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REVIEW

Age-Dependent Salt Hypertension in Dahl Rats: Fifty Years of Research

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Summary

Fifty years ago, Lewis K. Dahl has presented a new model of salt hypertension – salt-sensitive and salt-resistant Dahl rats. Twenty years later, John P. Rapp has published the first and so far the only comprehensive review on this rat model covering numerous aspects of pathophysiology and genetics of salt hypertension. When we summarized 25 years of our own research on Dahl/Rapp rats, we have realized the need to outline principal abnormalities of this model, to show their interactions at different levels of the organism and to highlight the ontogenetic aspects of salt hypertension development. Our attention was focused on some cellular aspects (cell membrane function, ion transport, cell calcium handling), intra- and extrarenal factors affecting renal function and/or renal injury, local and systemic effects of renin-angiotensin-aldosterone system, endothelial and smooth muscle changes responsible for abnormal vascular contraction or relaxation, altered balance between various vasoconstrictor and vasodilator systems in blood pressure maintenance as well as on the central nervous and peripheral mechanisms involved in the regulation of circulatory homeostasis. We also searched for the age-dependent impact of environmental and pharmacological interventions, which modify the development of high blood pressure and/or organ damage, if they influence the salt-sensitive organism in particular critical periods of development (developmental windows). Thus, severe self-sustaining salt hypertension in young Dahl rats is characterized by pronounced dysbalance between augmented sympathetic hyperactivity and relative nitric oxide deficiency, attenuated baroreflex as well as by a major increase of residual blood pressure indicating profound remodeling of resistance vessels. Salt hypertension development in young but not in adult Dahl rats can be attenuated by preventive increase of potassium or calcium intake. On the contrary, moderate salt hypertension in adult Dahl rats is attenuated by superoxide scavenging or endothelin-A receptor blockade which do not affect salt hypertension development in young animals.

Key words

Blood pressure • Ion transport • Cell membrane function • Cytosolic calcium • Body fluids • Hemodynamics • Vasoactive systems • Sympathetic nervous system • Nitric oxide • Calcium influx • Calcium sensitization

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Ontogenetic aspects of salt hypertension development in the rat

It is well known that ontogenetic factors play an important role in the development of hypertension and/or its complication (Zicha *et al.* 1986, Zicha and Kuneš 1999a, Kuneš and Zicha 2006). Young immature organism often responds to various dietary stimuli (such as high sodium intake, low potassium intake or protein malnutrition) in a different manner than the adult organism does. The same is true for the effects of antihypertensive drugs (e.g. ACE inhibitors) or dietary interventions aimed to lower blood pressure (BP) (high potassium intake, antioxidants, polyunsaturated fatty

acids) if they are applied to spontaneously hypertensive rats (SHR) prior to the onset or after the development of hypertension.

Increased NaCl intake is an integral part of numerous models of experimental hypertension [deoxycorticosterone acetate (DOCA)-salt, triiodothyronine-salt, partial nephrectomy-salt, adrenal-regeneration-salt, etc] in which BP elevation is always higher in immature animals (Zicha *et al*. 1986). Salt-dependent hypertension in sexually immature rats is usually more pronounced, occurs earlier after the application of the above hypertensive stimuli and is accompanied by a severe end-organ damage leading to its self-sustained persistence even if salt intake is reduced to normal values.

A greater susceptibility of weanling or prepubertal rats to salt-dependent hypertension has been first described by Skelton and Guillebeau (1956) who studied adrenal-regeneration-salt hypertension. This characteristic age dependence (Brownie *et al.* 1966) was later confirmed in our institute by Jiří Jelínek (Jelínek *et al.* 1966, Musilová *et al.* 1966, Kuneš and Jelínek 1984) and Jiří Křeček (Dlouhá *et al.* 1977, 1979) who studied various salt-dependent forms of experimental hypertension. Enhanced hypertensive response to high salt intake has also been reported in immature baboons compared to adult ones (Cherchovich *et al.* 1976).

Early interventions during critical periods of development (developmental windows) might have some late unexpected consequences (Křeček 1971, Kuneš and Zicha 2006, 2009). Recently, a nice example has been demonstrated in salt-sensitive Dahl/Rapp rats in which the early exposure to high-fat diet in prepuberty increased the incidence and severity of atherosclerotic coronary lesions elicited by high-fat/high-salt diet feeding in adulthood (Kiefer *et al.* 2002). High salt intake during lactation was reported to increase later salt preference in salt-sensitive but not in salt-resistant Dahl rats (Ferrell *et al.* 1986). Another interesting example was reported in salt-sensitive Dahl rats transgenic for human cholesteryl ester transfer protein. Decano *et al.* (2009) found that the early-life exposure of fetal or weanling rats to a moderate increase of salt intake (0.40 % NaCl diet instead of 0.23 % NaCl diet) caused earlier BP increase and unmasked the susceptibility to adult-onset stroke. Both changes were more pronounced in females than in males. Surprisingly, early salt intake did not increase coronary heart disease (Decano *et al.* 2009), although a very low-salt diet (0.008 % NaCl) applied from the age of 6 months significantly attenuated the incidence of coronary artery disease in late adulthood (Herrera *et al.* 2001).

Age-dependent salt hypertension in Dahl rats – ontogenetic aspects

George R. Meneely and Lewis K. Dahl were the prominent pioneers in the research of salt hypertension, who demonstrated that hypertensive effects of excess NaCl intake in the rat are proportional to the amount of salt ingested (Meneely *et al*. 1953, Dahl *et al.* 1968) and that these effects are attenuated by increased potassium intake (Meneely *et al*. 1957, Dahl *et al.* 1972). Fifty years ago, Dahl *et al.* (1962) succeeded to select two contrasting lines of Sprague Dawley rats – outbred salt-sensitive (DS) and salt-resistant (DR) rats. From these original outbred Brookhaven strains Rapp and Dene (1985) have derived Dahl/Rapp inbred salt-sensitive (SS/Jr) and salt-resistant (SR/Jr) strains which were later distributed by Harlan, Moellegaard, Seiwa and other commercial breeders. In parallel, Iwai and Heine (1986) have produced Dahl/Iwai inbred strains (DIS, DIR) which are currently used in Japan (Yamazaki *et al.* 1994). The research on Dahl rats in the Institute of Physiogy (Academy of Sciences of the Czech Republic, Prague) started after the establishment of our colony in 1985 when the breeding pairs of inbred SS/Jr and SR/Jr rats were kindly donated by John P. Rapp. For the nomeclature of currently used Dahl rat strains see Table 1.

Table 1. Principal outbred and inbred strains of Dahl rats.

	Original location	**Salt-sensitive**	**Salt-resistant**
Outbred Dahl rats	Brookhaven	DS	DR
Inbred Dahl/ Rapp rats	Toledo	SS/Jr	SR/Jr
Inbred Dahl/ Iwai rats	Brookhaven	DIS	DIR

Actually there are almost 2000 papers concerning this model of hypertension. Phenotypic differences between salt-sensitive and salt-resistant animals were reviewed by John P. Rapp (1982), who later summarized the genetic analysis of this model (Rapp

2000). Currently, the research on physiological genomics of salt hypertension is facilitated by the existence of a panel of consomic strains derived from SS/Jr and Brown Norway (BN) rats (Roman *et al.* 2002, Cowley 2003, Cowley *et al.* 2004).

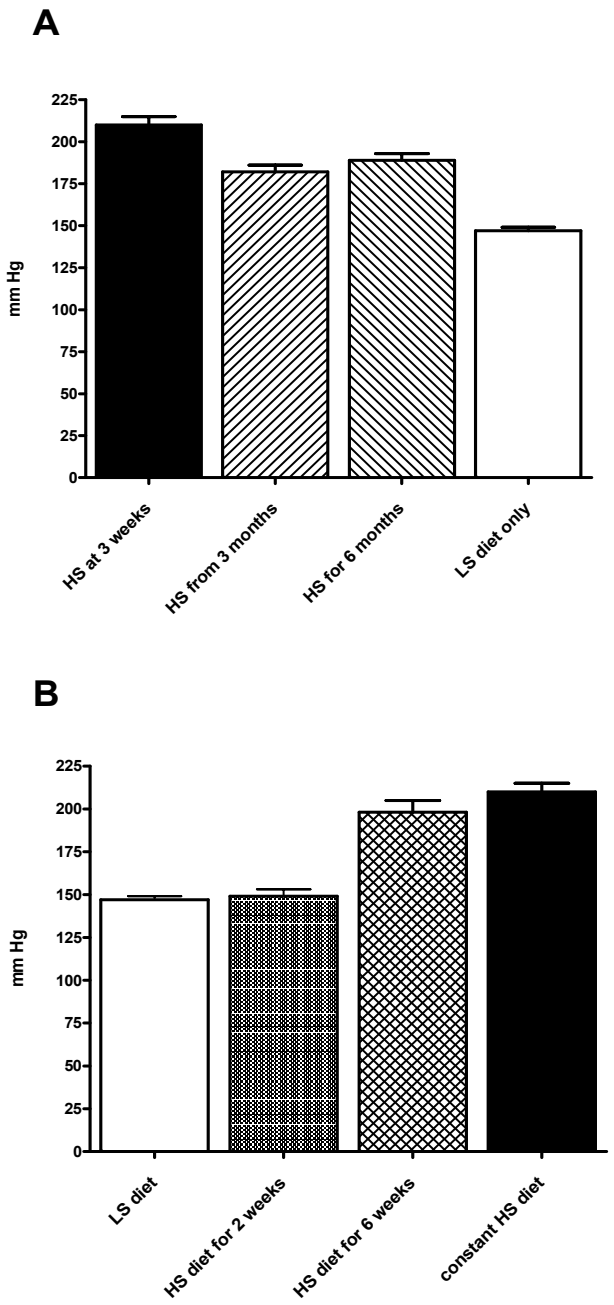

Fig. 1. Blood pressure response of DS rats to high salt intake which started at the age of 3 weeks, 4 or 7 months (**A**), blood pressure response of DS rats to a transient elevation of salt intake in prepuberty (**B**). Data modified from Dahl *et al.* (1968).

The enhanced development of salt hypertension in young (weanling or prepubertal) salt-sensitive Dahl rats was first demonstrated by Dahl *et al.* (1968) and this finding has been later confirmed by many authors (Iwai *et al.* 1977, Zicha *et al*. 1987a, Zicha and Duhm 1990, Dobešová *et al.* 1995, 2002, Yoneda *et al.* 2003, Kawarazaki *et al*. 2010). Using DS animals Dahl *et al.* (1968) described the basic differences in the response of young and adult rats to 8 % NaCl diet in terms of BP rise, survival rate, end-organ damage etc. They have also shown that high salt intake applied for 6 weeks (but not for 2 weeks) after weaning was capable to induce life-long self-sustaining severe hypertension in DS rats (Fig. 1).

Iwai *et al.* (1977) studied the long-term effects of chronic administration of thiazide diuretics in DS and DR rats. If chlorothiazide was added to a low-salt diet consumed from the age of 6 weeks, no major BP effects occurred in either rat strain. This early diuretic treatment had also no effect on moderate BP response of adult DS animals to high salt intake which started after the withdrawal of diuretics at the age of 31 weeks (Fig. 2A). If young 6-week-old DS rats were fed a high-salt diet containing chlorothiazide, their blood pressure rose initially to the same level as that of DS rats untreated with diuretics. Thereafter, blood pressure of chlorothiazide-treated DS rats dropped again to normotensive values (Fig. 2B). When chlorothiazide was omitted from high-salt diet at the age of 31 weeks, thiazide-pretreated DS rats developed a moderate salt hypertension characteristic for adult DS animals (Iwai *et al.* 1977). Thus, the early diuretic treatment of adolescent animals had no protective effects against the development of salt hypertension in adult animals (Fig. 2). The occurrence of early BP response to high salt intake in DS rats treated with diuretics might be related to the fact that thiazide diuretics do not affect sympathetic nerve activity in salt-loaded DS rats (Sasaki and Bunag 1983). Indeed, the guanethidine-induced sympathectomy prevented better the early than the late phase of salt hypertension (Křeček *et al.* 1987). This is in line with our observation that the early phase of salt hypertension depended solely on high salt intake, whereas the late phase was related to renal damage (Dlouhá *et al.* 1979, Zicha *et al.* 1982).

The most interesting data on early pharmacological interventions in salt-sensitive Dahl rats were obtained by Japanese authors. Nakaya *et al.* (2002) reported that chronic blockade of angiotensin type 1 (AT_1) receptors by candesartan at the age of 3-10 weeks prevented BP rise in salt-sensitive Dahl rats fed a high-salt diet and blood pressure remained normotensive for

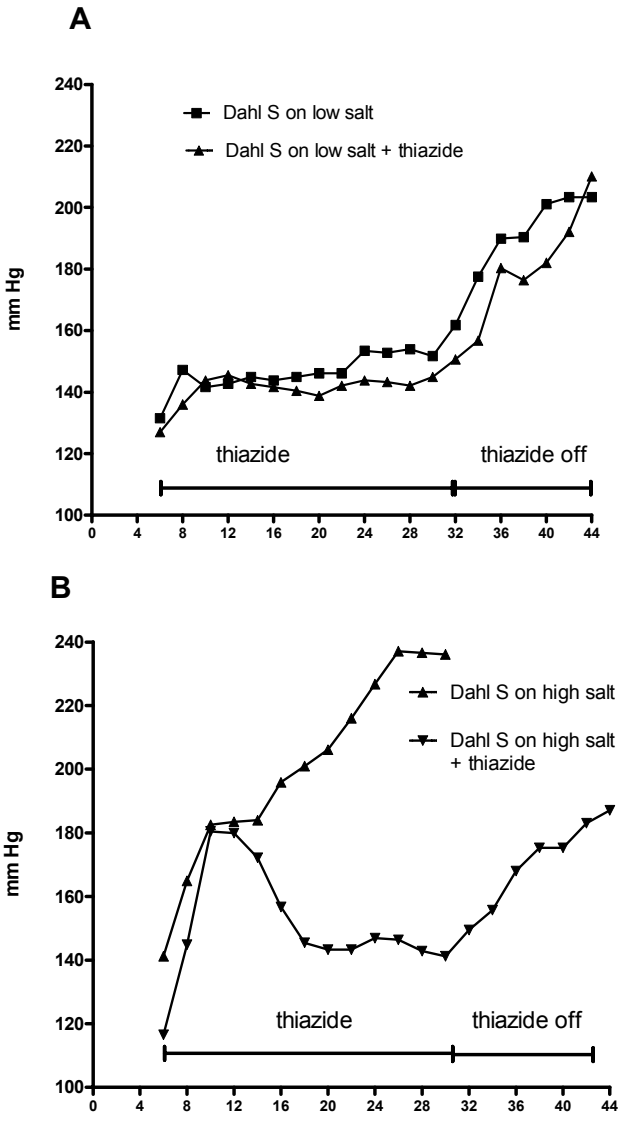

Fig. 2. Blood pressure response of young DS rats to a low-salt diet with or without thiazide diuretics (**A**), to a high-salt diet with or without thiazide diuretics (**B**). Data modified from Iwai *et al.* (1977).

additional 6 weeks when candesartan treatment was withdrawn. Similar results were obtained in olmesartan-treated DIS rats (Dejima *et al.* 2011). They ascribed these beneficial effects of transient blockade of AT_1 receptors by olmesartan to the enhanced expression of ATRAP (AT_1 receptor-associated protein), which promotes AT_1 receptor internalization and attenuates AT_1 receptor-mediated pathological processes. Finally, prepubertal blockade of mineralocorticoid receptors (MR) by eplerenone attenuated salt hypertension development in DIS rats and these BP effects persisted after drug withdrawal (Kawarazaki *et al.* 2010).

