	USA	Male	14 - 17 weeks	NI	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 109.1 ± 6.6 mmHg WKY: 116.5 ± 3.8 mmHg SHR: 218.5 ± 2.4 mmHg	X
Farmam and Bonvalet (1985)	France	Female	NI	NI	190 - 210 g	Direct registration of MAP from catheter in femoral artery WIS: 108.7 ± 4.1 mmHg WKY: 111.0 ± 5.4 mmHg SHR: 143.0 ± 2.2 mmHg	SHR > WIS = WKY
Gattone (1986)	USA	Male and female	newborns 1 to 6 weeks	Charles-River Breeding Laboratories, Wilmington, Massachusetts-EUA	Newborn: WIS- 6.06 ± 0.17 g WKY- 4.87 ± 0.09.g SHR- 5.01 ± 0.08 g 1 week: WIS- 15.6 ± 0.46 g WKY- 10.5 ± 0.23 g SHR- 8.9 ± 0.32 g 2 week: WIS- 34.7 ± 0.94 g WKY- 23.9 ± 0.95 g SHR- 17.7 ± 0.33 g 3 week: WIS- 45.8 ± 1.28 g WKY- 32.9 ± 1.54 g SHR- 28.4 ± 0.71 g 4 week: WIS- 99.8 ± 2.89 g WKY- 65.2 ± 1.29 g SHR- 57.8 ± 1.08 g 6 week: WIS- 178.9 ± 6.38 g WKY- 116.5 ± 3.32 g SHR- 103.7 ± 2.46 g	NI	X
Hopp et al. (1986)	USA	Male	NI	Charles-River Breeding Laboratories	250 - 300 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 119.8 ± 3.2 mmHg WKY: 126.6 ± 1.7 mmHg SHR: 204.8 ± 4.1 mmHg	X
Tamura et al. (1986)	USA	Male	NI	NI	230 - 300 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 119.8 ± 3.2 mmHg	X

						WKY: 126.6 ± 1.7 mmHg SHR: 204.8 ± 4.1 mmHg	
Tokushige et al. (1986)	USA	Male	NI	NI	230 - 300 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 107.7 ± 4.2 mmHg WKY: 117.3 ± 4.4 mmHg SHR: 190.3 ± 4.1 mmHg	X
Loeb and Bean (1986)	USA	Male and female	4 - 21 weeks	WIS- Harlan Laboratories Inc, Frederick, USA WKY and SHR- Charles-River Breeding Laboratories, Wilmington Massachusett- USA	WIS: 190 - 250 g WKY: NI SHR: NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 106.7 ± 8.9 mmHg WKY: 117.0 ± 17.8 mmHg SHR: 114.0 ± 10.5 mmHg	SHR = WIS = WKY
Head and Jong (1986)	Netherlands	Male	NI	Central Breeding Laboratories TNO, Zeist, The Netherlands	200 - 380 g	Direct registration of MAP from catheter in tail artery WIS: 113 ± 2 mmHg WKY: 126 ± 2 mmHg SHR: 169 ± 4 mmHg	SHR > WIS > WKY
Sladek, Davis and Sladek (1986)	USA	Male	15 to 16 weeks	Charles-River Breeding Laboratories	WIS: 327 ± 7 g WKY: 224 ± 1 g SHR: 283 ± 4 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 96 ± 3 mmHg WKY: 100 ± 4 mmHg SHR: 141 ± 3 mmHg	SHR > WIS = WKY
Feig, D'occhio and Boylan (1987)	USA	NI	4 months	Laboratory Supply Company, Indianapolis- USA	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 119.0 ± 2.7 mmHg WKY: 121.4 ± 2.4 mmHg SHR: 171.4 ± 6.0 mmHg	SHR > WIS = WKY
Khalil et al. (1987)	USA	Male	NI	NI	250 - 300 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 115 ± 3.3 mmHg WKY: 117 ± 3.0 mmHg SHR: 193 ± 3.0 mmHg	X
Lang and Johns (1987)	USA	Male	5 to 8 weeks	NI	NI	Direct registration of MAP from catheter in tail artery WIS: 103.1 ± 1.3 mmHg WKY: 99.9 ± 2.1 mmHg SHR: 125.2 ± 1.5 mmHg	X
Coskinas and Price (1987)	USA	Male and female	16 to 19 weeks	Charles-River Breeding Laboratories	WIS: 273 ± 6 g WKY: 206 ± 3 g SHR: 193 ± 4 g	SBP were estimated using the tail-cuff occlusion and electrosphygmomanometer method WIS: 110 ± 6 mmHg WKY: 106 ± 2 mmHg SHR: 156 ± 2 mmHg	SHR > WIS = WKY
Kunes et al. (1987)	Canada	NI	newborn	WIS- Taconic Farms, Germantown,	WIS: 5.69 ± 0.04 g WKY: 5.00 ± 0.06 g	NI	X

				New York WKY and SHR-Clinical Research Institute of Montreal-Canada	SHR: 4.78 ± 0.04 g		
Laviere et al. (1988)	Canada	NI	4,8,12, and 16 weeks	Charles River Laboratories, St-Constant, Quebec, Canada	4 weeks: WIS: 77 ± 3 g WKY: 58 ± 3 g SHR: 51 ± 2 g 8 weeks: WIS: 241 ± 6 g WKY: 148 v 6 g SHR: 151 ± 6 g 12 weeks: WIS: 360 v 6 g WKY: 228 ± 5 g SHR: 240 ± 1 g 16 weeks: WIS: 398 v 5 g WKY: 262 ± 11 g SHR: 290 ± 2 g	SBP were estimated using the tail-cuff occlusion and polygraph method 4 weeks: WIS: 92 ± 2 mmHg WKY: 96 ± 2 mmHg SHR: 100 ± 2 mmHg 8 weeks: WIS: 108 ± 2 mmHg WKY: 103 ± 2 mmHg SHR: 118 ± 3 mmHg 12 weeks: WIS: 111 ± 2 mmHg WKY: 110 ± 2 mmHg SHR: 138 ± 2 mmHg 16 weeks: WIS: 113± 2 mmHg WKY: 102 ± 5 mmHg SHR: 154 ± 2 mmHg	4 weeks: SHR > WIS SHR = WKY WIS = WKY 8 weeks: SHR > WIS = WKY 12 weeks: SHR > WIS = WKY 16 weeks: SHR > WIS > WKY
Belichard, Pruneau and Rochette (1988)	France	Male	23 weeks	Iffa Credo, Lyon, France	WIS: 392 ± 6 g WKY: 387 ± 4 g SHR: 357± 5 g	Direct registration of SBP from catheter in tail artery WIS: 116 ± 4 mmHg WKY: 123 ± 5 mmHg SHR: 190 ± 3 mmHg	SHR > WIS = WKY
Garcia et al. (1989)	Canada	NI	3 to 15 weeks	Taconic Farms, Germantown, New York	4 weeks: WIS: 66.9 ± 16.9 g WKY: 86.1 ± 15.7 g SHR: 66.9 ± 16.9 g 8 weeks: WIS: 253.6 ± 15.7 g WKY: 184.9 ± 14.5 g SHR: 175.3 ± 14.4 g 12 weeks: WIS: 365.7 ± 12.0 g WKY: 283.7 ± 10.8 g SHR: 234.3 ± 15.7 g 16 weeks: WIS: 404.2 ± 9.6 g WKY: 311.4 ± 15.7 g SHR: 276.5 ± 13.2 g	SBP were estimated using the tail-cuff occlusion and plethysmography method 4 weeks: WIS: 90.9 ± 9.8 mmHg WKY: 98.1 ± 10.9 mmHg SHR: 100.9 ± 9.8 mmHg 8 weeks: WIS: 108.4 ± 10 mmHg WKY: 103.4 ± 11.8 mmHg SHR: 121.2 ± 10.8 mmHg 12 weeks: WIS: 103.1 ± 8.9 mmHg WKY: 108.1 ± 12.8 mmHg SHR: 146.6 ± 8.9 mmHg 16 weeks: WIS: 105.6 ± 11.8 mmHg WKY: 98.4 ± 10.9 mmHg SHR: 159.1 ± 10.8 mmHg	4 weeks: SHR > WIS SHR = WKY WIS = WKY 8 weeks: SHR > WIS = WKY 12 weeks: SHR > WIS = WKY 16 weeks: SHR > WIS = WKY
Morton et al. (1990)	Scotland	Male	3 weeks	Harlan Laboratories, Bicester, England	WIS: 54.4 ± 7.7 g WKY: 49.7 ± 4.1 g SHR: 50.8 ± 6.1 g	Direct registration of intraarterial blood pressure from catheter in carotid artery WIS: 80.1 ± 6.3 mmHg WKY: 81.1 ± 8.7 mmHg SHR: 115.5 ± 17.8 mmHg	SHR > WIS = WKY
Widimský et	Canada	Male	4 to 9	WIS - Charles River	WIS: 71 - 309 g WKY: 70 - 281 g	SBP were estimated using the tail-cuff	SHR > WKY >

