ENVIGO

Research Models and Services

Inbred Rats

SHR (Spontaneous Hypertensive Rat)

Origin

Okamoto and Aoki, 1963, from an outbred Wistar Kyoto male with spontaneous hypertension and a female with slightly higher than normal blood pressure. Subsequently brother x sister pairs were selected for spontaneous hypertension (Okamoto, 1969; Okamoto *et al*, 1972). A number of sublines have been developed with a tendency to develop cardiovascular lesions and stroke (see particularly SHRSP) (Nagaoka *et al*, 1976), and hypercholesterolemia (Yamori, 1984). For a more recent review; see Yamori, (1994). From Department of Pathology, Faculty of Medicine, Kyoto University to National Institutes of Health, Bethesda in 1966.

SHR/NHsd

From National Institutes of Health to Harlan Laboratories. Harlan became Envigo in 2015.

Characteristics

Animal model

SHR rats express insulin resistance, and are a suitable model for insulin resistance and essential hypertension in non-obese humans (Swislocki and Tsuzuki, 1993). SHR rats are hyperactive and may be a useful model for childhood hyperkinesis and attention-deficit hyperactivity disorder (Sagvolden *et al*, 1993). SHR rats have been used as a model for screening anti-hypertensive drugs (Roba, 1976).

Anatomy

Low ten week body weight in males (Tanase *et al*, 1982). High relative heart weight in ten week old males (Tanase *et al*, 1982). SHR rats express insulin resistance, and are a suitable model for insulin resistance and essential hypertension in non-obese humans (Swislocki and Tsuzuki, 1993). SHR rats have fewer glomeruli than WKY rats, but they are of similar size, resulting in a reduced glomerular volume. This is consistent with the hypothesis that the kidney plays an important role in hypertension (Skov *et al*, 1994). Fetal but not placental weight is reduced compared with WKY (Johnston, 1995).

Behavior

SHR rats are hyperactive and may be a useful model for childhood hyperkinesis and attention-deficit hyperactivity disorder (Sagvolden *et al*, 1993).

Open field exploratory behavior was greater in SHR than WKY rats, and the most active SHR developed the most pronounced hypertension (Knardahl and Sagvolden, 1979). Muricidal behavior of 90% was reported (Roba, 1976).

Drugs

Genetically resistant to the induction of mammary tumors by dimethylbenz(a)anthracene due to a blockade of tumor promotion (Harris *et al*, 1994). Roba (1976) concluded that the strain is a suitable model for screening anti-hypertensive drugs.

Genetics

Cross analysis between SHR and Donryu rats indicated that the hypertensive trait of SHR is regulated by a single gene and several other genes with minor effect (Tanase, 1979; Roba, 1976). Esterase alleles have been described by Womack (1973). There is no evidence for substrain differentiation among SHR stocks from the major commercial suppliers in the USA both respect to phenotype and DNA fingerprints (Blizard *et al*, 1991).

Coat color genes	- *c* : albino.
Histocompatibility	- *RT1*^{k}
Biochemical markers	- Es-1^{a}, Es-2^{a}, Es-3^{b}, Es-4^{a}, Gc^{a}, Hbb^{a}, Pep-3^{a}, Pgd^{b}

Husbandry

The "Committee on the care and use of hypertensive rats (1976)" has issued guidelines for the breeding and care of this strain.

Life-span and spontaneous disease

Histopathologic changes appeared in males when they became eight months old, in females at an age of 12-15 months. Female SHR rats live significantly longer than males (Wexler *et al*, 1981).

A few cases of multiple osteosarcoma in the skull, caudal vertebrae, and fore- and hindlimbs were reported (Iida *et al*, 1979). Periarteritis nodosa, which starts at level of duodenal artery and proceeds posteriorly to the testicular arteries, is the most common lesion. Myocardial lesions and nephrosclerosis are common; cerebral lesions are usually seen in rats with blood pressure greater than 200 mm Hg (Roba, 1976).