There is a fascinating story about the research whether the early interventions in Dahl rats during gestation and lactation periods can modify later development of blood pressure and/or salt hypertension. At the beginning of this effort there are two excellent studies by Dene and Rapp (1985a,b) who studied the impact of embryo transfer between SS/Jr and SR/Jr mothers, cross-fostering of newborns between SS/Jr and SR/Jr dams, litter size manipulations as well as the influence of high salt intake of mothers during pregnancy or lactation. In fact, none of these early interventions affected BP rise elicited by feeding the SS/Jr offspring by 8 % NaCl diet since weaning, but we must keep in mind that Dene and Rapp (1985a,b) have used a protocol which always elicited a severe salt hypertension in young SS/Jr rats within four weeks. Although the early interventions had no effects on salt hypertension development, some of them (embryo transfer, litter size manipulation) lowered the mortality of SS/Jr rats exposed to this very high salt intake (Dene and Rapp 1985a,b).

There is a question what would happen if the SS/Jr offspring subjected to the above mentioned early interventions would be exposed to a moderate increase of salt intake after weaning or if the onset of high salt intake would be postponed to the adulthood. Fortunately, two laboratories did such experiments several years later. Both research groups evaluated the impact of either embryo transfer (Kubisch *et al.* 1998) or cross-fostering (Murphy and McCarty 1989) on spontaneous BP development which ultimately led to the occurrence of a moderate hypertension in salt-sensitive Dahl rats fed a low-salt diet (Kurtz and Morris 1985).

Under the conditions of low salt intake (0.3 % NaCl diet) the embryo transfer between SS/Jr and SR/Jr mothers considerably delayed and attenuated the spontaneous BP increase in those male SS/Jr offspring which were transferred to SR/Jr mothers. It also attenuated salt hypertension development if they were given 0.9 % saline to drink at the age of 11 weeks (Kubisch *et al.* 1998). Hypertension, which developed in SS/Jr rats fed 0.3 % NaCl diet, was almost completely abolished by intracerebroventricular administration of mineralocorticoid receptor antagonist and this antihypertensive effect was fully reversible. The same effects of MR antagonist were also found in the attenuated hypertension of SS/Jr rats subjected to embryo transfer to SR/Jr mothers (Kubisch *et al.* 1998). The attenuation of spontaneous BP elevation was also observed in SS/Jr females transferred as embryos to SR/Jr mothers. In contrast, no BP effect was induced by the transfer of SR/Jr embryos to SS/Jr mothers (Kubisch *et al.* 1998).

Murphy and McCarty (1989) evaluated the impact of cross-fostering on the future BP development under the conditions of normal salt intake (0.7 % NaCl diet). They reported that blood pressure of SS/Jr pups cross-fostered to SR/Jr dams was significantly decreased at the age of 60 and 100 days, although it was still elevated compared to SR/Jr rats. Cross-fostering of SR/Jr pups to SS/Jr dams had no influence on BP development. It should be mentioned that BP development in SS/Jr rats was not influenced by in-fostering to other SS/Jr mothers or cross-fostering to SHR mothers (Murphy *et al.* 1992). Thus hypertensive maternal environment is necessary for the full development of high blood pressure in salt-sensitive Dahl rats.

McCaughran *et al.* (1986a) paid a considerable attention to various ontogenetic aspects of hypertension development in SS/Jr rats. They reported a similar BP level in 25-day-old SS/Jr and SR/Jr pups, but in SS/Jr rats there was a stepwise BP increase in the next 20 weeks of life so that these animals developed a considerable hypertension even if they were fed 0.15 % NaCl diet only. There was a pronounced increase in the density of renal α_2-adrenoceptors in SS/Jr rats between days 25 and 50 of age (McCaughran *et al.* 1986a). The density of renal α_2-adrenoceptors was always higher in SS/Jr rats compared to SR/Jr animals, regardless of the postweaning diet or hypertension development. The only exceptions were the rats born to the mothers which were exposed to high salt intake during gestation. In these animals there was no significant difference in the density of renal α_2-adrenoceptors between SS/Jr and SR/Jr rats (McCaughran and Juno 1986). The density of α_2-adrenergic receptors remained elevated in salt-sensitive Dahl rats throughout their whole life and was further increased by high salt intake (Pettinger *et al.* 1982a,b). On the contrary, the density of renal α_1-adrenoceptors was similar in all age groups of Dahl rats of either genotype (McCaughran *et al.* 1986a). Not only α_2-adrenoceptors but also β-adrenoceptors were increased in the kidneys of SS/Jr rats aged 60 days which were studied under the conditions of high salt intake. The increased density of these adrenergic receptors was not affected by verapamil-induced attenuation of salt hypertension development (McCaughran and Juno 1988). Further studies (McCaughran *et al.* 1986b, McCaughran and Juno 1986) confirmed that high salt intake of dams during gestation did not influence the postnatal BP development in SS/Jr rats under the conditions of either low or high salt intake (0.4 % and 8 % NaCl diet, respectively). Nevertheless, if SS/Jr rats were weaned to a 2 % NaCl diet, a considerable late augmentation of salt hypertension development appeared in the rats whose mothers were exposed to high-salt diet during the pregnancy (McCaughran *et al.* 1986c).

Plasma renin activity (PRA) was also not affected by increased salt intake during gestation, but it became considerably suppressed by high salt intake after day 15 of postnatal age (Wilson *et al.* 1986). It means that the effect of high salt intake on PRA appears only in the weaning period when the rat pups start to consume solid food (Babický *et al.* 1973). Finally, high salt intake of rat mothers during lactation (2 % NaCl diet) retarded body growth of both SS/Jr and SR/Jr rats (Hua *et al.* 1990). At the age of 3 weeks this growth retardation was accompanied by a significant BP reduction in pups of both genotypes. However, renal blood flow (RBF), glomerular filtration rate (GFR) and fractional sodium excretion (FE_{Na}) were decreased in immature SS/Jr rats only. At the age of 8-9 weeks blood pressure was already elevated in salt-loaded mature SS/Jr rats in which RBF and GFR were still reduced. The acute volume expansion, which increased RBF, GFR and FE_{Na} in mature rats, failed to induce such changes in immature Dahl rats, namely in SS/Jr ones (Hua *et al.* 1990). The failure of immature Dahl rats to respond to volume expansion by renal vasodilatation, GRF increase and adequate natriuresis corresponds to the fundamental difference in the renal response of young and adult rats to volume expansion (Bengele and Solomon 1974, Misanko *et al.* 1979).

This chapter on the ontogenetic aspects of salt hypertension illustrates which difficulties can be encountered in the experiments designed to reveal the consequences of early interventions on later BP development. The careful choice of hypertensive stimuli of appropriate strength, which are applied in the adequate age period, might facilitate the demonstration of late effects of early interventions in critical developmental periods.

The effects of potassium or calcium intake on salt hypertension development

It is well known that dietary potassium supplementation prevents or considerably attenuates the development of salt hypertension (Meneely *et al.* 1957, Dahl *et al.* 1972, Manger *et al.* 2003). On the contrary, potassium deficiency exaggerated salt hypertension,

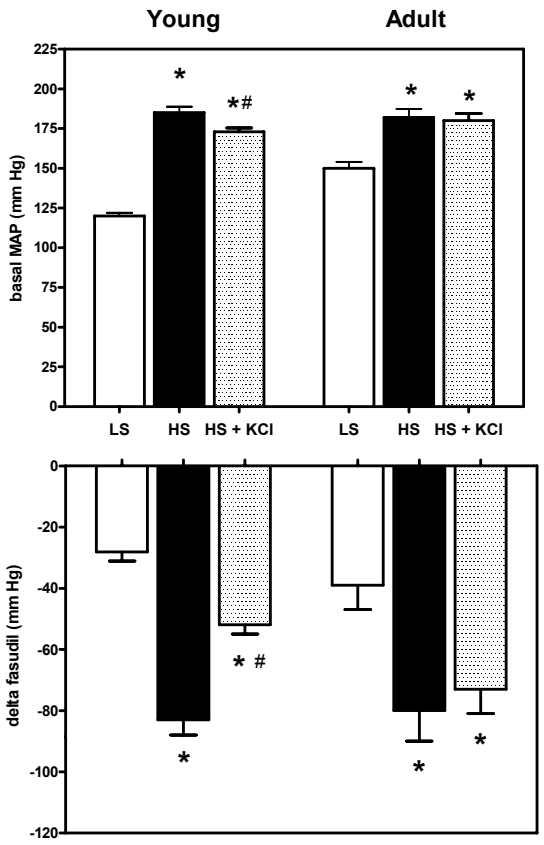

Fig. 3. The age-dependent effects of preventive dietary potassium supplementation in young and adult SS/Jr female rats on basal MAP values (top panels) and on MAP response to acute cumulative administration of fasudil (11 mg/kg b.w.) (bottom panels). Young rats were fed either low-salt diet (LS, 0.3 % NaCl), high-salt diet (HS, 5 % NaCl) or potassium-supplemented high-salt diet (HS+KCl, 5 % NaCl plus 3 % KCl) for 4 weeks from the age of 4 weeks, whereas the adult animals were fed the same diets for 9 weeks from the age of 20 weeks. Data are means ± S.E.M. Significantly different ($p<0.05$) from: * age-matched LS animals, # age-matched HS animals.

sympathetic vasoconstriction and renal damage in SS/Jr rats (Wu *et al.* 1996, 1998). Surprisingly, no major BP reduction was achieved by therapeutic dietary potassium supplementation in SS/Jr rats with established hypertension (Zicha *et al.* 2011).

The modification of potassium intake is a characteristic example of a dietary intervention which has typical age-dependent consequences because the preventive antihypertensive effects of high potassium intake can be observed only in young but not in adult SS/Jr rats (Zicha *et al.* 2011). Potassium supplementation had no beneficial BP effects in adult animals even in the case that a pronounced salt hypertension was elicited in adult SS/Jr rats by the prolonged exposure to high salt intake (Fig. 3). To our knowledge, the reason for such a fundamental age difference is not known.

The exact mechanisms of beneficial action of high potassium intake are still not fully understood. Although enhanced sympathetic activity is responsible for salt hypertension in Dahl rats (Takeshita and Mark 1978, Friedman *et al.* 1979, Huang and Leenen 1994, Zicha *et al.* 2001b), surprisingly little attention was paid to the influence of increased potassium intake on the activity of this important vasoconstrictor system in Dahl rats (Goto *et al.* 1981). Our recent study (Zicha *et al.* 2011) clearly demonstrated that the attenuation of sympathetic vasoconstriction was responsible for BP reduction induced by preventive dietary potassium supplementation in salt-loaded SS/Jr rats. Diminished sympathetic BP component in potassium-supplemented rats was accompanied by decreased BP response to acute nifedipine administration, suggesting the decisive role of norepinephrine-induced L-VDCC opening for the development and/or maintenance of high blood pressure in Dahl rats (Zicha *et al.* 2011).

On the contrary, several investigators proposed that dietary potassium supplementation improved endothelial dysfunction in salt hypertensive Dahl rats (Raij *et al.* 1988, Sudhir *et al.* 1993, Zhou *et al.* 1999a, Zhou *et al.* 2000). Decreased NO bioavailability might be a consequence of enhanced superoxide formation in hypertensive animals (Swei *et al.* 1997, Zicha *et al.* 2001b, Bayorh *et al.* 2004). One of the superoxide sources is NADPH oxidase which had an increased activity and/or expression in salt hypertensive Dahl rats and was lowered by dietary potassium supplementation (Fujii *et al.* 2003, Matsui *et al.* 2006, Kido *et al.* 2008). Nevertheless, our data do not support the above assumption because we did not observe any improvement of NO-dependent vasodilatation in young SS/Jr rats fed a 5 % NaCl diet supplemented with 3 % KCl. Moreover, vasodilatation mediated by PGI_2 or BK_{Ca} channels was also not enhanced by potassium supplementation in young salt-loaded SS/Jr rats (Zicha *et al.* 2011).

Dietary calcium intake is another example of age-dependent intervention because the increased calcium intake exerted just the opposite influence on salt hypertension development if it was applied to young or adult Dahl rats (Kuneš *et al.* 1988). High calcium intake from weaning attenuated the development of salt hypertension in young SS/Jr rats, whereas the same high-calcium diet enhanced salt hypertension development in adult animals. In contrast, increased calcium intake had no effects on blood pressure of SR/Jr rats of either age (Kuneš *et al.* 1988). The attenuation of hypertension

development by high calcium intake was observed not only in young salt-sensitive Dahl rats (Peuler *et al.* 1987) but also in immature SHR (Ayachi 1979, McCarron *et al.* 1981, Hatton *et al.* 1988). Multiple cellular and humoral mechanisms (calcium regulating hormones, calcitonin gene-related peptide, atrial natriuretic factor as well as RAS and SNS) were proposed to explain BP-lowering effects of supplemental dietary calcium (for review see Hatton and McCarron 1994). One of the interesting mechanisms, which was suggested to mediate these effects of dietary calcium on blood pressure, is based upon putative parathyroid hypertensive factor (PHF), the secretion of which was reduced by increased calcium intake and increased by calcium restriction (Lewanczuk *et al*. 1990).