al. (1991)			weeks	Laboratories, St-Constant, Quebec, Canada WKY and SHR: Taconic Farms, Germantown, New York- USA	SHR: 65 - 244 g	occlusion and plethysmography method WIS: 111 ± 7 mmHg WKY: 130 ± 5 mmHg SHR: 147.5 ± 5 mmHg	WIS
Pollock and Arendshorst (1991)	USA	Male	10 to 12 weeks	WIS- Chapel Hill Breeding Colonies, North Carolina- USA WKY and SHR- National institutes of Health stock- USA	WIS: 234 ± 11 g WKY: 246 ± 8 g SHR: 232 ± 7 g	Direct registration of intraarterial blood pressure from catheter in femoral artery WIS: 130 ± 6 mmHg WKY: 126 ± 6 mmHg SHR: 151 ± 6 mmHg	SHR > WIS = WKY
Boylan, Liew and Feig (1991)	USA	NI	6 - 21 weeks	University of Connecticut School of Medicine, Farmington, USA	NI	SBP Method was not indicated 7 weeks: WIS: 124 ± 13.2 mmHg WKY: 142.8 ± 10.9 mmHg SHR: 151.5 ± 8.5 mmHg 9 weeks: WIS: 123 ± 15.7 mmHg WKY: 151 ± 11.4 mmHg SHR: 146.2 ± 10.6 mmHg 11 weeks: WIS: 125.8 ± 10.2 mmHg WKY: 143.9 ± 10.2 mmHg SHR: 177.2 ± 15.3 mmHg 13 weeks: WIS: 130.9 ± 18.7 mmHg WKY: 149.1 ± 13.6 mmHg SHR: 172 ± 13.1 mmHg 15 weeks: WIS: 138.9 ± 16.5 mmHg WKY: 154.7 ± 17 mmHg SHR: 179.9 ± 8.5 mmHg 17 weeks: WIS: 137.8 ± 3.4 mmHg WKY: 144.1 ± 15.7 mmHg SHR: 174.9 ± 16.1 mmHg 19 weeks: WIS: 127.7 ± 148.7 mmHg WKY: 148.7 ± 21.6 mmHg SHR: 194.8± 21.2 mmHg 21 weeks: WIS: 136.7 ± 18.7 mmHg WKY: 141.8 ± 17.4 mmHg SHR: 202.2 ± 6.8 mmHg	X
Schiffrin et al. (1992)	Canada	NI	4, 7, 8, 12 and 16 weeks	WIS- Charles River, St Constant, Quebec, Canada	4 weeks: WIS: 82 ± 2 mmHg WKY: 86 ± 2 mmHg SHR: 84 ± 2 mmHg	SBP were estimated using the tail-cuff occlusion and plethysmography	4 weeks: SHR = WIS = WKY 7 weeks:

				WKY and SHR- Taconic Farms, Germantown, New York, USA	8 weeks: WIS: 107 ± 2 mmHg WKY: 102 ± 2 mmHg SHR: 120 ± 2 mmHg 12 weeks: WIS: 105 ± 2 mmHg WKY: 109 ± 2 mmHg SHR: 147 ± 2 mmHg 16 weeks: WIS: 108 ± 1 mmHg WKY: 102 ± 2 mmHg SHR: 159 ± 2 mmHg	method 4 weeks: WIS: 82 ± 2 mmHg WKY: 86 ± 2 mmHg SHR: 84 ± 2 mmHg 8 weeks: WIS: 107 ± 2 mmHg WKY: 102 ± 2 mmHg SHR: 120 ± 2 mmHg 12 weeks: WIS: 105 ± 2 mmHg WKY: 109 ± 2 mmHg SHR: 147 ± 2 mmHg 16 weeks: WIS: 108 ± 1 mmHg WKY: 102 ± 2 mmHg SHR: 159 ± 3 mmHg	SHR > WIS = WKY 8 weeks: SHR > WIS = WKY 12 weeks: SHR > WIS = WKY 16 weeks: SHR > WIS = WKY
Saltzman, Delano and Schmid-Schönbein (1992)	USA	NI	15 - 16 weeks	Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	NI	Direct registration of MAP from catheter in femoral artery WIS: 118 ± 8 mmHg WKY: 120 ± 9 mmHg SHR: 160 ± 8 mmHg	X
Tabrizchi and Triggle (1992)	Canada	Male	12 - 13 weeks	NI	NI	Direct registration of SBP from catheter in iliac artery WIS: 125 ± 3 mmHg WKY: 112 ± 2 mmHg SHR: 181 ± 6 mmHg	SHR > WIS = WKY
Mamuya, Chobabnan and Brecher (1992)	USA	Male	6 weeks 10 weeks 24 weeks 40 weeks	Charles-River Breeding Laboratories, Burlington, Massachusetts, USA Taconic Farms, Germantown, New York- USA	NI	SBP were estimated using the tail-cuff occlusion and a photoelectric cell detector method 6 weeks NI 10 weeks WIS: 108 ± 4 mmHg WKY: NI SHR: 165 ± 5 mmHg 24 weeks WIS: NI WKY: 113 ± 6 mmHg SHR: 177 ± 9 mmHg 40 weeks WIS: 109 ± 6 mmHg WKY: 136 ± 12 mmHg SHR: 185 ± 12 mmHg	X
Klee et al. (1993)	USA	NI	16 - 18 weeks	Mollegaard, Skensved, Denmark,	330 - 380 g	DBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 92 ± 8 mmHg WKY: 83 ± 7 mmHg SHR: 117 ± 5 mmHg	SHR = WIS = WKY
Huang and Koller (1993)	USA	Male	12 weeks	NI	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 103.9 ± 3.0 mmHg WKY: 119.1 ± 7.8 mmHg SHR: 194.9 ± 3.0 mmHg	SHR > WIS = WKY
McLellan et al. (1993)	Escotland	NI	11 weeks	Charles River Breeding Laboratories,	WIS: 288.1 ± 3.4 g WKY: 255.3 ± 3.5 g	SBP were estimated using the tail-cuff occlusion and	SHR > WIS = WKY