High blood pressure, reaching 171 mmHg at ten weeks of age (Tanase *et al*, 1982). Blood pressure of about 200 mm in mature males and 175 mm in mature females (Roba, 1976). According to Yamori (1984), the rats develop hypertension spontaneously without exception at the age of 7-15 weeks. There is a systolic blood pressure plateau of about 200 mmHg. The genetic basis is polygenic, with at least three major genes involved (Tanase and Suzuki, 1971; Yen *et al*, 1974).

There is a high incidence of cardiovascular disease (Okamoto *et al* 1973), but a low incidence of stroke, which can be increased to about 30% with chronic stress (Yamori, 1984). Alloxan diabetes further increases blood pressure, but the animals respond to anti-hypertensive drugs (Okamoto, 1969). Yamori states that SHR rats show a functional increase in peripheral vascular resistance, which mostly depend on neurogenic mechanisms, which probably originate in a disorder of central blood pressure regulation. The blood pressure per se and increased neurogenic tone accelerate cardiovascular protein synthesis and induce structural vascular changes, which contribute to the maintenance of the hypertension. Studies on cultured vascular smooth muscle suggest a genetic predisposition to hyperplastic growth of these cells and its stimulation by ß-adrenergic mechanisms. According to Dietz *et al* (1984) there is an abnormality of intracellular electrolyte balance with increased intracellular sodium and calcium concentration. Grobecker *et al* (1975) found that in young SHR rats the plasma levels of both noradrenaline and dopamine-ß-hydroxylase were increased over control WKY rats, but total catecholamines were not significantly different. Catecholamine content of the adrenals was reduced. Circulating thyrotrophin levels were markedly elevated over two control strains (Werner *et al*, 1975). There was a reduced ^{131}I metabolism and increased thyroid weight relative to Wistar controls (Fregley, 1975).

Environmental and dietary factors can influence the degree of hypertension (Yamori *et al* 1978; Yamori *et al* 1986). A high (8%) salt diet increased systolic blood pressure, but not so much as in strain SS/Jr (Adams and Blizard, 1991). A polymorphism in the heat shock protein 70 (hsp70) mapping in the RT1 complex was found to be associated with variation in blood pressure of 15 mm Hg among recombinant inbred strains (Hamet *et al*, 1992). Strain is significantly more sensitive to the hypotensive effects of GABA than normotensive Sprague Dawley or WKY rats, with evidence that the effects are mediated by the brain angiotensin system (Roberts *et al*, 1993). Plasma renin and angiotensin II levels are not elevated (Cambell *et al*, 1995). Glucose turnover in lean and obese (carrying the fatty gene) SHR rats has been described by Berdanier *et al*, (1993). There is reduced cancellous bone mass in SHR compared with WKY (Wang *et al*, 1993). The Y-chromosome of SHR increases blood pressure when backcrossed to strain WKY for 11 generations (Ely *et al*, 1993). There is a deficit in visual acuity at 40-66 days, prior to the onset of hypertension, and it is particularly marked in the blue spectrum (Rogers *et al*, 1993).

Miscellaneous

Characteristics of the SHR strain have been described by Festing (1979), De Jong (1984) and Greenhouse *et al* (1990).

Nutrition

High dietary calcium (2.5%) attenuated the time course of hypertension (Ayachi, 1979). Reduction of dietary vitamin E prevents the development of hypertension, possibly due to a significant increase in prostaglandin catabolism (Pace-Asciak and Carrara, 1979). Sodium chloride solutions were preferred to deionized water (Roba, 1976; Forman and Falk, 1979). Caloric restriction without sodium restriction reduces blood pressure (Young *et al*, 1978).

Physiology and biochemistry

Renal vascular resistance is elevated (Fink and Brody, 1979; Arendshorst and Beierwaltes, 1979a). Renal function studies indicate that kidneys of SHR require a higher arterial pressure than kidneys of WKY to excrete a given amount of salt and water (Arendshorst and Beierwaltes, 1979b; Beierwaltes and Arendshorst, 1978). Renal blood flow autoregulation was as efficient as in WKY rats (Arendshorst, 1979). PGE2 synthesis in aortas and PGE2Q in inferior cava walls were increased (Limas and Limas, 1977). PGE2 synthesis in renomedullary microsomes was increased (Limas and Limas, 1979).

Reproduction

Long gestation period: 22.55 ± .31 days (Peters, 1986).

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