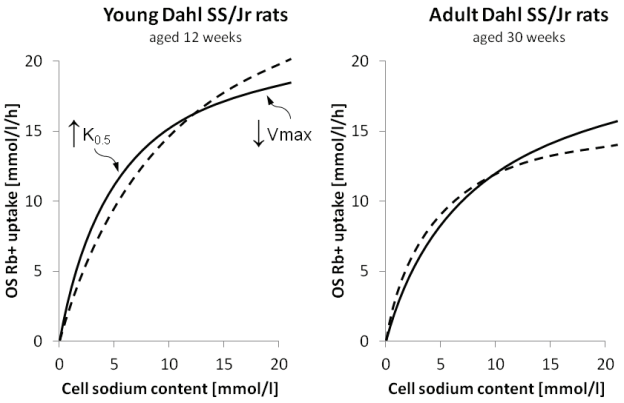

Fig. 4. Kinetic alterations of ouabain-sensitive Rb^+ uptake mediated by the Na,K-pump in erythrocytes of young and old SS/Jr male rats fed either low-salt diet (LS, 0.06 % NaCl, broken lines) or high-salt diet (HS, 8 % NaCl, full lines) for 7 weeks from the ages of 5 weeks and 23 weeks, respectively (data modified from Zicha and Duhm 1990). V_{max} – maximal transport rate, $K_{0.5}$ – internal sodium concentration at half-maximal velocity of the Na,K-pump.

Red blood cell ion transport – altered Na,K-pump activity

Our initial studies in Dahl rats were focused on ion transport, namely on the function of Na,K-pump (Zicha *et al.* 1987a) because we have reported a greater importance of circulating digoxin-like factor (DLF) in young than in adult DOCA-salt hypertensive rats (Zicha *et al.* 1984, Kuneš *et al.* 1985, Zicha *et al.* 1985). We therefore proposed a major role of DLF in the enhanced BP response of young animals to high salt intake (Zicha *et al.* 1986). To our surprise, Na,K-ATPase activity was suppressed in the heart and kidneys of young salt hypertensive SS/Jr rats but ouabain-sensitive (OS) Rb^+ (K^+) uptake (mediated by the Na,K-pump) was increased in erythrocytes of these animals (Zicha *et al.* 1987a). The latter finding was in a good agreement with the report of Overbeck *et al.* (1981) who found increased Na,K-pump activity in arteries of salt hypertensive SS/Jr rats. Our later studies carried out in Munich (Zicha and Duhm 1990) revealed different alterations in the transport kinetics of the Na,K-pump in erythrocytes of young and old SS/Jr rats. Figure 4 shows that chronic high salt intake increased the affinity of the Na,K-pump to internal Na^+ content (Na^+_i), but decreased the maximal velocity of OS Rb^+ uptake in erythrocytes of young animals, whereas the opposite changes were seen in erythrocytes of old rats (Zicha and Duhm 1990). Thus the measurement of ion transport in intact erythrocytes, which is carried out at 5-10 mmol Na^+_i/l, disclosed the acceleration of OS Rb^+ uptake, reflecting the increased affinity of the Na,K-pump to Na^+_i which was elevated due to enhanced passive Na^+ entry into the red blood cells of young salt hypertensive rats. The same was probably true for OS Rb^+ uptake measured in non-homogenized arteries of Dahl rats (Overbeck *et al.* 1981). On the contrary, Na,K-ATPase activity is determined in tissue homogenates at high saturating NaCl concentrations (100 mmol/l) in the incubation media so that this measurement reflects the maximal velocity rather than the actual activity of this enzyme. This might explain why Zicha *et al.* (1987a) observed the attenuation of renal Na,K-ATPase activity in young salt hypertensive SS/Jr rats, whereas the activity of this enzyme was reduced in adult animals. Thus the changes in renal Na,K-ATPase activity induced by high salt intake in young and adult SS/Jr rats (Zicha *et al.* 1987a) corresponded to the changes in the maximal velocity of the Na,K-pump in erythrocytes of these two age groups (Zicha and Duhm 1990). Enhanced passive Na^+ entry and increased Na,K-pump activity in erythrocytes of young salt hypertensive animals are also in line with the findings of Vasdev *et al.* (1988, 1990a, 1990b) who reported the increase of both amiloride-sensitive Na^+ uptake and ouabain-sensitive Rb^+ uptake in aortas of young salt hypertensive Dahl rats. It is also interesting to mention that McCormick *et al.* (1989) reported elevated plasma levels of ouabain-like compound and increased red blood cell Na^+ content but unchanged OS Rb^+ uptake in the erythrocytes of 5-week-old DS rats which were fed a low-salt diet. In their experiments erythrocyte Na^+_i correlated with both blood pressure and Na,K-pump activity in erythrocytes of these immature Dahl rats.

We have further tried to elucidate the role of the tentative mutation in α1 subunit of the Na,K-pump which was reported in salt-sensitive Dahl rats by Herrera and Ruiz-Opazo (1990) or Herrera *et al.* (1998). Unfortunately, our experiments failed to disclose any significant relationship of *Atp1a1* locus to either blood pressure or red blood cell OS Na^+ and Rb^+ (K^+) transport in F_2 hybrids of SS/Jr x SR/Jr rats (Zicha *et al.* 2001a). This negative findings was confirmed by many other investigators (for overview see Mokry and Cuppen 2008). However, functional abnormalities of the Na,K-pump in erythrocytes of SS/Jr rats were closely related to plasma cholesterol levels (Zicha *et al*. 2001a) which are elevated in salt hypertensive Dahl rats (Dahl 1960, Zicha *et al.* 2001a,b). It should be noted that blood pressure of Dahl F_2 hybrids correlated not only with plasma cholesterol but also with plasma triglycerides (Zicha *et al.* 2001a, Vokurková *et al.* 2003), but plasma triglycerides had no significant relationship to red blood cell ion transport (Vokurková *et al.* 2003), indicating thus a dissociation between ion transport alterations and metabolic syndrome features described in salt-sensitive Dahl rats (Reaven *et al.* 1991a,b, Kotchen *et al.* 1991a). On the basis of these findings we studied membrane lipid composition in erythrocytes of Dahl rats (Vokurková *et al.* 2005a). Our data indicated that the total cholesterol content of erythrocyte membrane was an important determinant of ion transport mediated by the Na,K-pump, Na,K cotransport and cation leaks, but surprisingly erythrocyte membrane cholesterol did not correlate with blood pressure. Further analysis of membrane phospholipid composition suggested that membrane sphingomyelins as well as phosphatidyl-serines and/or phosphatidylinositols play an important role in the control of red blood cell ion transport (Vokurková *et al.* 2005a). The induced changes in membrane content of cholesterol or phospholipids are known to modify the activity of the Na,K-pump and Na,K-cotransport in human erythrocytes (Claret *et al.* 1978, Engelmann *et al.* 1990a).

In the above studies we have repeatedly observed that the erythrocytes of some salt hypertensive SS/Jr rats were characterized by decreased mean cell hemoglobin content (MCHC), enhanced Na,K-pump activity and augmented Na^+ leak (Zicha and Duhm 1990). This seems to be related to the occurrence of immature cells during chronic anemia described in these animals (Overbeck *et al.* 1981, Luckhaus *et al.* 1982). In our studies MCHC correlated significantly with multiple parameters of erythrocyte ion transport in salt hypertensive SS/Jr rats (Vokurková *et al.* 2005a). Low MCHC is typical for immature human erythrocytes which are also characterized by enhanced Na,K-pump activity and augmented Na^+ leak but decreased Na,K-cotransport activity (Furukawa *et al.* 1981, Engelmann *et al.* 1990b). We have therefore studied the erythrocytes of Wistar rats subjected to repeated hemorrhage (Vokurková *et al.* 2005b). The erythrocytes were divided by repeated centrifugation into immature (light, 34 % reticulocytes) and mature cells (dense, 7 % reticulocytes). These immature red blood cells exhibited lower MCHC, elevated activity of the Na,K-pump, reduced activity of the Na,K-cotransport and increased cation leak as well as higher concentrations of total cholesterol and total phosholipids in their cell membrane (Vokurková *et al.* 2005b).

Thus, ion transport abnormalities could be related more closely to the immaturity of the cells rather than to hypertension, reflecting a well-known faster proliferation of various cell types (vascular smooth muscle cells, fibroblasts, blood cells etc) in SHR (Sen *et al.* 1972, Hadrava *et al*. 1989, Marche *et al.* 1995, Bačáková and Kuneš 2000). It would be desirable to consider ion transport alterations in hypertension always in terms of their dependence on the age of animals and/or the maturity of their cells (for review see Zicha and Kuneš 1999b).

Endogenous Na,K-pump inhibitors

There are several endogenous inhibitors of the Na,K-pump – brain and adrenal ouabain-like compound(s) (OLC) and tissue marinobufagenin which differ by their specificity to α3 and α1 Na,K-ATPase isoforms. Gomez-Sanchez *et al.* (1994) were the first who demonstrated a possible pathogenetic role of OLC in Dahl rats because they attenuated salt-hypertension development by immunization of SS/Jr rats against ouabain. In parallel, Leenen *et al.* (1994) demonstrated that high salt intake increased both plasma and central nervous OLC levels to a greater extent in salt-sensitive than salt-resistant Dahl rats. Brain OLC, which is involved in the central nervous pathways responsible for sympathoexcitation, plays an important role in various salt-dependent forms of experimental hypertension (for review see van Huysse 2007 and Leenen 2010). OLC is released following mineralocorticoid receptor activation and opening of epithelial Na^+ channels. This compound

lowers membrane potential by inhibiting Na,K-pump, augmenting thus the activity of angiotensinergic sympathoexcitatory pathway which is primarily stimulated by increased cerebrospinal Na^+ concentration (Leenen 2010). Adrenal OLC was also proposed to participate in the pathogenesis of DOCA-salt or ACTH-induced hypertension (for review see Blaustein and Hamlyn 2010).

Marinobufagenin (MBG), which can be isolated not only from toad skin but also from rat adrenals or pituitary tissue, is a preferential inhibitor of the α1 isoform of Na,K-pump which is located on the basolateral membrane of renal tubules. In a series of consecutive papers Bagrov and Fedorova have demonstrated that both OLC and MBG can be detected in salt-sensitive and salt-resistant Dahl rats. Tissue and plasma levels as well as urinary excretion of both compounds are elevated following acute salt loading, but MBG increase is long-lasting in contrast with a short-term OLC rise (Fedorova *et al.* 2000). Chronic increase of salt intake caused a major elevation of urinary MBG excretion in SS/Jr but not in SR/Jr rats, whereas OLC excretion was not changed in either rat strain (Fedorova *et al.* 2001). A detailed follow-up of urinary excretion of these two Na,K-pump inhibitors in young SS/Jr rats subjected to high salt intake revealed that there was a progressive increase of MBG excretion throughout salt hypertension development, while only a transient increase of OLC excretion can be seen in the first week of high-salt diet feeding (Fedorova *et al.* 2002). One of the most interesting findings was that brain OLC stimulated adrenocortical MBG levels through angiotensin type 1 receptor pathway (Fedorova *et al.* 2005). Furthermore, not only the rise of brain OLC in salt-loaded animals but also intrahippocampal administration of low ouabain doses stimulated adrenocortical levels and urinary excretion of MBG (Fedorova *et al.* 2007). Finally, Bagrov *et al.* (2009) have shown that acute salt loading elicited a smaller increase of OLC excretion but a greater increase of MBG excretion in SS/Jr rats compared to Sprague Dawley animals. This was accompanied by a smaller inhibition of Na,K-pump in the renal medulla but a greater one in the aorta of SS/Jr rats.

Despite three decades of intensive research the exact role of endogenous Na,K-pump inhibitors in salt hypertension is still not fully understood, namely their action on the vasculature and peripheral SNS (for details see Blaustein *et al.* 2012).

Abnormal lipid metabolism and cell membrane function

Abnormalities of lipid metabolism have a crucial importance for functional and structural alterations of cell membrane in both dyslipidemia and/or hypertension (for review see Zicha *et al.* 1999a). During our long-term cooperation with Marie-Aude Devynck we have studied membrane microviscosity as well as the regulation of cytosolic calcium and pH in platelets and erythrocytes of rats with various forms of experimental hypertension including Prague hypertriglyceridemic rats (Zicha *et al.* 1996a, Kuneš *et al.* 1997, Devynck *et al.* 1998, Kuneš *et al.* 2000, Pernollet *et al.* 2001), Lyon hypertensive rats (Le Quan Sang *et al.* 1994a, Zicha *et al.* 1995), Sabra hypertension-prone rats (Pernollet *et al.* 1994, Le Quan Sang *et al.* 1994b, Zicha *et al.* 1996b) and Dahl salt-sensitive rats (Zicha *et al.* 1997, 1999b).

The microviscosity of membrane lipid core, which is reflected by steady-state diphenylhexatriene (DPH) fluorescence anisotropy, was increasing with age in platelets of SS/Jr rats fed a low-salt diet. The changes of membrane microviscosity did not precede BP rise because DPH anisotropy in platelets of SS/Jr (but not SR/Jr) rats was substantially increased after 10 weeks (but not after 5 weeks) of high salt intake (Zicha *et al.* 1999b). Platelet DPH anisotropy was positively related to both blood pressure and plasma triglycerides, whereas it had an inverse relation to cytosolic pH which was significantly decreased in platelets of salt hypertensive SS/Jr rats (Zicha *et al.* 1997, 1999b). Surprisingly, DPH fluorescence anisotropy was significantly decreased in erythrocytes of salt-sensitive (SS/Jr) rats compared to SR/Jr animals, but there was no significant influence of high salt intake or hypertension on this membrane parameter (Kuneš *et al.* 1994, Zicha *et al.* 1999b). Unfortunately, we do not have any data about the influence of red blood cell maturity on the microviscosity of their cell membranes.