				Margate- USA	SHR: 238.3 ± 6.4 g	plethysmography method WIS: 155.3 ± 3.8 mmHg WKY: 142.2 ± 3.2 mmHg SHR: 212.9 ± 3.5 mmHg	
Morano et al. (1993)	Germany	NI	NI	WIS and WKY- NI SHR- Savo-Ivanovas, Kiss Leg, Germany	WIS: 261 ± 11 g WKY: 186 ± 3 g SHR: 250 ± 4 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 96.4 ± 4 mmHg WKY: 117.9 ± 2 mmHg SHR: 172.9 ± 4 mmHg	SHR > WIS = WKY
Perez, Petroff and Mattiazzi (1993)	Argentina	Male	6 months	WIS- NI WKY and SHR - Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	WIS: 332.19 ± 10.53 g WKY: 292.79 ± 6.33 g SHR: 268.91 ± 3.76 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 126.25 ± 2.28 mmHg WKY: 129.43 ± 1.8 mmHg SHR: 194.19 ± 3.69 mmHg	SHR > WIS = WKY
Touyz, Tolloczko and Schiffrin (1993)	Canada	Male	3, 9 and 17 weeks	WIS- Charles River, St-Constant, Quebec, Canada WKY and SHR- Taconic Farms, Germantown, New York- USA	3 weeks WIS: 57 ± 7 g WKY: 74 ± 6 g SHR: 29 ± 4 g 9 weeks WIS: 299 ± 12 g WKY: 273 ± 24 g SHR: 215 ± 4 g 17 weeks WIS: 505 ± 22 g WKY: 470 ± 17 g SHR: 326 ± 10 g	SBP were estimated using the tail-cuff occlusion and a photoelectric cell detector 3 weeks WIS: 102 ± 6 mmHg WKY: 102 ± 7 mmHg SHR: 123 ± 9 mmHg 9 weeks WIS: 112 ± 7 mmHg WKY: 107 ± 8 mmHg SHR: 154 ± 15 mmHg 17 weeks WIS: 121 ± 8 mmHg WKY: 108 ± 16 mmHg SHR: 204 ± 12 mmHg	3 weeks SHR > WIS = WKY 9 weeks SHR > WIS = WKY 17 weeks SHR > WIS = WKY
David-Dufilho et al (1994)	France	Male	12 - 14 weeks	NI	WIS: 293 ± 8 g WKY: 296 ± 5 g SHR: 281 ± 5 g	Direct registration of SBP from catheter in aortic artery WIS: 139 ± 4 mmHg WKY: 137 ± 3 mmHg SHR: 184 ± 3 mmHg	X
Grisk et al. (1995)	Germany	Male	19 - 24 weeks	Charles River Wiga GmbH, Sulzfeld, Germany	WIS: 521 ± 8 g WKY: 334 ± 12 g SHR: 359 ± 8 g	MAP was estimated using the tail-cuff occlusion and plethysmography method WIS: 105 ± 3 mmHg WKY: 72 ± 4 mmHg SHR: 140 ± 8 mmHg	X
Bian and Bukoski (1995)	USA	Male	12 - 15 weeks	Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	NI	SBP was estimated using the indirect pneumatic tail-cuff technique WIS: 126 ± 2.3 mmHg WKY: 117 ± 1.4 mmHg SHR: 157 ± 1.7 mmHg	SHR > WIS > WKY
Touyz, Tolloczko and Schiffrin (1995)	Canada	NI	3, 9 and 17 weeks	WIS- Charles River. St. Constant, Quebec, Canada WKY and SHR-	3 weeks: WIS: 58 ± 1 g WKY: 78 ± 0.8 g SHR: 37 ± 0.8 g 9 weeks: WIS: 300 ± 4 g	SBP were estimated using the tail-cuff occlusion and plethysmography method 3 weeks:	3 weeks SHR > WIS = WKY 9 weeks SHR > WIS = WKY

				Taconic Farms Inc. Germantown, New York- USA	WKY: 277 ± 5 g SHR: 221 ± 2 g 17 weeks: WIS: 480 ± 3 g WKY: 497 ± 6 g SHR: 329 ± 2 g	WIS: 103 ± 2 mmHg WKY: 101 ± 2 mmHg SHR: 123 ± 3 mmHg 9 weeks: WIS: 110 ± 2 mmHg WKY: 106 ± 3 mmHg SHR: 221 ± 2 mmHg 17 weeks: WIS: 107 ± 2 mmHg WKY: 116 ± 3 mmHg SHR: 204 ± 3 mmHg	17 weeks SHR > WIS = WKY
Blume et al. (1997)	Germany	NI	12 weeks	WIS- Dr Karl Thomae GmbH- Germany WKY and SHR- Mollegaard Breeding Farm, Skensved, Denmark	WIS: 280 - 300 g WKY: 280 - 300 g SHR: 240 260 g	Direct registration of SBP from catheter in carotid aortic artery WIS: 90±8 mmHg WKY: 93±7 mmHg SHR:165±11 mmHg	SHR > WIS = WKY
Gattu et al. (1997)	USA	Male	12 weeks	WIS- Harlan Sprague Dawley, Indianapolis- USA WKY and SHR- Taconic Farms, Germantown, New York- USA	NI	SBP Method was not indicating WIS: 127 ± 9.04 mmHg WKY: 129 ± 6.25 mmHg SHR: 192 ± 5.2 mmHg	SHR > WIS = WKY
Touyz and Schiffrin (1997)	Canada	Male	17 weeks	WIS- Charles River, St Constant, Quebec, Canada WKY and SHR- Taconic Farms, Germantown, New York, USA	WIS: 444 ± 2.5 g WKY: 478 ± 7.8 g SHR: 318 ± 2.3 g	SBP were estimated using the tail-cuff occlusion and photoelectric pulse sensor method WIS: 106 ± 3.6 mmHg WKY: 111 ± 3.1 mmHg SHR: 194 ± 2.5 mmHg	SHR > WIS = WKY
Tanigawa, Inoue and Tamura (1999)	Japan	Male	10 weeks	WIS- Shizuoka Laboratory Center, Hamamatsu, Japan WKY and SHR- Charles River Laboratories, Atsugi, Japan	WIS: 312 ± 3 g WKY: 293 ± 3 g SHR: 255 ± 3 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: NI WKY: 163 ± 4 mmHg SHR: 220 ± 7 mmHg	X
Casellas et al. (2000)	USA	Male	12 weeks	Iffa Credo, Lyon, France	WIS: 424 ± 9 g WKY: 266 ± 6 g SHR: 329 ± 7 g	NI	X
Dalle Lucca et al. (2000)	Brazil	Male	NI	Wistar Institute, Philadelphia- USA	300 - 30 g	MAP was estimated using the tail-cuff occlusion and plethysmography method WIS: 114 ± 24 mmHg WKY: 128 ± 24 mmHg SHR: 194 ± 18 mmHg	SHR > WIS = WKY
Hancock and Lindsay (2000)	USA	Male	NI	Harlan Sprague Dawley, Indianapolis- USA	300 - 400 g	BP were estimated using the tail-cuff occlusion and plethysmography method WIS: 116 ± 10 mmHg WKY: 92 ± 15 mmHg SHR: 154 ± 6 mmHg	SHR > WIS = WKY
Kawasaki et	Japan	Male	15 weeks	Charles River Laboratories,	NI	Direct registration of MAP from catheter in	SHR > WIS =

al. (2000)				Shizuoka, Japan		carotid aortic artery WIS: 95.5 ± 2.7 mmHg WKY: 97.8 ± 1.8 mmHg SHR: 187.7 ± 1.5 mmHg	WKY
Ibarra, López-Guerrero and Villalobos-Molina (2001)	Mexico	Male	6 months	NI	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 125 ± 20 mmHg WKY: 135 ± 10 mmHg SHR: 192 ± 10 mmHg	X
Borges et al. (2002)	Brazil	Female	20 - 30 weeks	WIS - Wistar Institute, Philadelphia-USA WKY and SHR-National Institutes of Health, Bethesda, Maryland, USA	200 - 220 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 130 ± 6 mmHg WKY: 135 ± 7 mmHg SHR: 160 ± 5 mmHg	SHR > WIS = WKY
Aiello et al. (2004)	Argentina	Male	4 - 5 months	WIS - School of medical sciences, Argentina WKY and SHR - Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	WIS: 324.9 ± 9.2 g WKY: 305.3 ± 5.1 g SHR: 314.5 ± 4.5 g	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 118.5 ± 1.0 mmHg WKY: 119.8 ± 1.6 mmHg SHR: 175.8 ± 1.8 mmHg	SHR > WIS = WKY
Shcherbin and Tsyrlin (2004)	Russia	Male	19 - 24 weeks	NI	280 - 310 g	Direct registration of MAP from catheter in carotid femoral artery WIS: 117 ± 7.1 mmHg WKY: 123 ± 2.1 mmHg SHR: 164 ± 5.7 mmHg	SHR > WIS = WKY
Kubo and Hagiwara (2006)	Japan	Male	15 - 16 weeks	WIS- NI WKY and SHR-Disease Model Cooperative Research Association, Kyoto, Japan	NI	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 101 ± 2 mmHg WKY: 114 ± 2 mmHg SHR: 169 ± 2 mmHg	X
Orduna, Hong and Bouzas (2007)	Mexico	Male	60 days	WIS- Harlan, Mexico City, Mexico WKY and SHR-Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	190 - 250 g	MAP was estimated using the tail-cuff occlusion and plethysmography method WIS: 102 ± 4.51 mmHg WKY: 124 ± 5.26 mmHg SHR: 175 ± 8.33 mmHg	SHR > WIS = WKY
Bizot et al. (2007)	France	Male	70 -95 days	Centre d'Elevage René Janvier, France	WIS: 296 ± 7 g WKY: 248 ± 7 g SHR: 201 ± 2 g	NI	X
Wheal et al. (2007)	England	Male	SHR: ~20 weeks	WIS and SHR-Charles River Breeding Laboratories, United Kingdom	WIS: 350 - 450 g WKY and SHR: 300 g	Direct registration of MAP from catheter in tail artery WIS: 111 ± 2 mmHg	SHR > WKY > WIS

				WKY- Harlan Laboratories, United Kingdom		WKY: 120 ± 3 mmHg SHR: 176 ± 5 mmHg	
Ribeiro, Afonso e Macedo (2007)	Portugal	Male	5 - 9 weeks	Charles River-Spain	250 - 300 g	Direct registration of SBP from femoral in tail artery WIS: 1118.1 ± 12.81 mmHg WKY: 106.7 ± 8.66 mmHg SHR: 159.2 ± 13.34 mmHg	SHR > WIS = WKY
Orduna et al. (2008)	Mexico	Male	60 days	WIS- Harlan, Mexico City, Mexico WKY and SHR- Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	WIS: 281.3 g WKY: 253.3 g SHR: 228 g	MAP was estimated using the tail-cuff occlusion and plethysmography method WIS: 108.3 ± 3.0 mmHg WKY: 109.2 ± 2.6 mmHg SHR: 143.9 ± 9.9 mmHg	SHR > WIS = WKY
Percy et al. (2009)	Australia	Male	3 months and 21 - 24 months	NI	3 months WIS: 360 ± 16 g WKY: 257 ± 56 g SHR: 262 ± 17 g 21 - 24 months: WIS: 689 ± 53 g WKY: 444 ± 32 g SHR: 392 ± 32 g	SBP were estimated using the tail-cuff occlusion and plethysmography method 3 months WIS: 118 ± 3 mmHg WKY: 133 ± 2 mmHg SHR: 205 ± 4 mmHg 21 - 24 months: WIS: 138 ± 4 mmHg WKY: 148 ± 7 mmHg SHR: 200 ± 6 mmHg	X
Castelló-Ruiz et al. (2011)	Spain	Male	15 - 17 weeks	NI	NI	Direct registration of MAP from catheter in femoral artery WIS: 113 ± 4 mmHg WKY: 111 ± 6 mmHg SHR: 140 ± 7 mmHg	SHR > WIS = WKY
Sanada et al. (2011)	Brazil	Female	20 weeks	animal care facility of the Department of Neurology, School of Medicine of Ribeirao Preto	WIS: 358.9 ± 21.5 WKY: 242.7 ± 29.4 SHR: 310.9 ± 30.2	SBP were estimated using the tail-cuff occlusion and plethysmography method WIS: 134.8 ± 18.4 mmHg WKY: 179.6 ± 33.4 mmHg SHR: 217 ± 10.3 mmHg	SHR > WIS SHR = WKY WIS = WKY
Wang, Thonsen and Frøkiær (2013)	Denmark	Male	10 - 11 weeks	Mollegaard Breeding Farm, Skensved, Denmark	200 - 300 g	Direct registration of MAP from catheter in femoral artery WIS: 113 ± 4 mmHg WKY: 115 ± 3 mmHg SHR: 148 ± 3 mmHg	SHR > WIS = WKY
Nam et al. (2014)	USA	Male	6- 7 weeks	Charles River Laboratories, Kingston, New York- USA	WIS: 376.0 ± 9.3 g WKY: 254.9 ± 3.8 g SHR: 268.8 ± 3.9 g	NI	X
Jordan et al. (2016)	USA	Male	28 - 77 days	Charles River Laboratories	WIS: 356 ± 11 g WKY: 254 ± 5 g SHR: 255 ± 5 g	NI	X
Rostron et al. (2017)	England	NI	10 weeks	Charles River Laboratories, Kisslegg,	WIS: 204 ± 1.8 g WKY: 188 ± 5 g SHR: 132 ± 2.5 g	NI	X