In contrast to SHR, cytosolic calcium level ($[Ca^{2+}]_i$) was not elevated in platelets of salt hypertensive SS/Jr rats fed 4 % NaCl diet (Zicha *et al.* 1996c, 1997). The absence of $[Ca^{2+}]_i$ elevation was earlier reported in platelets of DOCA-salt hypertensive rats (Murakawa *et al.* 1986, Baba *et al.* 1987, Ishida *et al.* 1994) or salt hypertensive DIS rats (Ishida *et al.* 1995, Otsuka *et al.* 1997). Although platelet $[Ca^{2+}]_i$ was not significantly altered in Dahl rats, its value correlated positively with systolic BP but not with diastolic BP. The correlation of

$[Ca^{2+}]_i$ with pulse pressure was especially strong. Similar relationships were also disclosed in platelets of Sabra or Lyon rats (Zicha *et al.* 1996c). Interestingly, in salt-sensitive rats high salt intake was associated with a decreased rate of thrombin-induced Ca^{2+} entry (Ishida *et al.* 1995) or Mn^{2+} entry through receptor-operated Ca^{2+} channels into the platelets of Sabra or Dahl rats (Zicha *et al.* 1996c) and this attenuation was independent of basal BP level. Thus, salt hypertensive Dahl rats or Sabra hypertension-prone rats differed substantially from genetically hypertensive Lyon rats in which Mn^{2+} entry was accelerated (Zicha *et al.* 1996c). A decrease in thrombin-induced Ca^{2+} entry into the platelets of salt hypertensive Dahl rats was confirmed by Li *et al.* (2001) who also demonstrated increased intracellular Ca^{2+} stores and enhanced SERCA-dependent Ca^{2+} uptake in platelets of these animals. It should also be noted that we did not find any significant relationship between plasma lipids and platelet Ca^{2+} handling in Dahl rats (Zicha *et al.* 1997).

Insulin resistance, inflammation and organ damage

Distinct features of metabolic syndrome (such as insulin resistance, hyperinsulinemia, hypertriglyceridemia or abdominal obesity) can be disclosed in salt-sensitive Dahl rats and these symptoms are exacerbated by high salt intake (Reaven *et al.* 1991a). Decreased glucose uptake and utilization were reported in salt hypertensive Dahl rats both at the whole-body level and in particular tissues such as adipocytes or skeletal muscle (Ogihara *et al.* 2002). Despite the insulin resistance of these rats, the early steps of insulin signaling are augmented. Since tyrosine phosphorylation of the insulin receptor and insulin receptor substrates, the activation of phosphatidylinositol 3-kinase (PI3K) and phosphorylation of Akt (protein kinase B) were enhanced in salt-sensitive Dahl rats fed a high-salt diet, the defect of insulin signaling, which is responsible for insulin resistance in these rats, must be located downstream of PI3K and Akt activation (Ogihara *et al.* 2002). Indeed, the number of insulin receptors, their affinity and binding parameters as well as their mRNA levels or tissue distribution in liver, muscle or kidney were similar in SS/Jr and SR/Jr rats (Sechi *et al.* 1997). It could be supposed that chronic administration of PPARγ agonists as insulin sensitizers would attenuate salt hypertension development or at least mitigate its progression. Nevertheless, both preventive (Sartori-Valinotti *et al.* 2010) or therapeutic (Bolten *et al.* 2007) effects of rosiglitazone treatment on blood pressure were relatively weak and they were not directly related to metabolic action of PPARγ activators (Bolten *et al.* 2007). Surprisingly, insulin sensitivity of SS/Jr rats was improved more effectively by ACE inhibitor quinapril rather than by AT_1 receptor blocker losartan, indicating a substantial role of endogenous kinins (Nakagawa *et al.* 1999).

Recently, Leopoldo Raij and his colleagues documented the link between metabolic and cardiovascular alterations in salt hypertension which involves vascular inflammation. It seems that angiotensin II-induced superoxide overproduction interferes not only with insulin signaling pathways leading to a decreased production of nitric oxide (NO) in metabolic and cardiovascular tissues (Zhou *et al.* 2009), but it also activates nuclear factor κB (NF-κB) pathway leading to a low-grade inflammation of renal vessels (Zhou *et al.* 2010). NF-κB activation in salt hypertensive Dahl rats can be blocked by chronic treatment with either tempol (superoxide dismutase mimetic) or candesartan (AT_1 receptor blocker) (Zhou *et al.* 2010). Both treatments attenuated salt hypertension development and improved insulin sensitivity in these rats (Zhou *et al.* 2009).

Renal inflammation accompanied by increased formation of reactive oxygen species (ROS), NF-κB activation and tumor necrosis factor-α (TNF-α) upregulation has been repeatedly reported in salt hypertensive Dahl rats (Gu *et al.* 2006, Chandramohan *et al.* 2008). Chronic administration of interferon γ, a potent immunomodulator, ameliorated renal injury in salt hypertensive DIS rats (Ishimitsu *et al.* 1992). Preventive administration of interleukin-2, which stimulates the proliferation and maturation of thymus-derived lymphocytes, also attenuated salt hypertension development, reduced cardiac hypertrophy and improved glomerular filtration rate in DIS rats (Ishimitsu *et al.* 1994). Immunosuppressive therapy attenuated the progression of malignant arteritis in the kidneys of salt hypertensive DIS rats (Uehara *et al.* 1997). Chronic anti-immune therapy with mycophenolate mofetil (Tian *et al.* 2007a), chronic antioxidant administration (Tian *et al.* 2007b) or chronic fish oil supplementation (Diaz Encarnacion *et al.* 2008) reduced ROS formation, decreased NF-κB activation, ameliorated renal inflammatory injury and lowered blood pressure in salt hypertensive Dahl rats. Vascular inflammation and

altered function of regulatory T lymphocytes in blood vessels of salt-sensitive Dahl rats were also reported by Viel *et al.* (2010).

The process of glomerular injury and renal fibrosis is associated with an increased expression of transforming growth factor-β (TGF-β). Renal levels of TGF-β mRNA were markedly elevated in salt hypertensive Dahl rats (Tamaki *et al.* 1996) and this elevation could be reduced by chronic AT_1 receptor blockade (Otsuka *et al.* 1998, Dejima *et al.* 2010), statin treatment (Zhou *et al.* 2008a) or eplerenone administration (Onozato *et al.* 2007). Dahly *et al.* (2002) demonstrated that chronic administration of antibody against TGF-β reduced blood pressure, proteinuria and renal injury in SS/Jr rats fed a high-salt diet. Ying and Sanders (2003) reported that the aortic production of TGF-β_1 and NO correlated linearly in both SS/Jr and SR/Jr, but TGF-β_1 production was always considerably higher in SS/Jr rats at any level of NO production. High salt intake augmented TGF-β_1 production in SS/Jr rats only. It seems that the inhibitory effect of NO on TGF-β_1 production was reduced in SS/Jr animals. Thus, the augmented vascular and glomerular production of TGF-β_1 and the diminished NO formation might contribute to the development of hypertensive nephrosclerosis (Ying and Sanders 2003). Indeed, gene silencing of TGF-β_1 promoter lowered not only TGF-β_1 expression but also proteinuria and glomerulosclerosis in salt hypertensive Dahl rats, suggesting a new approach for the treatment of progressive renal disease (Matsuda *et al.* 2006, 2011). Similar beneficial effects on hypertensive glomerulosclerosis was achieved by the reduction of TGF-β_1 mRNA expression (Tahira *et al.* 2007).

The suppression of TGF-β expression by chronic administration of statins could explain their influence on blood pressure and proteinuria in salt hypertensive Dahl rats (Wilson *et al.* 1998, Zhou *et al.* 2004, Kido *et al.* 2005). Statin treatment lowered ROS production, prevented the downregulation of endothelial NO synthase (eNOS), increased NO bioavailability, improved NO-dependent endothelial relaxation and reduced renal damage in salt hypertensive Dahl animals (Zhou *et al.* 2008a, for review see Schulman *et al.* 2006). It should be mentioned that atorvastatin exerted these beneficial effects in both preventive and therapeutic experiments (Zhou *et al.* 2004). Statin-induced inhibition of Rho kinase pathway helps to explain the increase of endothelial NOS-mediated NO production (Rikitake and Liao 2005).

It has been demonstrated that not only TGF-β_1 but also proinflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) and lectin-like oxidized LDL receptor-1 (LOX-1) play an important role in hypertensive nephropathy (Nagase *et al.* 2000, Chiba *et al.* 2002, Dahly *et al.* 2002, Ueno *et al.* 2003). Zhou *et al.* (2006) observed increased ROS production, impaired endothelium-dependent vasodilatation and enhanced expression of LOX-1 and MCP-1 in salt hypertensive Dahl rats and these changes could be abolished by the inactivation of NADPH oxidase (the inhibition of the assembly of $p47^{phox}$ subunit with $gp91^{phox}$), although this intervention had no significant effects on blood pressure. Furthermore, Zhou *et al.* (2008a) reported that chronic atorvastatin treatment attenuated proteinuria and glomerulosclerosis, normalized oxidative stress, TGF-β_1, LOX-1 and MCP-1 expression as well as restored eNOS activity, but it had only modest BP lowering effects. On the contrary, the administration of thiazide diuretics effectively reduced blood pressure and proteinuria, but it did not affect oxidative stress, LOX-1 and MCP-1 expression or endothelial dysfunction (Zhou *et al.* 2008b). Chronic administration of low doses of eplerenone reduced proteinuria and glomerulosclerosis as well as the expression of LOX-1-mediated adhesion molecules, inhibited PKCε-MAPK-p90RSK pathway and improved endothelial dysfunction but again without BP reduction (Kobayashi *et al.* 2005). The inhibition of p38MAPK had also no effect on high blood pressure of salt hypertensive DIS rats, but it suppressed renal NADPH oxidase expression and superoxide formation, increased eNOS and iNOS expression in the kidney, enhanced NO bioavailability and attenuated renal TNF-α and interleukin-1β production, leading thus to the amelioration of renal damage (Tojo *et al.* 2005). These data suggest that the complex activation of TGF-β_1, LOX-1, adhesion molecules, protein kinase Cε (PKCε), mitogen-activated protein kinase (MAPK) and Rho kinase pathways in salt hypertensive Dahl rats is involved in pathogenetic processes leading to organ damage rather than in the mechanisms directly regulating blood pressure. Further evidence for this assumption was brought by Hiroaki Matsuoka and his colleagues who studied cardiac dysfunction and/or heart failure in salt hypertensive DIS rats. The blockade of particular steps of the above mentioned cascade by subdepressor doses of β-blocker betaxolol (Kobayashi *et al.* 2004), Rho kinase inhibitor Y-27632 (Mita *et al.* 2005), mineralocorticoid receptor inhibitor eplerenone (Kobayashi *et al.* 2006a), ACE inhibitor quinapril or NADPH oxidase inhibitor apocynin (Kobayashi *et al.* 2006b) exerted major

cardioprotective effects without significant BP reduction.

On the basis of the sophisticated experimental data (Shibata *et al.* 2008) an alternative pathway for the activation of mineralocorticoid receptors (MR) was proposed by Fujita (2010). Rac1, a small GTP-binding protein, which is a member of the Rho family of GTPases, is involved in numerous biological processes, including cytoskeletal organization, cell migration or NADPH oxidase activation. High salt intake activates renal Rac1 in salt-sensitive animals and Rac1 induces MR activation. Hyperglycemia as a part of metabolic syndrome activates MR through Rac1 activation. It is evident that not only MR inhibition by eplerenone but also Rac1 inhibition attenuates proteinuria and renal injury. Thus the abnormal activation of the aldosterone/MR pathway plays a key role in the development of salt-sensitive hypertension and renal injury in metabolic syndrome (Fujita 2010). This seems to be pertinent even for salt hypertension of Dahl rats.

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD 1) is one of the factors important for the regulation of insulin sensitivity in salt hypertensive animals (Usukura *et al.* 2009). High salt intake increased significantly corticosterone concentration, 11β-HSD 1 expression and activity as well as the expression of glucocorticoid receptors and TNF-α in adipose tissue of DIS compared to DIR rats. These changes of glucocorticoid receptors and 11β-HSD 1 activity in adipose tissue contribute to the decreased insulin sensitivity in salt hypertensive Dahl rats (Usukura *et al.* 2009). The knockdown of renal medullary 11β-HSD 1 with small-interfering RNA attenuated the early phase of salt hypertension in SS/Jr rats (Liu *et al.* 2008).

Salt hypertension in Dahl rats is associated with numerous metabolic abnormalities (insulin resistance), vascular inflammation of renal vessels and renal injury (glomerulosclerosis, fibrosis). The underlying complex alterations of intracellular signaling might explain why the above abnormalities can be partly dissociated from BP elevation so that some therapeutic interventions can ameliorate end-organ damage without major BP reduction, while the other lower blood pressure without major improvement of renal and cardiac injury.

Sodium and water retention, body fluids, systemic hemodynamics and kidney function

The theory of Arthur C. Guyton (1992) on the regulation of circulatory homeostasis presumes the important involvement of body fluid expansion in the pathogenesis of salt hypertension. Indeed, blood volume expansion has been reported in salt hypertensive Dahl rats (Overbeck *et al.* 1981, Simchon *et al.* 1989), but this is true only for SS/Jr animals exposed to high salt intake from youth but not for those subjected to the same stimulus solely in adulthood (Zicha *et al.* 1987a, Dobešová *et al.* 1995). Salt hypertension induced by feeding of adult SS/Jr rats with 8 % NaCl diet is accompanied even by the reduction of plasma and blood volumes (Dobešová *et al.* 1995). Moreover, we observed that the expansion of blood volume and extracellular fluid volume appears relatively late in the development of salt hypertension, i.e. several weeks after a major BP rise (Dobešová *et al.* 1995). Nevertheless, Simchon *et al.* (1991) reported that blood volume expansion and increased cardiac output preceded the elevation of systemic resistance in the early stages of salt hypertension development in young Dahl rats. This would be in agreement with the importance of increased cardiac output in very young SHR which is followed by a later increase of systemic resistance (Smith and Hutchins 1979, Lundin and Hallbäck-Nordlander 1980, Evenwel *et al.* 1983). However, Ganguli *et al.* (1979) demonstrated the early increase of cardiac output not only in DS but also in DR rats and the rise in systemic resistance was decisive for BP elevation elicited by high salt intake in DS rats. Finally, He *et al.* (1997) observed that L-arginine supplementation of young salt-loaded DIS rats increased cardiac output but lowered their blood pressure due to a decrease in systemic resistance.