				Germany			
Kawabe et al. (2016)	USA	Male	14 weeks	Charles-River Breeding Laboratories, Wilmington Massachusetts-USA	NI	Direct registration of MAP from catheter in femoral artery WIS: 103.3 ± 2.5 mmHg WKY: 90.3 ± 2.6 mmHg SHR: 147.1 ± 2.8 mmHg	X
Rezende et al. (2021)	Brazil	Male	16, 48 and 72 weeks	NI	16 weeks WIS: 420 ± 30.75 g WKY: 363.85 ± 26.47 g SHR: 282 ± 13.61 g 48 weeks WIS: 479.85 ± 40.73 g WKY: 386 ± 45.27 g SHR: 400 ± 24.73 g 72 weeks WIS: 527 ± 31.02 g WKY: 442 ± 26.40 g SHR: 436 ± 27.09 g	SBP and MAP were estimated using the tail-cuff occlusion and plethysmography method 16 weeks SBP WIS: 123.29 ± 4.89 mmHg WKY: 134.71 ± 6.82 mmHg SHR: 156.57 ± 11.38 mmHg MAP WIS: 99 ± 10.11 mmHg WKY: 109.85 ± 11.24 mmHg SHR: 121 ± 19.25 mmHg 48 weeks SBP WIS: 116.14 ± 8.15 mmHg WKY: 142.85 ± 14.50 mmHg SHR: 195.14 ± 13.29 mmHg MAP WIS: 85.71 ± 10.57 mmHg WKY: 116.28 ± 10.11 mmHg SHR: 146.42 ± 21.73 mmHg 72 weeks SBP WIS: 120.42 ± 5.22 mmHg WKY: 143 ± 9.09 mmHg SHR: 193.57 ± 18.12 mmHg MAP WIS: 96 ± 7.16 mmHg WKY: 109.42 ± 22.38 mmHg SHR: 162 ± 23.34 mmHg	16 weeks SBP SHR > WIS = WKY MAP SHR > WIS SHR = WKY WIS = WKY 48 weeks SBP SHR > WIS SHR > WKY WKY > WIS MAP SHR > WIS SHR > WKY WKY > WIS 72 weeks SBP SHR > WIS = WKY MAP SHR > WIS = WKY

WIS- Wistar; WKY- Wistar Kyoto; SHR- Spontaneously Hypertensive Rat; g- gram; mmHg- millimeter of mercury; NI- not indicated; SBP- Systolic blood pressure; DBP- Diastolic blood pressure; MAP- mean arterial pressure.

Another point to be highlighted is the method used for measuring blood pressure. Two methods have been widely used. Direct measurement through the insertion of an arterial catheter was used in 26 studies, while 43 studies measured blood pressure indirectly via tail plethysmography. Both are valid methods; the difference between them is that catheter insertion is highly invasive, while plethysmography is not. Finally, the last column of Table 2 presents the statistical results of each study comparing the measured blood pressure between strains.

3.2. Meta-analysis

3.2.1. Systolic blood pressure – WIS vs. WKY

After pooling the data from fifty-two studies, the mean effect size was 0.41 (95% CI 0.09, 0.72), which indicates that SBP was higher in WKY compared to that in WIS with a small and significant effect size ($p < 0.05$, Fig. 3; *supplemental content*

1). According to a random-effect analysis, heterogeneity was observed among these studies (I^2 = 88.5%; *Q* = 689.2, df = 79, *p* = 0.00).

3.2.2. Systolic blood pressure – WIS vs. SHR

After merging the data from fifty-two studies, the mean effect size was 6.08 (95% CI 5.37, 6.79), which indicates that SBP was greater in SHRs than in WISs, with a large and significant effect size (*p* < 0.05, Fig. 3; *supplemental content 2*). According to a random-effect analysis, heterogeneity was observed amid these studies (I^2 = 93.8%; *Q* = 1281.2, df = 79, *p* = 0.00).

3.2.3. Systolic blood pressure – WKY vs. SHR

After combining the data from fifty-one studies, the mean effect size was 5.66 (95% CI 4.97, 6.35), which indicates that SBP was higher in SHRs than in WKYs, with a large and significant effect size (*p* < 0.05, Fig. 3; *supplemental content 3*). According to a random-effect analysis, heterogeneity was observed between these studies (I^2 = 94.4%; *Q* = 1401.1, df = 79, *p* = 0.00).

3.2.4. Mean blood pressure – WIS vs. WKY

After merging the data from twenty-four studies, the mean effect size was 0.35 (95% CI -0.21, 0.92), which indicates that MBP was similar between WIS and WKY (*p* > 0.05, Fig. 3; *supplemental content 4*). According to a random-effect analysis, heterogeneity was observed among these studies (I^2 = 89.0%; *Q* = 262.5, df = 29, *p* = 0.00).

3.2.5. Mean blood pressure – WIS vs. SHR

After pooling the data from twenty-four studies, the mean effect size was 5.47 (95% CI 4.38, 6.56), which indicates that MBP was greater in SHR than in WIS with a large and significant effect size (*p* < 0.05, Fig. 3; *supplemental content 5*). According to a random-effect analysis, heterogeneity was observed between these studies (I^2 = 93.0%; *Q* = 413.2, df = 29, *p* = 0.00).

3.2.6. Mean blood pressure – WKY vs. SHR

After merging the data from twenty-four studies, the mean effect size was 5.21 (95% CI 4.13, 6.28), which indicates that MBP was higher in SHRs than in WKYs, with a large and significant effect size (*p* < 0.05, Fig. 3; *supplemental content 6*). According to a random-effect analysis, heterogeneity was observed among these studies (I^2 = 93.0%; *Q* = 414.4, df = 29, *p* = 0.00).

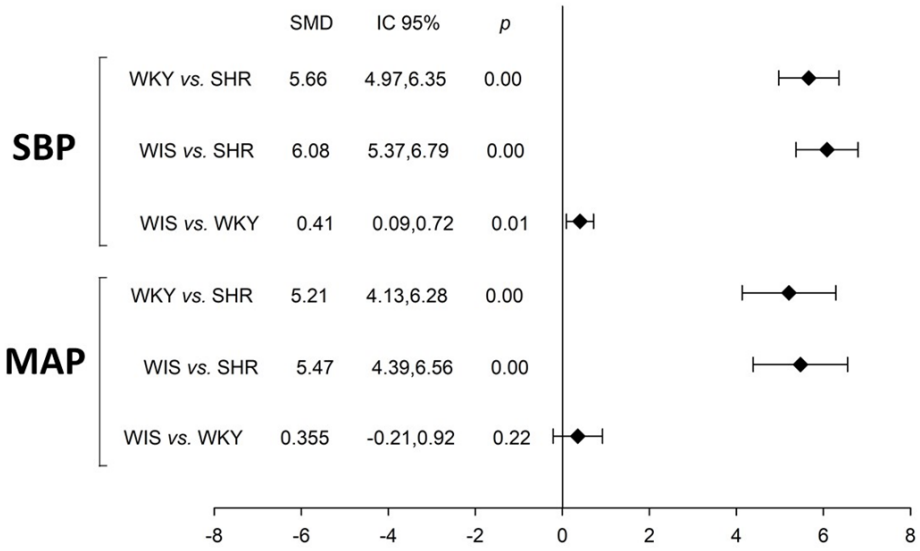

Figure 3 Forest plot of systolic blood pressure (SBP) and mean arterial pressure (MAP) of WIS, WKY and SHR. SMD- standardized mean difference; W- weight.