In the course of salt hypertension development there is a gradual impairment of autoregulatory control of renal blood flow in SS/Jr rats. RBF autoregulation was abolished if high salt intake started at weaning, whereas the later onset of high-salt diet feeding was associated with a partially preserved autoregulation (Karlsen *et al.* 1997). Since renal morphological changes develop before the loss of dynamic autoregulation, the impaired autoregulation appears to be the result but not the cause of the process leading to renal failure in salt hypertensive Dahl rats (Karlsen *et al.* 1997). The loss of RBF autoregulation in hypertensive animals seems to be due to a compromised myogenic response, whereas there was no evidence of decreased tubuloglerular feedback (TGF) responsiveness in salt hypertensive SS/Jr rats (Karlsen *et al.* 1998). When Wilcox and Welch (1996) compared TGF response in SS/Jr and Sprague Dawley rats, they reported blunted TGF response in SS/Jr rats during low salt intake but not during high salt intake. They ascribed

these findings to a defective regulation of nephron NO release in SS/Jr rats subjected to high salt intake.

The study of renal structural properties in maximally vasodilated perfused kidneys of Dahl rats fed a low-salt diet revealed hypertrophic remodeling of interlobular arteries (without narrowing of preglomerular resistance vessel) as well as a glomerular permeability defect which is responsible for the attenuation of GFR in prehypertensive SS/Jr rats (Tomoda *et al.* 2000). High perfusion pressure accelerates the development of glomerular injury and interstitial fibrosis in the kidneys of SS/Jr rats (Mori *et al.* 2008).

Salt hypertensive Dahl rats are characterized by abnormal pressure-natriuresis (Tobian *et al.* 1978, Roman 1986, Roman and Kaldunski 1991, Patel *et al.* 1993, Hu and Manning 1995) which results from altered intrarenal generation of angiotensin II (Ang II) and 20-hydroxyeicosatetraenoic acid (20-HETE), enhanced ROS formation and low NO bioavailability (for review see Zou and Cowley 1999, Roman 2002). Lower sodium excretion by DS than by DR kidneys at any renal perfusion pressure was attributed to abnormal NaCl transport in particular nephron segments, e.g. increased chloride transport in the thick ascending limb of loop of Henle (TALH) (Kirchner 1990). NO was found to inhibit chloride reabsorption in TALH and this inhibition was attenuated in DS compared to DR rats (Garcia *et al.* 1999), explaining thus the increased NaCl reabsorption in salt-sensitive animals. Furthermore, the impaired renal NO formation facilitates Ang II-induced vasoconstriction in renal medulla (Szentivanyi *et al.* 2002). Under the condition of high salt intake, NO production was reduced in salt-sensitive animals, whereas it was increased in salt-resistant rats (Chen and Sanders 1993, Hu and Manning 1995, Simchon *et al.* 1996). One of the possible explanation for reduced NO formation might be higher levels of circulating endogenous NOS inhibitor – asymmetrical dimethyl-L-arginine – in SS/Jr rats compared to SR/Jr rats fed a high-salt diet (Matsuoka *et al.* 1997). The supplementation of salt-sensitive Dahl rats with L-arginine improved renal hemodynamics, reversed NADPH oxidase upregulation and attenuated the development of salt hypertension (Chen and Sanders 1991, Patel *et al.* 1993, Hu and Manning 1995, He *et al.* 1997, Miyata and Cowley 1999, Mattson and Wu 2000, Fujii *et al.* 2003). Increased renal vascular resistance, impaired renal vasodilatation and attenuated urinary cGMP excretion are characteristic features of young salt-sensitive Dahl rats fed a high-salt diet. This is not only due to their decreased NO production but also due to their hyporesponsiveness to vasodilators such as atrial natriuretic peptide or sodium nitroprusside as it was demonstrated by Simchon *et al.* (1989, 1992, 1996).

A molecular basis for decreased renal guanylate cyclase activity was described by Gupta *et al.* (1997). The importance of impaired cGMP formation for salt hypertension development in Dahl rats was recently confirmed by Geschka *et al.* (2011). They reported that chronic administration of riociguat (BAY 63-2521), which sensitizes soluble guanylate cyclase to endogenous NO and also directly stimulates cGMP production, attenuated salt hypertension development, improved rat survival and their heart function and prevented fibrotic tissue remodeling.

Although no abnormality of sodium or water transport was disclosed in the cortical collecting duct of SS/Jr rats (Hawk and Schafer 1991), the cells of inner medullary collecting duct (IMCD) from SS/Jr rats transported more sodium than IMCD cells from SR/Jr rats (Husted *et al.* 1996). Higher IMCD Na^+ transport in SS/Jr rats was not due to a higher number of Na,K-pump sites but they operated at a higher fraction of their maximum capacity (Husted *et al.* 1997). The main reason for a higher rate of Na^+ transport in IMCD cells of SS/Jr rats was a primary increase in the conductive permeability of the apical membrane for Na^+ (Husted *et al.* 1997) which is mediated by epithelial Na^+ channels (ENaC). Although these channels are not different in SS/Jr and SR/Jr rats (Shehata *et al.* 2007), the regulation of these channels by aldosterone or high salt intake seems to be altered in salt hypertensive Dahl rats (Aoi *et al.* 2006, 2007). The mRNA expression of α, β and γ ENaC subunits was abnormally increased by high salt intake in salt-sensitive Dahl rats (Aoi *et al.* 2007). This abnormal ENaC activation occurred despite the suppression of both plasma and kidney aldosterone levels in these animals and it was clearly enhanced in salt hypertensive Dahl rats (Kakizoe *et al.* 2009). Serum- and glucocorticoid-induced serine/threonine kinase 1 (SGK1) stimulates the activity and expression of renal ENaC. SGK1 expression was enhanced by high salt intake in the kidneys of salt-sensitive rats but suppressed in the kidneys of salt-resistant Dahl rats or Sprague Dawley rats (Farjah *et al.* 2003, Aoi *et al.* 2007). In addition, both strains of Dahl rats also differed in aldosterone-induced regulation of ENaC and SGK1 because aldosterone application decreased mRNA expression of β and γ ENaC subunits in the kidneys of salt-sensitive but not salt-resistant rats,

whereas it increased the expression of α ENaC subunits in both strains. Furthermore, aldosterone increased SGK1 expression in salt-resistant rats only (Aoi *et al.* 2006). Prostasin, a glycosylphosphatidyl-inositol-anchored serine protease, seems to play a pivotal role in ENaC activation. Chronic inhibition of this enzyme reduced the development of salt hypertension, proteinuria and renal injury in salt-sensitive Dahl rats (Maekawa *et al*. 2009).

TALH of salt-sensitive Dahl rats is also characterized by additional abnormalities of ion transport systems such as the overexpression of chloride channels (CLC-K2) (Castrop *et al.* 2000) or the increased activity of Na,K,2Cl cotransporter (NKCC2) (Alvarez-Guerra and Garay 2002). O´Connor *et al.* (2008, 2009) described enhanced amiloride-sensitive superoxide production in TALH of SS/Jr rats which was not mediated by Na^+/H^+ exchanger.

Metabolites of arachidonic acid are also important players in the control of renal function in salt hypertensive Dahl rats. 20-hydroxyeicosatetraenoic acid is known to inhibit the activity of Na,K,2Cl-cotransporter in TALH and renal outer medullary K^+ channel, both of them being important for sodium and chloride excretion (for review see Roman 2002). The formation of 20-HETE by cytochrome P450-4A ω hydrolase in the renal outer medulla is reduced in SS/Jr rats (Ma *et al.* 1994), predisposing these rats to the enhanced sodium and chloride reabsorption and salt retention when exposed to high salt intake (Stec *et al.* 1996, Hoagland *et al.* 2004). The induction of cytochrome P450-4A (CYP4A) activity by fibrates improved pressure-natriuresis relationship in SS/Jr rats (Alonso-Galicia *et al.* 1998) and attenuated salt hypertension development in this rat strain (Roman *et al.* 1993, Wilson *et al.* 1998). On the other hand, the inhibition of medullary 20-HETE synthesis induced salt sensitivity in Sprague Dawley and Lewis rats (Stec *et al.* 1997, Hoagland *et al.* 2003). CYP4A is located on rat chromosome 5 and the respective chromosomal region cosegregated with blood pressure in F_2 hybrids of SS/Jr x Lewis rats (Stec *et al.* 2006). The transfer of this region from Lewis into SS/Jr rats improved pressure-natriuresis and attenuated the development of salt hypertension and renal injury (Roman *et al.* 2006, Williams *et al*. 2008).

Further important metabolites of arachidonic acid such as epoxyeicosatrienoic acids (EETs) also exert an important role in salt hypertension development. Liclican *et al.* (2009) induced the salt sensitivity in salt-resistant Dahl rats through the inhibition of cytochrome P450 epoxygenase, leading to a decreased formation of vasodilator and natriuretic EETs.

Although increased systemic resistance is a dominant hemodynamic abnormality in salt hypertensive Dahl rats, the importance of early blood volume expansion and the increase of cardiac output cannot be excluded. Impaired renal sodium and water excretion in salt-sensitive Dahl rats has been recognized a long time ago. The central role of kidney in this hypertensive model is manifested by abnormal pressure-natriuresis relationship due to the altered intrarenal formation of Ang II, 20-HETE, ROS, NO and EETs. A special attention should be paid to the changes in blood flow and ion transport in the inner renal medulla (with a special respect to the function of TALH) in salt hypertensive animals.

Balance of vasoconstrictor and vasodilator systems

Hypertensive effects of high salt intake exerted by the changes in the balance of vasoconstrictor and vasodilator systems seem to be more important than those caused by the increase of hemodynamically active intravascular volume. As far as the altered balance of vasoactive systems in salt-dependent hypertension is concerned, our initial studies in young and adult DOCA-salt hypertensive rats indicated that sympathetic nervous system is responsible for the maintenance of high blood pressure in young animals, whereas pressor effects of angiotensin II and vasopressin play a more important role in adult rats (Zicha *et al.* 1987b, 1989).

The contribution of vasoconstrictor effects of endogenous angiotensin II to the maintenance of high blood pressure in young salt hypertensive SS/Jr Dahl rats was almost negligible, whereas the acute captopril administration to adult salt hypertensive SS/Jr rats lowered their blood pressure by 10-15 mm Hg (Table 2). The association of captopril-induced BP changes with basal blood pressure is also more significant in adult than in young Dahl animals (Table 3). This absence of actual pressor action of circulating Ang II contrasts with the fact that chronic blockade of renin-angiotensin system (RAS) by either ACE inhibitors (Fernandez *et al.* 1988, Hirawa *et al.* 1994, Quaschning *et al.* 2001) or AT_1 receptor blockers (Maitland *et al.* 2006, Takeda *et al.* 2007, Liang and Leenen 2008) considerably attenuated salt hypertension development and/or renal damage occurrence. However, our experiments revealed that the mild BP reduction induced by chronic preventive

Table 2. Basal and residual values of mean arterial pressure (MAP) as well as its particular components mediated by sympathetic vasoconstriction (pentolinum-induced BP fall) and NO-dependent vasodilatation (L-NAME-induced BP rise) in young and adult Dahl female rats subjected to 8 % NaCl diet feeding for 4 weeks from the age of 4 or 12 weeks, respectively.

	Young				Adult				
	SR/Jr LS	**SR/Jr HS**	**SS/Jr LS**	**SS/Jr HS**	**SR/Jr LS**	**SR/Jr HS**	**SS/Jr LS**	**SS/Jr HS**	
n	12	20	11	17	18	20	16	21	LSD
Basal MAP (mm Hg)	114±3	113±3	121±5	201±6*$^{\#}$	114±3	115±2	141±4$^{+\S}$	176±5*$^{\#\S}$	12
Residual MAP (mm Hg)	54±2	54±2	62±2^{+}	104±7*$^{\#}$	52±3	57±7	76±4$^{+\S}$	90±5*$^{\#\S}$	14
Δ captopril (mm Hg)	-3.8±0.9	-3.1±0.9	-4.1±1.5	-6.2±2.6	-6.3±1.0	-1.5±1.2	-8.5±1.2	-12±2.5$^{\#\S}$	4.9
Δ pentolinium (mm Hg)	-63±3	-59±3	-63±5	-106±5*$^{\#}$	-63±2	-67±2	-77±4$^{+\S}$	-96±4*$^{\#\S}$	10
Δ L-NAME (mm Hg)	57±3	51±3	71±5^{+}	72±5$^{\#}$	53±2	49±3	78±4^{+}	84±5$^{\#\S}$	11
% Δ captopril	-3.4±0.8	-2.7±0.9	-3.3±1.2	-3.0±1.2	-5.4±0.8	-1.3±1.1^{+}	-6.1±0.9	-6.7±1.4$^{\#\S}$	3.2
% Δ pentolinium	-55±1	-52±2	-52±3	-53±2	-56±1	-59±1	-54±2	-55±2	NS
% Δ L-NAME	50±3	46±3	60±4	37±3*$^{\#}$	48±3	43±2	56±3	49±3§	8.5

Data are mean ± S.E.M. BP changes are shown either as absolute values (Δ) or they are expressed as relative values (% Δ), i.e. in percentages of their basal BP values. LSD – least significant difference at $p<0.05$ level. Significant differences: * vs. SS-LS, $^{\#}$ vs. SR-HS, $^{+}$ vs. SR-LS, § vs. young rats. NS – not significant on the basis of ANOVA test. These data were modified from Zicha *et al.* (2001b), Dobešová *et al.* (2002) and Zicha *et al.* (2012).

Table 3. The relationships between basal mean arterial pressure (MAP) and its particular components representing angiotensin II-dependent vasoconstriction (Δ captopril), sympathetic vasoconstriction (Δ pentolinium) and NO-dependent vasodilatation (Δ L-NAME) in young and adult SS/Jr and SR/Jr Dahl female rats as well as in SS/Jr x SR/Jr F_2 hybrids.