3.2.7. Body Mass – WIS vs. WKY

After combining the data from thirty-seven studies, the mean effect size was -3.66 (95% CI -4.40, -2.92), which indicates that body weight was lower in WKY compared to WIS with a large and significant effect size (*p* < 0.05, Fig. 4;

supplemental content 7). According to a random-effect analysis, heterogeneity was observed amidst these studies (I^2 = 95.4%; Q = 1359.0, df = 62, p = 0.00).

3.2.8. Body Mass – WIS vs. SHR

After pooling the data from thirty-seven studies, the mean effect size was -6.82 (95% CI -7.78, -5.86), which indicates that body mass was inferior in SHRs than in WISs, with a large and significant effect size (p < 0.05, Fig. 4; *supplemental content 8*). According to a random-effect analysis, heterogeneity was observed among these studies (I^2 = 95.8%; Q = 1468.4, df = 62, p = 0.00).

3.2.9. Body Mass – WKY vs. SHR

After merging the data from thirty-seven studies, the mean effect size was -1.74 (95% CI -2.38, -1.10), which indicates that body weight was lower in SHRs than in WKY rats, with a large and significant effect size (p < 0.05, Fig. 4; *supplemental content 9*). According to a random-effect analysis, heterogeneity was observed between these studies (I^2 = 95.4%; Q = 1357.1, df = 62, p = 0.00).

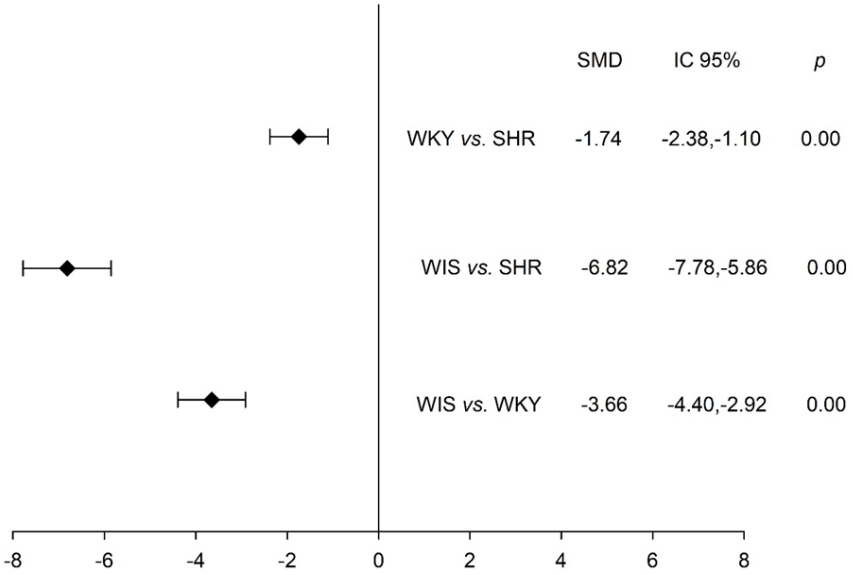

Figure 4 Forest plot of body mass of WIS rats, WKY rats and SHRs. SMD- standardized mean difference; W- weight.

4. Discussion

This work aimed to systematically review and perform a meta-analysis on studies regarding the blood pressure and body mass of the WIS, WKY and SHR strains, since these variables are determinants for selecting SHR control in scientific research. The main results were as follows: i) systolic blood pressure: SHRs exhibit a higher SBP than controls, and WKYs have a greater SBP than WISs; ii) mean arterial pressure: SHRs present higher values than controls; and iii) body mass: WISs show greater body mass than SHRs and WKYs, and WKYs exhibit higher body mass than SHRs.

Methodology is the theory of the organization of scientific research (Novikov and Novikov, 2013). The planning and application of an adequate method is critical for scientific research success and credibility. In this sense, the selection of appropriate experimental and control models in agreement with the study objectives is essential. In studies on hypertension, the use of the SHR model is widely accepted; nevertheless, the strain to be used as its control is not consensual in the literature.

The number of studies on hypertension increased exponentially from the 1960s to the 1990s. The epidemiological transition theory explains the transition of mortality causes and disease incidence over time (Omran, 1971). World development has led to life expectation increases and decreases in the number of deaths by hunger or infectious diseases (Omran, 1971). However, this change led to a high worldwide incidence of chronic and degenerative diseases, such as hypertension, which generated great demand for its understanding in the first half of the last century (N. Alexander, et al 1954; I. H. Page, 1939; Smirk and Hall, 1958). There was a collective effort by research groups to develop an experimental model to study EAH (N. Alexander, et al 1954; E. L. Phelan, et al 1962; E. L.; Phelan and Smirk, 1962; Smirk and Hall, 1958), which culminated in the development of the SHR model by Okamoto in 1963 in Japan (Okamoto and Aoki, 1963). Consequently, the availability of such a model that reliably mimics the characteristics of the disease promoted important advances in the understanding of hypertension.