	Young		**Adult**		**All (n = 135)**		**F_2 hybrids**	
Number of rats	60		75		135		122	
Basal MAP x								
Δ captopril	-0.251	p = 0.06	-0.479	p<0.001	-0.347	p<0.001	-0.339	p<0.001
Δ pentolinium	-0.869	p<0.0001	-0.847	p<0.0001	-0.856	p<0.0001	-0.772	p<0.0001
Δ L-NAME	0.301	p<0.05	0.506	p<0.0005	0.390	p<0.0005	0.339	p<0.001
Residual MAP	0.770	p<0.0001	0.707	p<0.0001	0.734	p<0.0001	0.569	p<0.0001
% Δ captopril	-0.035	NS	-0.315	p<0.01	-0.169	p = 0.05	-0.285	p<0.005
% Δ pentolinium	-0.020	NS	0.171	NS	0.068	NS	-0.277	p<0.01
% Δ L-NAME	-0.545	p<0.001	-0.150	NS	-0.359	p<0.001	-0.139	NS

Data represent correlation coefficients r. Residual MAP was recorded after the combined blockade of renin-angiotensin system by captopril and sympathetic nervous system by pentolinium. Relative MAP changes (% Δ) were expressed in percentage of basal MAP values.

treatment of salt hypertensive SS/Jr rats with ACE inhibitor captopril lowered their blood pressure by the attenuation of sympathetic vasoconstriction but not by the reduction of Ang II-dependent vasoconstriction (Dobešová and Zicha, unpublished data). Similarly, our earlier studies in rats with spontaneous or NO-deficient hypertension indicated that chronic captopril treatment prevented BP rise mainly by the attenuation of the sympathetic BP component (Zicha *et al.* 2006, Paulis *et al.* 2007). This is in agreement with the important

participation of angiotensin II in the central nervous mechanisms controlling sympathetic outflow (for review see Leenen 2010). Although there is no doubt on the importance of RAS in the pathogenesis of salt hypertension, the peripheral vasoconstrictor effects of Ang II seem to be of minimal significance.

Rapp *et al.* (1989, 1990) were the first who demonstrated the cosegregation of S allele of the polymorphic renin gene with blood pressure in different sets of F_2 hybrids. Further evidence for the importance of renin gene was obtained in congenic or consomic strains in which renin gene from SR/Jr or BN rats was introgressed into SS/Jr background (Amaral *et al.* 2001, Cowley *et al.* 2001, Hoagland *et al.* 2004, Taylor *et al.* 2006a, Bugenhagen *et al.* 2010). Actually these strains are often used to confirm or exclude the participation of renin gene in particular phenotypes of salt hypertensive Dahl rats. The overwhelming majority of positive results obtained in SS.13^{BN} rats might indicate either the extreme importance of RAS in multiple regulatory systems essential for the development of salt hypertension in Dahl rats or the considerable fragility of the polygenic system which is disrupted if a single component is missing. Vascular reactivity is one of the promising areas of research in which these special rat strains are very useful. The introgression of either renin gene region from SR/Jr rats (Drenjancevic-Peric *et al.* 2004) or chromosome 13 from BN rats into SS/Jr background (SS.13^{BN}) (Drenjancevic-Peric *et al.* 2003) restored the impaired acetylcholine-induced vasodilatation in cremaster muscle of SS/Jr rats fed a high-salt diet. Furthermore, the reduced acetylcholine-induced or hypoxia-induced relaxations of middle cerebral artery from SS/Jr rats fed a low-salt diet were also caused by an abnormal RAS regulation because they were restored by renin gene transfer from BN or SR/Jr rats (Drenjancevic-Peric *et al.* 2005, 2010). Moreover, the attenuation of RAS regulatory mechanisms by chronic high salt intake or chronic losartan treatment of SS.13^{BN} rats abolished these relaxations restored by the renin gene transfer (Drenjancevic-Peric and Lombard 2004, 2005). Durand and Lombard (2011) ascribed the attenuation of NO-dependent vasodilatation in cerebral arteries of SS/Jr to the increased levels of superoxide which were lowered by the enhanced expression of Cu/Zn superoxide dismutase in the respective congenic strain possessing BN renin gene.

The dysbalance between sympathetic nervous system (SNS) and nitric oxide, as principle vasoactive systems, plays a major role in the maintenance of salt hypertension. Enhanced sympathetic vasoconstriction (Mark 1991, Huang and Leenen 1998) together with enhanced norepinephrine turnover (Kotchen *et al.* 1991b, Kuneš *et al.* 1991) in salt hypertensive Dahl rats are accompanied by a reduced production of vasodilator and natriuretic nitric oxide (Lüscher *et al.* 1987, Chen and Sanders 1991, Hu and Manning 1995, Simchon *et al.* 1996, He *et al.* 1997). Our studies on vasoactive balance carried out in young salt hypertensive SS/Jr rats (Zicha *et al.* 2001b) confirmed the decisive role of sympathetic hyperactivity and suggested that NO-dependent vasodilatation was attenuated by enhanced production of superoxide anions interacting with the available NO at the vascular level.

Sympathetic hyperactivity in salt hypertensive Dahl rats results from the increased sympathoexcitation and/or decreased sympathoinhibition mediated by complex central nervous mechanisms (for review see Leenen 2010, Huang and Leenen 2011, Blaustein *et al.* 2012, Oki *et al.* 2012). The increased sympathoexcitation in salt hypertensive Dahl rats seems to result from the enhanced response of vasomotor neurons of rostral ventrolateral medulla (RVLM) to excitatory amino acids (Ito *et al.* 2001), although Tsuchihashi *et al.* (1997) did not observe any difference in the effects of these amino acids in DIS and DIR rats. The injection of Ang II into RVLM or in the vicinity of the hypothalamic paraventricular nucleus elicited a greater tonic activation of vasomotor neurons in salt hypertensive Dahl rats which can be prevented by AT_1 receptor antagonists (Ito *et al.* 2003).

This Ang II-dependent excitatory process is further amplified by the central nervous pathway(s) involving endogenous brain aldosterone and mineralocorticoid receptors (Gomez-Sanchez *et al.* 1992, 2005), epithelial sodium channels (Gomez-Sanchez and Gomez-Sanchez 1995) and endogenous brain ouabain-like compound (Huang and Leenen 1994, Huang *et al.* 2009). Sympathetic hyperactivity of salt hypertensive Dahl rats is triggered by the increased Na^+ concentration in the cerebrospinal fluid (CSF) (Nakamura and Cowley 1989, Simchon *et al.* 1999, Huang *et al.* 2004). The underlying mechanisms of the enhanced sympatho-excitation in salt hypertensive animals seem to involve the reduced NO release in paraventricular nucleus (Gabor and Leenen 2011) and angiotensin II-induced activation of glutamate receptors in this nucleus (Gabor and Leenen 2012).

There are several fundamental findings

concerning the above mentioned central nervous mechanisms. First of all, the increase of CSF Na^+ concentration precedes BP increase (Huang *et al.* 2004). Second, the increase of CSF Na^+ concentration elicits a more pronounced sympathetic activation and a greater BP rise in young than in adult salt-sensitive Dahl rats (Huang *et al.* 2001). Third, intracerebroventricular infusion of aldosterone to SS/Jr rats causes a similar response as high salt intake, i.e. brain ouabain-like compound increase, sympathetic hyperactivity and hypertension (Huang *et al.* 2005). Finally, high salt intake increases brain RAS preferentially in SS/Jr rats, i.e. ACE activity, Ang II levels and AT_1 receptor density (Zhao *et al.* 2001, Wang *et al.* 2003a).

The possible role of brain aldosterone in the pathogenesis of salt hypertension has attracted the attention since the demonstration that intracerebroventricular but not subcutaneous infusion of selective MR antagonist RU28318 blocked the development of salt hypertension in SS/Jr rats (Gomez-Sanchez *et al.* 1992). The same effect was achieved by the blockade of brain steroidogenesis in salt-sensitive Dahl rats using the intracerebroventricular infusion of trilostane (3β-hydroxysteroid dehydrogenase inhibitor) (Gomez-Sanchez *et al.* 2005). Aldosterone synthase mRNA expression was found to be enhanced in the brain of SS/Jr rats, whereas no significant changes in mRNA expression of mineralocorticoid receptors, 11β-hydroxylase or 11β-hydroxysteroid dehydrogenase type 1 or 2 were detected in the brainstem, hypothalamus or hippocampus of SS/Jr rats (Gomez-Sanchez *et al.* 2010). Central infusion of aldosterone synthase inhibitor FAD286 prevented sympathetic hyperactivity and hypertension elicited by the elevation of cerebrospinal Na^+ concentration in Wistar rats (Huang *et al.* 2008). Indeed, a chronic intracerebroventricular infusion of aldosterone synthase inhibitor FAD286 or MR antagonist spironolactone prevented salt hypertension development in SS/Jr rats (Huang *et al.* 2009, Gomez-Sanchez *et al.* 2010).

It should be noted that MR can be activated by the surplus of glucocorticoids which are normally inactivated by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD 2). The expression and/or activity of this enzyme was decreased in blood vessels of salt-sensitive Dahl rats (Takeda *et al.* 1994, Mazancová *et al.* 2003b) and the reduced 11β-HSD 2 activity in mesenteric arteries of salt hypertensive Dahl rats was accompanied by their enhanced vasoconstrictor response to norepinephrine (Takeda *et al.* 1994). On the other hand, Fenton *et al.* (2003) observed that under the conditions of low salt intake 11β-HSD 2 levels were increased in inner medullary collecting duct of SS/Jr rats compared to SR/Jr ones. This abnormality, which leads to decreased local corticosterone concentrations, was associated with a decreased expression of α subunit of ENaC that was normalized by the chronic inhibition of 11β-hydroxysteroid dehydrogenase in SS/Jr rats using carbenoxolone infusion (Fenton *et al.* 2003). In fact, Pohlová *et al.* (2000) observed a higher activity of 11β-HSD 2 in the renal medulla and cortex of SS/Jr rats fed a low-salt diet, but chronic elevation of salt intake increased 11β-HSD 2 activity in the kidney of SR/Jr rats only, abolishing thus the strain difference in the activity of this enzyme. This might also be associated with a decreased corticosterone inactivation in salt hypertensive Dahl rats. Moreover, Mazancová *et al.* (2003a) reported a significantly lower net activity of 11β-hydroxysteroid dehydrogenase in placental tissue of SS/Jr rats leading to lower corticosterone inactivation and less efficient placental protection of SS/Jr fetuses from the deleterious effects of intrauterine glucocorticoid surplus. Indeed, chronic inhibition of 11β-hydroxysteroid dehydrogenase in pregnant rats by carbenoxolone increased blood pressure in their offspring (Lindsay *et al.* 1996).

Increased brain oxidative stress can also participate in the central sympathoexcitation which mediates BP elevation in young salt hypertensive Dahl rats (Fujita *et al.* 2007) or Sprague Dawley rats (Fujita *et al.* 2012). In fact, chronic administration of antioxidants such as N-acetylcysteine attenuated the development of salt hypertension in SS/Jr rats by a reduction of sympathetic vasoconstriction (Kuneš *et al.* 2004b). Not only central but also peripheral mechanisms contribute to the increased sympathetic nerve activity because high salt intake can suppress catechol-O-methyltransferase activity *via* blunting α_2-adrenoceptor signaling (Hirano *et al.* 2007).

Finally, decreased baroreflex efficiency and resulting attenuation of sympathoinhibition might also contribute to the increased sympathetic nervous activity in salt-sensitive Dahl rats (Gordon *et al.* 1981, Miyajima and Bunag 1987, Peuler *et al.* 1989). Baroreflex impairment as a cause of elevated sympathetic tone was recently confirmed by the radiotelemetric study of blood pressure and heart rate in SS/Jr and $SS.13^{BN}$ rats fed either a low-salt or a high-salt diets (Bugenhagen *et al.* 2010). Our study on baroreflex control of heart rate (Nedvídek and Zicha 2000) disclosed a major impairment

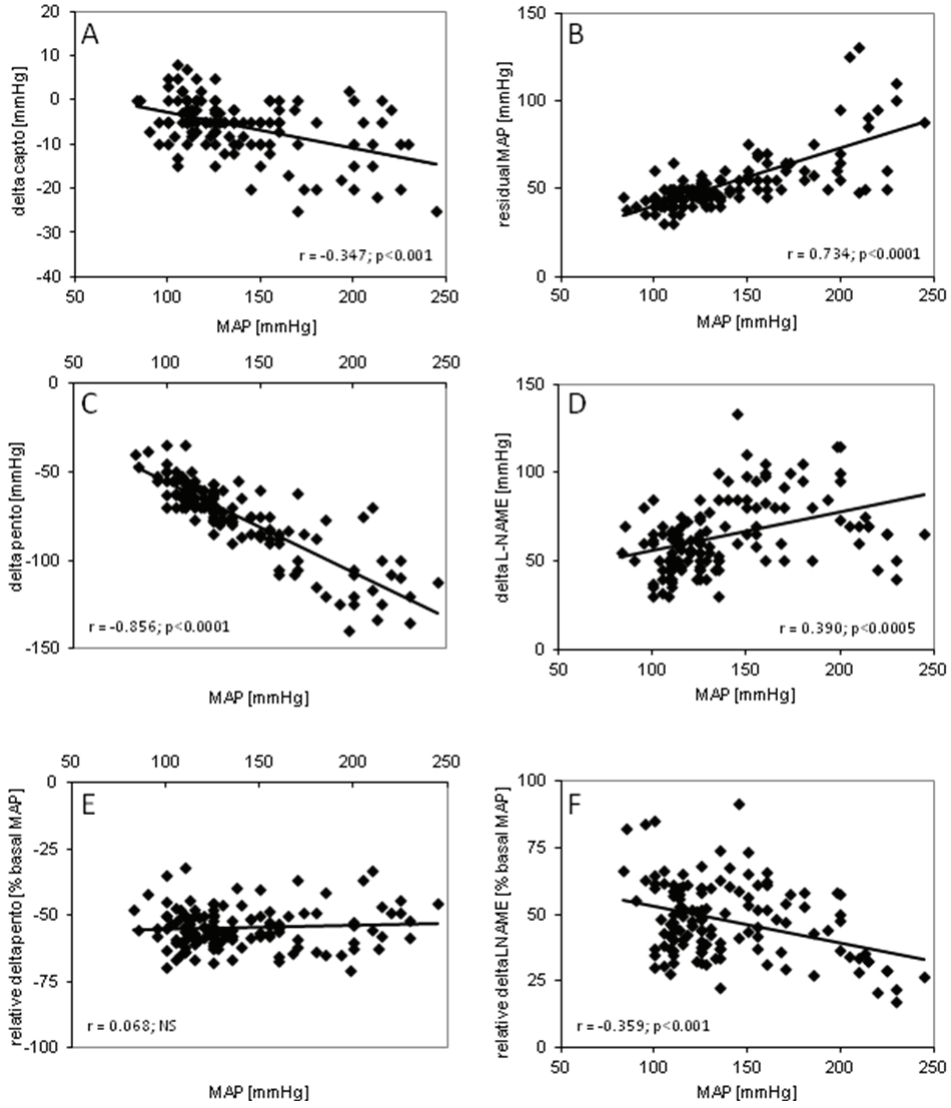

Fig. 5. The relationships between basal MAP values and captopril-induced MAP changes (**A**), residual MAP (**B**), pentolinium-induced (**C**) or L-NAME-induced MAP changes (**D**) in the whole population of Dahl female rats (n=135) listed in Table 2. BP changes are shown either as absolute values (**A-D**) or expressed in percentage of basal BP values (**E, F**) (data modified from Zicha *et al.* 2001b and Dobešová *et al.* 2002).

of the baroreflex efficiency in young salt hypertensive SS/Jr rats, whereas there were only marginal changes in adult animals. This is in agreement with a less pronounced sympathetic hyperactivity in adult salt hypertensive SS/Jr rats in which smaller amounts of superoxide anions and no signs of NO deficiency were demonstrated (Dobešová *et al.* 2002). A comparison of the balance between sympathetic vasoconstriction and NO-dependent vasodilatation in young and adult salt hypertensive SS/Jr rats is summarized in Table 2.

A subsequent detailed phenotypic analysis of SS/Jr x SR/Jr F_2 hybrids subjected to high salt intake in youth (Dobešová *et al.* 2002) confirmed our conclusions on the major importance of sympathetic hyperactivity for BP maintenance. Moreover, we have clearly demonstrated that NO-dependent vasodilatation in salt hypertensive Dahl animals is attenuated only relatively as compared to the magnitude of BP rise and/or elevation of sympathetic vasoconstriction (Table 3). When we analyzed the relationships of sympathetic vasoconstriction (pentolinium-induced BP changes) or NO-dependent vasodilatation (L-NAME-induced BP changes) to basal BP values, it was clear that in both F_2 hybrids (Dobešová *et al.* 2002) and progenitor rats (Fig. 5) the slope of the relationship of sympathetic BP component (pentolinium-induced BP fall) was much steeper than that of NO-dependent BP component (L-NAME-induced BP rise). It is thus evident that NO-dependent vasodilatation can hardly compensate for BP elevation driven by the enhanced sympathetic vasoconstriction in salt hypertensive Dahl rats. Moreover, the presence of relative NO deficiency in young rats is clearly evident if BP changes are expressed in the percentage of basal blood pressure (Table 2, Fig. 5). A similar role of sympathetic hyperactivity and relative NO deficiency in BP maintenance was also observed in other forms of genetic

hypertension such as Prague hereditary hypertriglyceridemic rats (Kuneš *et al.* 2002) or SHR (Zicha *et al.*, to be published).

The adrenergic vasoconstriction in SS/Jr rats fed a high-salt diet was enhanced by 20-HETE (Raffai *et al.* 2010) which also increased resting tone of resistance vessels in salt hypertensive animals (Wang *et al.* 2009). In fact, 20-HETE production tended to be increased by high salt intake in small resistance vessels of SS/Jr rats (Wang *et al.* 2009, Raffai *et al.* 2010). This is in contrast with suppressed 20-HETE production in renal medulla of these animals (Ma *et al.* 1994). In fact, myogenic activation of resistance vessels in skeletal muscle of salt hypertensive SS/Jr rats is partly a function of 20-HETE production, whereas this is not the case for myogenic activation of resistance vessels in normotensive SS/Jr rats fed a low-salt diet (Frisbee *et al.* 2001). The underlying mechanisms of 20-HETE-induced vasoconstriction, which include the increase of calcium conductance through L-VDCC channels and the inhibition of calcium-activated K^+ channels (BK_{Ca} channels), are reviewed by Roman (2002).

There is also the evidence that calcium-activated chloride channels participate in α-adrenergic vasoconstriction. The *in vivo* and *in vitro* study on mesenteric vascular bed of Dahl rats indicated that the inhibition of these channels with niflumic acid attenuated α-adrenergic vasoconstriction less in salt hypertensive SS/Jr rats than in normotensive SR/Jr animals (Parai and Tabrizchi 2005a, b).

Since the enhanced α-adrenergic activity is associated with the opening of L-type voltage-dependent calcium channels (L-VDCC), whereas NO contributes to their closure (Pintérová *et al.* 2009), it is not surprising that salt hypertension in Dahl rats was associated with augmented BP response to acute administration of nifedipine or other calcium antagonists (Sharma *et al.* 1984, Kuneš *et al.* 2004a). The magnitude of nifedipine-induced BP reduction was always proportional to the basal BP level (Kuneš *et al.* 2004a, Pintérová *et al.* 2009, Zicha *et al.* 2011).

A comparison of young and adult salt hypertensive SS/Jr rats also revealed a major age-dependent difference in the residual blood pressure which is recorded as minimal blood pressure at maximal NO-induced vasodilatation following the acute blockade of both RAS and SNS. This parameter reflects structural remodeling and/or changes in basal tone of resistance vessels. Residual blood pressure was elevated more in young than in adult salt hypertensive animals (Dobešová *et al.* 2002), confirming a major structural remodeling of resistance vessels in young salt hypertensive Dahl rats reported by Lee and Triggle (1986). There was also a positive correlation between basal and residual BP values in our set of Dahl F_2 hybrids as well as in young and adult Dahl rats, indicating the importance of structural and/or functional alterations of resistance vasculature for the severity of salt hypertension (Table 3).

Recently, we have compared the efficacy of three major vasodilator systems – prostacyclin (PGI_2), Ca^{2+}-activated K^+ channels of large conductance (BK_{Ca}) and nitric oxide – in Dahl rats (Behuliak *et al.* 2011). It was demonstrated that PGI_2 and to a certain extent also BK_{Ca} channels are able to enhance their vasodilator action in young salt hypertensive SS/Jr rats, whereas this was not the case of NO. BP response to acute NO synthase inhibition by L-NAME tended to be decreased in salt hypertensive animals compared to SS/Jr rats fed a low-salt diet and there was a clear-cut evidence of relative NO deficiency in these hypertensive rats. Furthermore, the different adaptation of these three vasodilator systems can be documented by the absence of a significant correlation between basal blood pressure and L-NAME-induced BP elevation which contrasted with positive correlations of basal blood pressure with BP changes induced by the acute inhibition of PGI_2 formation by indomethacin or acute blockade of BK_{Ca} channels by tetraethylammonium (Behuliak *et al.* 2011).

In contrast with the studies showing larger effects of various pharmacological interventions in young salt hypertensive Dahl rats, some vasoactive systems play a more important role in adult than in young animals, endothelin-1 (ET-1) being a typical example. The acute blockade of its ET_A receptors by ambrisentan (BSF 208075) caused only a moderate BP decrease which was similar in both age groups of salt hypertensive SS/Jr rats (Zicha *et al.* 2012). However, chronic ambrisentan administration attenuated salt hypertension development only in adult but not in young animals and this BP reduction was due to the attenuation of sympathetic BP component (Zicha *et al.* 2012). Our finding suggests ET-1 involvement in the central nervous mechanisms regulating sympathetic tone as it was proposed by Rossi *et al.* (2004).

There is a similar age-dependent involvement of superoxide anions in the pathogenesis of salt hypertension in Dahl rats. Chronic administration of

tempol (superoxide dismutase mimetic) attenuated salt hypertension development only in adult but not in young SS/Jr rats (Vaněčková *et al.*, to be published). The underlying mechanism of this tempol-induced chronic BP reduction was again a decrease in sympathetic BP component. It is possible that both endothelin-1 and superoxide anions are involved in the same central nervous mechanisms regulating sympathetic tone as it was suggested by D´Angelo *et al.* (2010).

There is no doubt about the dysbalance of vasoconstrictor and vasodilator systems (namely SNS and NO) in salt hypertension. Neither central nor peripheral BP-lowering action of NO (or other vasodilators) can effectively counterbalance the enhancement of centrally driven sympathetic outflow. The major role of SNS in BP maintenance of young salt hypertensive Dahl rats becomes partially attenuated in adult animals in which other pressor systems (Ang II, ET-1 etc) also participate in the maintenance of elevated blood pressure.

Superoxide formation, NO synthesis and NO-dependent vasodilatation

Oxidative stress is enhanced in salt hypertensive Dahl rats in which higher ROS production was demonstrated in blood vessels (Swei *et al.* 1997, Bayorh *et al.* 2004) and kidneys (Trolliet *et al.* 2001, Meng *et al.* 2002). Plasma levels of hydrogen peroxide (Swei *et al.* 1997, Yamamoto *et al.* 2007) and 8-isoprostane (Trolliet *et al.* 2001, Forde *et al.* 2003, Bayorh *et al.* 2004) were elevated in these animals in which increased urinary excretion of 8-isoprostane and decreased urinary excretion of NO metabolites and cGMP were also reported (Trolliet *et al.* 2001, Forde *et al.* 2003, Zhang *et al.* 2004). Acute intravenous tempol administration caused a more pronounced transient BP reduction in salt hypertensive SS/Jr rats as compared to normotensive animals (Zicha *et al.* 2001b).

The sources of superoxide anions in hypertensive animals seem to be xanthine oxidase (Swei *et al.* 1999), mitochondrial oxidative processes (Taylor *et al.* 2006a), uncoupled NO synthase (Taylor *et al.* 2006b, Satoh *et al.* 2010) and especially NADPH oxidase (Tojo *et al.* 2002, Zhang *et al.* 2004, Taylor *et al.* 2006a). The latter enzyme is known to be activated by Ang II (Hitomi *et al.* 2006, Schulman *et al.* 2006). This is a reason why ROS production in salt hypertensive Dahl rats can be lowered by the chronic treatment with either ACE inhibitors (Tsutsui *et al.* 2001, Tojo *et al.* 2002) or AT_1 receptor blockers (Bayorh *et al.* 2005, Satoh *et al.* 2010). Similarly, the chronic mineralocorticoid receptor blockade by eplerenone decreased blood pressure, oxidative stress and NADPH protein expression in the kidney (Bayorh *et al.* 2011). Chronic administration of various antioxidants such as α-tocopherol (Forde *et al.* 2003), vitamins C and E (Tian *et al.* 2005), tempol (Nishiyama *et al.* 2004, Ozawa *et al.* 2004, Hisaki *et al.* 2005) or apocynin (Taylor *et al.* 2006, Tian *et al.* 2008) not only attenuated oxidative stress, but also improved vascular relaxation, reduced renal damage and lowered blood pressure of salt-sensitive Dahl rats subjected to high salt intake.

Meng *et al.* (2002) demonstrated an increased oxidative stress and the attenuation of superoxide dismutase activity in the kidney of SS/Jr rats fed a high-salt diet. Their later study (Meng *et al.* 2003) revealed that intravenous tempol infusion lasting three weeks attenuated salt hypertension development in SS/Jr rats aged 8-10 weeks and this BP reduction was achieved without any increase in sodium or water excretion. Major attenuation of renal medullary superoxide release and salt hypertension development was also induced by the addition of N-acetylcysteine into the high-salt diet (Tian *et al.* 2006). Similar but less pronounced BP effects were observed in SS/Jr rats chronically supplemented with vitamins C and E (Tian *et al.* 2007b) or in animals subjected to chronic inhibition of NADPH oxidase by apocynin (Tian *et al.* 2008). These antioxidants ameliorated all the changes elicited by high salt intake in the kidneys of SS/Jr rats aged 8-10 weeks, i.e. the upregulation of $gp91^{phox}$ and $p47^{phox}$ subunits of NADPH oxidase, augmented the activity of NADPH oxidase, enhanced superoxide release and increased hydrogen peroxide content as well as elevated vascular resistance as it was reported by Tian *et al.* (2005, 2007b, 2008). NADPH oxidase seems to be a major source of superoxide production in the renal medulla of SS/Jr rats. The disruption of its $p67^{phox}$ subunit in SS/Jr rats significantly attenuated salt hypertension development, lowered renal medullary oxidative stress and ameliorated renal injury (Feng *et al.* 2012). Apocynin infusion into the medullary interstitium lowered not only superoxide production but also attenuated initial BP elevation induced by high salt intake in 10-week-old animals (Taylor *et al.* 2006a). Enhanced superoxide and hydrogen peroxide production in renal outer medulla, which is stimulated by Ang II, reduced NO-mediated tubular-vascular cross-talk between the thick ascending limb of

loop of Henle and the contractile pericytes of surrounding vasa recta (Taylor and Cowley 2005, Mori *et al.* 2007).

Concerning BP effects of superoxide scavenging by tempol, there is a considerable difference between our acute and chronic studies. The acute administration of tempol lowered blood pressure significantly more in young than in adult salt hypertensive SS/Jr rats and this BP reduction was ascribed to the augmented NO-dependent vasodilatation (Zicha *et al.* 2001b, Dobešová *et al.* 2002). On the contrary, chronic preventive tempol treatment attenuated the development of salt hypertension only in adult (but not in young) SS/Jr rats and this was due to the reduction of sympathetic vasoconstriction. The results of our chronic experiments are in line with the age-dependent difference in superoxide levels in the aorta of salt hypertensive SS/Jr rats which were more elevated in adult than in young animals (Vaněčková *et al.*, to be published). The relationships between blood pressure and vascular superoxide production or levels of conjugated dienes (indicators of oxidative stress) in Dahl rats were similar to those which we described in rats with NO-deficient L-NAME-induced hypertension (Rauchová *et al.* 2005). It would be desirable to compare the effects of preventive and therapeutic administration of antioxidants in both age groups as we did with N-acetylcysteine in young and adult SHR (Pecháňová *et al.* 2006, 2007). N-acetylcysteine might be a very useful drug because it combines ROS scavenging with NO storage in the form of S-nitrosothiols.