The use of the SHR model to study hypertension requires a normotensive strain as a control, and WKY rats were identified as the ideal model since they are in the SHR background (Okamoto and Aoki, 1963; Okamoto, et al 1966). However, there are controversial results on blood pressure and other variables from the WKY strain. Our meta-analysis confirmed that WKY rats presented higher SBP than WIS rats, another strain used as an SHR control. This information led to concerns about the use of WKY as a control of hypertensive animals, and a series of comparative studies as well as a search for an ideal model to be used as SHR control took place. According to our review, Tobia, Lee and Walsh (1974) published the first study using more than one experimental model as SHR control. They investigated the regional blood flow of iliac and mesenteric arteries of WIS, WKY and SHR and found that WIS presented higher peripheral resistance than WKY, indicating the latter as a better control for SHR (Tobia, Lee, and Walsh, 1974). Later, Frohlich and Pfeffer included WIS rats as controls for SHRs since WIS is the background of the WKY strain (Frohlich and Pfeffer, 1975). They evaluated the adrenergic mechanism of hypertension and found similar results from normotensive animals (Frohlich and Pfeffer, 1975). However, many other factors are involved in the onset and development of the disease, which prompted the use of both models as SHR control in many studies in the following year – with the peak observed between the 1980s and 1990s. These studies allowed the identification of the effects of the disease and contributed to the characterization of experimental models (Aiello et al 2004; Akemi Sato, Vanderlei Menani, Ubriaco Lopes, and Colombari, 2001; D. Alexander, Gardner, Tomonari, Fine, and Aviv, 1990; Altura, Carella, and Altura, 1980; Belichard, Pruneau, and Rochette, 1988; Bian and Bukoski, 1995; Bizot, et al 2007; Blume et al 1997; Borges, Feres, Vianna, and Paiva, 2002; Borkowski and Quinn, 1983; Boylan, Van Liew, and Feig, 1991; Brace et al 2015; Brooksby, Levi, and Jones, 1993; Bueno et al 2004; Casellas, Bouriquet, Artuso, Walcott, and Moore, 2000; Castello-Ruiz et al 2011; Collis, de May, and Vanhoutte, 1979; Coskinas and Price, 1987; Cox, 1979; Dalle Lucca, Dalle Lucca, Borges, Ihara, and Paiva, 2000; David-Dufilho, Pernollet, Morris, Astarie-Dekequer, and Devynck, 1994; Dela Pena et al 2017; Docherty and Warnock, 1986; Dommett and Rostron, 2011, 2013; Dumont and Lemaire, 1995; Dumont, Sabourin, and Lemaire, 1990; Dunn, Pfeffer, and Frohlich, 1978; Farman and Bonvalet, 1985; Feig, D'Occhio, and Boylan, 1987; Feng and Arendshorst, 1996; Feres, Borges, Silva, Paiva, and Paiva, 1998; Feres, Vianna, Paiva, and Paiva, 1992; Findlay, 1996; Fox et al 2002; Frohlich and Pfeffer, 1975; Garcia, Gauquelin, Thibault, Cantin, and Schiffrin, 1989; Gattone, 1986; Gattu, Pauly, Boss, Summers, and Buccafusco, 1997; Grisk et al 1995; Gros et al 2000; Grunblatt et al 2015; Haack, Schaffer, and Simpson, 1980; Hancock and Lindsay, 2000; Hard, et al 1985; Harris, Grigor, and Millar, 1990; Harvey et al 2013; Harvey, Sen, Deaciuc, Dwoskin, and Kantak, 2011; Hausler, Girard, Baumann, Ruch, and Otten, 1983; Head and de Jong, 1986; Herman et al 2011; Hilgenfeldt and Schott, 1987; Hill, Herbst, and Sanabria, 2012; Hodgins and Frohlich, 1978; Hopp et al 1986; Huang, Sun, and Koller, 1993; Ibarra, Lopez-Guerrero, and Villalobos-Molina, 2001; Ibias, Daniels, Miguens, Pellon, and Sanabria, 2017; Ibias, Miguens, and Pellon, 2016; Ibias and Pellon, 2011; Ibias, Pellon, and Sanabria, 2015; Johnson and Macia, 1979; Jordan, Harvey, Baskin, Dwoskin, and Kantak, 2014; Jordan, Lemay, Dwoskin, and Kantak, 2016; Jordan, Taylor, Dwoskin, and Kantak, 2016; Kawabe, Iwasa, Kawabe, and Sapru, 2016; Kawasaki, Nuki, Yamaga, Kurosaki, and Taguchi, 2000; Kawasaki, Saito, and Takasaki, 1990; Khalil et al 1987; Kino et al 1985; Kitami, Fukuoka, Hiwada, and Inagami, 1999; Kitamura, Ishise, Pegram, Kawamura, and Frohlich, 1981; Klee, Vater, Schmid-Schonbein, and Seiffge, 1993; Kodavanti et al 2015; Krukoff and Calaresu, 1984; Kubo and Hagiwara, 2006; Kunes, Pang, Cantin, Genest, and Hamet, 1987; Lang and Johns, 1987; Langen and Dost, 2011; Lariviere, Baribeau, St-Louis, and Schiffrin, 1989; Leyssac, Jensen, and Holstein-Rathlou, 1986; Loeb and Bean, 1986; Lukacsko, 1983; Lukacsko, Messina, and Kaley, 1980; Lundin, et al 1982; Magee and Schofield, 1992, 1994; Magnusson and Meyerson, 1993; Mamuya, Chobanian, and Brecher, 1992; Martin and Quock, 1984; McLellan, Milligan, Houslay, and Connell, 1993; Miasiro, Paiva, Pereira, and Shimuta, 1985; Morano et al 1993; Morton et al 1990; Mullins and Banks, 1976; Mullins, Kleinman, Russell, and Srivastava, 1982; Nakamura, Nakamura, Fine, and Aviv, 1988; Nam, Clinton, Jackson, and Kerman, 2014; Nickerson, 1976; Nishiyama, et al 1976; Nordborg and Johansson, 1980; O'Donnell and Volicer, 1981; Oliveira et al 2009; Orduna, Garcia, Menez, Hong, and Bouzas, 2008; Orduna, Hong, and Bouzas, 2007; Orduna, Valencia-Torres, and Bouzas, 2009; Paré, 1989; Pare, 1989a, 1989b; Percy, Brown, Power, Johnson, and Gobe, 2009; Perez, Petroff, and Mattiazzi, 1993; Picotti, Carruba, Ravazzani, Bondiolotti, and Da Prada, 1982; Pollock and Arendshorst, 1991; Postnov and Orlov, 1980; Preuss and Goldin, 1983; Preuss et al 1998; Ribeiro, Afonso, and Macedo, 2007; Rodionov et al 1989; Rostron, Gaeta, Brace, and Dommett, 2017; Rowland, Li, Fregly, and Smith, 1995; Rybnikovaa, Vetrovoia, and Zenkoa, 2018; Sagvolden, et al 1993; Sakamoto et al 2006; Saltzman, DeLano, and Schmid-Schonbein, 1992; Sanada, et al 2011; Sandow, Gzik, and Lee, 2009; Schiffrin et al 1992; Schini, Kim, and Vanhoutte, 1991; Shcherbin and Tsyrlin, 2004; Silva, Frediani-Neto, Ferreira, Paiva, and Paiva, 1994; Sitsen, Nijkamp, and Jong, 1987; Sladek, Davis, and Sladek, 1986; Somkuwar, Darna, Kantak, and Dwoskin, 2013; Somkuwar, Jordan, Kantak, and Dwoskin, 2013; Somkuwar, Kantak, Bardo, and Dwoskin, 2016; Somkuwar, Kantak, and Dwoskin, 2015; Sonntag, Schalike, and Brattstrom, 1990; Stein, Katzeff, Norton, De Wet, and Rosendorff, 1990; Tabrizchi and Triggle, 1992; Takahashi et al 1983; Tamura et al 1986; Tanigawa, Inoue, and Tamura, 1999; Tobia, et al 1974; Toivanen et al 1986; Tokushige et al 1986; Touyz and Schiffrin, 1997; Touyz, Tolloczko, and Schiffrin, 1994, 1995; Tran, DeLano, and Schmid-Schonbein, 2010; Tremblay et al 1993; Turrin, dos Santos, and da Veiga, 1993; Umehara et al 2013; van den Bergh et al 2006; Van Liew, Zamlauski-Tucker, and Feld, 1993; Wang, Thomsen, and Frokiaer, 2013; Webb, VANHOUTTE, and BOHR, 1980; Wheal, Bennett, Randall, and Gardiner, 2007; Wickens, Macfarlane, Booker, and McNaughton, 2004; Widimsky, Kuchel, Tremblay, and Hamet, 1991).

4.1. Geographic distribution

We found studies developed in the four continents, with 55 in the Americas and 23 in Europe, thus the continents that most contributed to the characterization of the strains. It is important to highlight those 36 published papers originating from the United States of America. On the other hand, Africa was the only continent that has not developed any work on this issue, while Oceania developed just one study. This analysis of geographic distribution points out that the concern about which model should be used as SHR control was global and encouraged this methodological organization by including the three strains in all these studies around the world.

4.2. Laboratory of supplying animals

Another important issue to be considered is the laboratory of origin of the experimental models (Tab. 1). The laboratories that most frequently supplied animals for the studies were *Charles River* (WIS- 29; WKY- 28; SHR- 29), followed by *Harlan Laboratories* (WIS- 6; WKY- 3; SHR- 2) and *Taconic Farms, Germantown, New York- USA* (WIS - 3; WKY- 8; SHR- 8). The studies pointed to the animals withdrawing from several sites of the *Charles River* and *Harlan laboratories*, while just one was from the *Taconic Farms*.

The choice of the laboratory for supplying the animals is important since there are studies indicating biological variability between WKY rats and SHRs from different laboratories. The animals presented mainly different levels of MAP (Kurtz and Morris, 1987). Moreover, the genetic variability of these strains was tested, and differences between WKY rats from different laboratories and even between animals from the same laboratory were detected (Kurtz, et al 1989). Kreutz et al. (1997) reported that there are WKY strains with chromosome distinctions – which were linked to differences in diastolic and systolic blood pressure (Hilbert et al 1991; Jacob et al 1991) - and they were named WKY0 and WKY1, where WKY1 had higher baseline arterial pressure values (Kreutz et al 1997). Langen and Dost (2011) demonstrated a behavioral and genetic deviation between animals from *Harlan* and *Charles River* laboratories and considered that they are different substrains (Langen and Dost, 2011). Other studies confirmed the great genetic variability between WKY rats from different laboratories and that WKY rats from *Charles River* are good models for behavior disorder studies, such as anxiety and depression (Brace, et al 2015; Ibias, et al 2017; Jordan, Lemay, et al 2016; Langen and Dost, 2011; Somkuwar, Darna, et al 2013; Somkuwar, et al 2015). A recent literature review that collected information on the genetic basis of SHRs and their background confirmed that there is genetic variability in animals from different laboratories and indicated that genetic variants present in the outbred strains from which SHRs are created generated differences in hypertension development (Doris, 2017). Such information indicates the need for prior examination regarding the genetic origin and characteristics of the animals provided by the laboratories, since there are certainly several differences between the procedures and between the raised and supplied animals.

4.3. The experimental dilemma

One of the dilemmas faced by the researchers is to pair the experimental groups by age, body mass or blood pressure. We observed that most studies matched for age. Gattone (1986) used newborn animals, aiming to observe the variables studied early in life and in the first weeks of development (Gattone, 1986). On the other hand, Rezende et al. (2021) used older animals (i.e., 72 weeks), aiming to observe the aging effect on the studied variables (de Rezende et al 2021). It is noteworthy that there is a well-defined progression to hypertension development in the SHR model (Bing et al 1995; Boluyt, Bing, and Lakatta, 1995). Hypertension peaks at the age of 16 weeks in this model, and for this reason, most studies use four-month-old SHRs (Bing, et al 1995; Brooksby, et al 1993; Doggrell and Brown, 1998; Touyz, et al 1995).

The WIS strain showed a higher body mass compared to the WKY and SHR in most studies, which was confirmed by the meta-analysis (Fig. 10 and 11). Body mass is one of the factors to be observed and considered when selecting the experimental model. However, the essential variable to be considered is blood pressure. Clearly, the SHRs presented higher systolic and mean blood pressure, as expected (Fig. 5, 6, 8 and 9). Three studies showed higher blood pressure in WIS rats than in WKY rats (Bian and Bukoski, 1995; Head and de Jong, 1986; Lariviere, et al 1989), while in the other three studies, WKY rats presented greater values for blood pressure (de Rezende, et al 2021; Wheal, et al 2007; Widimsky, et al 1991). The meta-analysis revealed that the WKY exhibits higher SBP than WIS (Fig. 4). Regarding MAP, no difference was observed between controls (Fig. 7). It is important to emphasize that, despite this difference, both animals are classified as normotensive, since the cutoff point for determining the disease in rodents is 150 mmHg (Okamoto and Aoki, 1963).

Some studies recommend caution in using the WKY strain as an SHR control. For instance, Hopp et al. indicated that WKY from the *National Institutes of Health* presented a propensity for blood pressure elevation (Hopp, et al 1986). Because of that, they decided to exclude WKY animals that presented SBP above 130 mmHg, and they affirmed that it was difficult to use WKY as an SHR control without analyzing this variable and indicated the parallel use of WIS and WKY (Hopp, et al 1986). Moreover, the study by Tamura et al. included only animals of this strain presenting SBP below 130 mmHg (Tamura, et al 1986). Furthermore, WKY presents properties of smooth muscle very close to those observed in SHR, indicating a relationship with the hypertension state (Silva, et al 1994).

The parallel use of WKY and WIS as adequate SHR controls has been suggested (Brace, et al 2015; Dunn, et al 1978; Gattone, 1986; Hard, et al 1985; Jordan, Lemay, et al 2016; Stein, et al 1990; van den Bergh, et al 2006). For example, Dun et al. indicated that such comparisons may produce new insights into the hypertension effects that may not be apparent if only WKY rats are used as controls (Dunn, et al 1978). Moreover, Somkuwar et al. reported that studies using only WKY as a reference control have been disapproved because some variables may be either under- or overestimated if the parallel control is not used (Somkuwar, Darna, et al 2013). In 1978, Hodgins and Frohlich indicated the use of the two strains since there appear to be physical and hemodynamic differences between them. Thus, neither WIS nor WKY alone is the appropriate control when investigating hypertension-related parameters (Hodgins and Frohlich, 1978). According to Lundin et al one control (i.e., WKY) complements the other (i.e., WIS) (Lundin, et al 1982).

The studies included in this review had different objectives and analyzed a wide range of variables. In the first decades, between 1970 and 2000, the focus was on autonomic variables, in which studies sought to understand the factors underlying the development of EAH. However, it was discovered that the SHR and WKY animals could also be used as models for studies on behavioral disorders, such as depression, locomotor action, hyperactivity and attention deficit hyperactivity disorder (Hard et al 1985). In recent decades, mainly after 2005, several studies using the three experimental strains have promoted the analysis of behavioral disorders and their treatment, and this was a little explored area until then.

5. Final considerations

This systematic review and meta-analysis show that WIS and WKY strains exhibit similarities and differences depending on which variable is analyzed. This finding indicates that the choice of the strain to be used as SHR control requires a deep analysis. Our results support this theory and reinforce that both strains may be used as SHR controls. Therefore, the researchers need to be cautious and analyze which animal strain to be selected as the SHR control, based on the study objectives, considering factors such as laboratory of origin of animals, body mass and mainly, blood pressure.

Ethical Considerations

Not Applicable.

Conflict of Interest

The authors declare no conflicts of interest.

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