Our earlier studies on NO synthase (NOS) activity in the kidneys of young and adult Dahl rats fed high-salt diet disclosed that high salt intake lowered NOS activity in both young and adult animals (Pecháňová *et al.*, to be published). We were also interested in the expression of particular NOS isoforms in Dahl rats. Some abnormalities of the gene for inducible NOS isoform (*Nos2*) were reported in salt-sensitive Dahl rats (Deng and Rapp 1995, Chen *et al.* 1998). Unfortunately, we did not confirm the occurrence of any of the above reported *Nos2* gene polymorphisms in our colony of SS/Jr rats (Hojná *et al.* 2005). Our later study, which was focused on protein expression of all three NOS isoforms in the brain and kidneys (Hojná *et al.* 2010), revealed the suppressed expression of neuronal (nNOS) and inducible (iNOS) isoforms in the diencephalon and brainstem of young salt hypertensive SS/Jr rats. In addition, under the conditions of low salt intake the protein expression of endothelial (eNOS) isoform was decreased in the kidneys of SS/Jr rats compared to SR/Jr rats and this suppression of eNOS expression was further augmented in SS/Jr rats subjected to high salt intake from weaning (Hojná *et al.* 2010). Similar findings on protein expression of particular NOS isoforms were earlier reported in adult salt hypertensive DS rats (Ni and Vaziri 2001). Although both above mentioned papers disclosed a decreased nNOS expression in the brain of salt hypertensive Dahl rats, Tandai-Hiruma *et al.* (2005) reported higher nNOS expression and NOS activity in the brainstem of salt hypertensive animals as well as a more pronounced BP elevation and a greater rise of renal sympathetic nerve activity after the acute intracerebroventricular administration of S-methyl-L-thiocitrulline which is a rather selective inhibitor of nNOS. These data are in line with the findings of Serino *et al.* (2001) on hypothalamic expression of nNOS in Dahl/Rapp rats. Using *in situ* hybridization they found that high salt intake increased nNOS mRNA more in SS/Jr rats than in SR/Jr rats. On the basis of these results they suggested that the increased NOS activity in the hypothalamus of hypertensive SS/Jr rats may be insufficient to prevent the increased sympathetic nervous activity, vasopressin release and salt hypertension development. The acute intraperitoneal administration of another "selective" nNOS inhibitor 7-nitroindazole also increased renal sympathetic nerve activity more in salt hypertensive SS/Jr rats than in other normotensive groups, indicating that neuronal NO-mediated suppression of sympathetic outflow was greatly enhanced in salt hypertension (Nishida *et al.* 2001).

On the other hand, chronic inhibition of nNOS by intravenous infusion of 7-nitroindazole did not affect blood pressure of salt-loaded SS/Jr rats, but it abolished the salt resistance of SR/Jr rats (Tan *et al.* 1999). Similarly, Rudd *et al.* (1999) reported that chronic administration of three different iNOS inhibitors also enabled BP rise in salt-loaded SR/Jr rats. Tan *et al.* (2000) demonstrated that intravenous infusion of aminoguanidine (another "selective" iNOS inhibitor) induced a considerable BP rise in both SS/Jr and SR/Jr rats subjected to high salt intake, whereas renal medullary aminoguanidine infusion elicited a moderate BP increase in SS/Jr animals only (Tian *et al.* 2003). These important changes in salt sensitivity induced by chronic blockade of nNOS or iNOS always occurred without any major alterations of renal hemodynamics or water and sodium excretion.

Salt hypertensive DS rats are characterized by a downregulation of eNOS and impaired NO bioavailability in blood vessels and kidneys (Hayakawa

and Raij 1997, Hayakawa and Raij 1998). The increased superoxide production by NADPH oxidase was linked to the functional upregulation of Ang II and was accompanied by insufficient NO bioavailability (Zhou *et al.* 2003).

Formerly, Lüscher *et al.* (1987) and Nishida *et al.* (1998) demonstrated that vascular contractions to norepinephrine are increased but vascular relaxation to acetylcholine are attenuated in salt hypertensive Dahl rats. These differences between hypertensive animals and their normotensive controls were abolished by pretreatment of vessels with NOS inhibitors. On the contrary, L-arginine pretreatment augmented this difference because norepinephrine-induced contraction was attenuated more in normotensive than in hypertensive vessels (Nishida *et al.* 1998). Impaired acetylcholine-induced relaxation was also observed in norepinephrine-precontracted afferent arterioles in the kidney of salt hypertensive Dahl rats and this attenuated vasodilatation was improved by acute or chronic tempol treatment which augmented both NO-dependent and EDHF-mediated component of acetylcholine-induced vasodilatation (Ozawa *et al.* 2004), although the former component seemed to be more important in salt-sensitive Dahl rats (Hayakawa *et al.* 1993).

A detailed research on microvascular structure and function has been performed in skeletal muscle of salt hypertensive Dahl rats (for review see Boegehold 2002). The dissipation of intraluminal pressure across particular segments of vascular bed in exteriorized spinotrapezius muscle of salt hypertensive SS/Jr rats demonstrated that the increased luminal pressure can be detected up to the level of proximal resistance arterioles which effectively protect capillary network from abnormally high hydrostatic pressure (Boegehold 1991). Resting arteriolar diameters in spinotrapezius muscle were already diminished in SS/Jr rats fed a low-salt diet and these changes were even more pronounced in salt hypertensive animals (Boegehold 1993a). These alterations were due to the increased vascular tone rather than due to the remodeling of the vascular wall because all these changes were entirely eliminated at the maximal vasodilatation induced by adenosine (Boegehold and Kotchen 1990). The resting diameters of distal (downstream located) resistance arterioles were not reduced and no arteriolar rarefaction has been detected in spinotrapezius muscle of salt hypertensive Dahl rats (Boegehold 1993a, Boegehold and Kotchen 1990).

About 50 % of increased vascular resistance was due to arteriolar constriction, whereas the changes in small feed arteries were responsible for the remaining increase of systemic resistance (Boegehold 1991, Boegehold *et al.* 1991). Sympathetic hyperactivity caused about 50 % of increased vascular resistance in isolated hindquarters of salt hypertensive Dahl rats (Takeshita and Mark 1978). Reduced NO bioavailability in salt hypertensive animals accounted for a considerable part of non-neurogenic mechanisms of increased vascular tone in salt hypertensive SS/Jr rats (Boegehold 1992, Boegehold 1993b). It was found that the acute blockade of NO synthesis by L-NAME application caused arteriolar constriction, while L-arginine application induced arteriolar dilatation in normotensive SS/Jr rats, whereas both interventions had negligible effects on arteriolar diameter in salt hypertensive animals. Since acetylcholine- or nitroprusside-induced vasodilatations were not altered in skeletal muscle arterioles of salt hypertensive Dahl rats, high salt intake seems to suppress basal NO release from the endothelium (Boegehold 1992). Later studies in SR/Jr or Sprague Dawley rats confirmed that high salt intake can attenuate flow-dependent arteriolar dilation in skeletal muscle just through the suppression of NO formation (Boegehold 1993c, Boegehold 1995) and/or through enhanced NO inactivation by high ROS levels (Lenda *et al.* 2000). Decreased Cu/Zn superoxide dismutase activity (Lenda and Boegehold 2002a) together with elevated activities of NADPH oxidase and xanthine oxidase (Lenda and Boegehold 2002b) were responsible for a decrease in NO bioavailability in salt hypertensive Dahl rats.

There are two important factors which were suggested to contribute to the decreased NO bioavailability in salt hypertensive Dahl rats. The first one concerns arginase activity which might reduce substrate levels for NO synthase because L-arginine is metabolized to L-ornithine instead of L-citrulline. Johnson *et al.* (2005) observed attenuated acetylcholine-induced or flow-mediated vasodilatation in gracilis muscle arterioles of salt hypertensive SS/Jr rats which was restored either by arginase inhibition or by L-arginine pretreatment. Another factor contributing to the endothelial dysfunction in salt hypertensive SS/Jr rats is endogenous carbon monoxide which is produced by vascular heme oxygenase (HO). The formation HO-derived carbon monoxide, an established inhibitor of endothelial NO production, was increased and aortic HO was upregulated in salt hypertensive animals (Johnson *et al.* 2003, Teran *et al.* 2005). Progressive BP rise was

accompanied by a gradual impairment of endothelium-dependent vasodilatation which was restored by acute pretreatment of blood vessels with HO inhibitor. Beneficial effects of HO inhibition on flow-mediated vasodilatation in gracilis muscle arterioles of salt hypertensive SS/Jr rats were abolished by exogenous carbon monoxide. It should also be noted that acute *in vivo* HO inhibition lowered considerably high blood pressure of salt hypertensive animals (Teran *et al.* 2005).

Using young male SS/Jr and SR/Jr rats subjected to high salt intake from weaning Chen and Sanders (1991) demonstrated the importance of NO deficiency for the development of salt hypertension. Their acute experiments in anesthetized animals revealed a slightly greater BP rise following NOS inhibition by N^G-monomethyl-L-arginine (L-NMMA) but normal BP fall after L-arginine infusion in salt hypertensive SS/Jr rats. Chronic L-arginine or L-citrulline administration enhanced urinary cGMP excretion and fully prevented salt hypertension development. Later Chen and Sanders (1993) ascribed the attenuation of NO production in salt hypertensive SS/Jr rats to the defect in the activity of dexamethasone-suppressible inducible NOS which was considered to be based upon the mutation of *Nos2* gene in vascular smooth muscle of SS/Jr rats (Chen *et al.* 1998). However, this mutation of iNOS was absent not only in our colony of SS/Jr animals (Hojná *et al.* 2005) but also in the original Brookhaven DS rats (Chen *et al.* 1998).

Thus, the role of nitric oxide and ractive oxygen species in the maintenance of increased systemic resistance of salt hypertensive SS/Jr rats is not simple. Using our *in vivo* approach to estimate the whole-body NO-dependent vasodilatation (Zicha *et al.* 2001b, Dobešová *et al.* 2002) we have always observed a moderate augmentation of BP response to acute L-NAME administration in SS/Jr rats compared to SR/Jr ones. High salt intake never significantly enhanced this BP response in young or adult animals of either Dahl strain so that the relative NO deficiency was disclosed in young severely hypertensive SS/Jr rats. Surprisingly, chronic ROS scavenging by tempol attenuated salt hypertension development only in adult but not in young SS/Jr rats, although young salt hypertensive SS/Jr rats were characterized by greater BP response to acute tempol administration and by smaller BP response to acute L-NAME administration compared to adult salt hypertensive animals (Table 2). Perhaps the involvement of ROS and NO might differ in severe and moderate forms of salt hypertension which are typical for young and adult Dahl rats, respectively.

Other vasodilator and natriuretic systems

Decreased urinary kallikrein excretion was one of the first abnormal phenotypes described in salt-sensitive Dahl rats (Carretero *et al.* 1978, Rapp *et al.* 1984, Arbeit and Serra 1985, Bouhnik *et al.* 1992). High salt intake decreased BP response to the infusion of bradykinin antagonist only in SS/Jr but not in SR/Jr rats (Benetos *et al.* 1993). Ideishi *et al.* (1994) reported that chronic taurine administration, which activated renal kallikrein, retarded salt hypertension development in SS/Jr rats. Chronic blockade of bradykinin B_2 receptor had no BP effect in salt-loaded SS/Jr rats (Ideishi *et al.* 1994), but it permitted salt-induced BP rise in SR/Jr rats (Mukai *et al.* 1998). Polymorphism in *Klk1* gene for kallikrein 1 cosegregated with blood pressure in DS x LEW F_2 hybrids and was associated with reduced mRNA and protein kallikrein expression in the kidneys of DS rats (Iwai *et al.* 2005).

High salt intake upregulated kininogen but downregulated tissue kallikrein expression in salt-sensitive Dahl rats (Wang *et al.* 1996). The preventive delivery of human tissue kallikrein gene moderately attenuated salt hypertension development but considerably ameliorated cardiac hypertrophy and renal injury in salt-sensitive Dahl rats. The lowering of high blood pressure was ascribed to the enhanced cGMP formation (Chao *et al.* 1998a). The therapeutic delivery of human tissue kallikrein gene to Dahl rats with established salt hypertension also lowered their blood pressure and partially reversed the organ damage (Chao *et al.* 1998b). Similar effects were achieved by chronic bradykinin infusion to salt-sensitive Dahl rats fed a high-salt diet, although bradykinin infusion did not influence their blood pressure. Kinin-induced protection against renal injury was associated with increased renal NO production, reduced NADPH oxidase activity and decreased superoxide generation. Lower oxidative stress was accompanied by reduced TGF-β_1 expression and decreased phosphorylation of MAPK (Chao *et al.* 2007). Therapeutic administration of human tissue kallikrein gene caused similar changes of cell signaling as bradykinin infusion (Zhang *et al.* 2004), but there was a moderate BP reduction. These beneficial effects could be abolished by the treatment with bradykinin B_2 receptor antagonist icatibant (Bledsoe *et al.* 2006). Similarly, bradykinin B_2 receptor antagonist prevented the

therapeutic effects of long-term infusion of subdepressor doses of rat urinary kallikrein on renal injury in salt hypertensive DIS rats (Hirawa *et al.* 1999). Further studies demonstrated that the activation of bradykinin B_2 receptors and a subsequent enhanced NO formation by eNOS were involved in the renoprotective and cardioprotective effects of chronic AT_1 receptor blockade in salt hypertensive DIS rats (Yokota *et al.* 2003, Yoshida *et al.* 2007).

Atrial natriuretic peptide (ANP) exerts numerous effects on circulatory homeostasis ranging from the control of renal sodium reabsorption over the influence on aldosterone secretion control up to the vasorelaxation. Some of its effects were not altered in salt-sensitive Dahl rats because ANP-induced attenuation of aldosterone secretion (Racz *et al.* 1986) or ANP-induced relaxation of non-renal vessels (Snajdar and Rapp 1985, Simchon *et al.* 1992) were similar in both rat strains. Thus, ANP administration induced similar reduction of systemic resistance in salt-sensitive and salt-resistant Dahl rats (Simchon *et al.* 1989, 1992) and ANP-induced BP reduction was proportional to basal BP level, i.e. BP change induced by ANP was greater in hypertensive than normotensive rats (Sonnenberg *et al.* 1987).

However, one of the main abnormalities of salt-sensitive Dahl rats is the blunted renal natriuretic response to ANP (Hirata *et al.* 1984, Steele and Challoner-Hue 1988a), although some investigators failed to confirm this defect (Sonnenberg *et al.* 1987, Sterzel *et al.* 1987, Brier *et al.* 1995). In contrast to salt-resistant Dahl rats fed 1 % NaCl diet, the infusion of ANP did not cause any significant rise in renal blood flow and glomerular filtration rate in salt-sensitive rats in which no major ANP-induced rise of urinary sodium excretion was observed (Simchon *et al.* 1989). The absence of ANP-induced attenuation of renal vascular resistance in salt-sensitive Dahl rats was accompanied by the hypersensitivity of renal vascular bed to norepinephrine and angiotensin II. In addition, endothelin-1 increased renal vascular resistance in salt-sensitive rats but lowered it in salt-resistant Dahl rats (Simchon *et al.* 1992). ANP elicited much smaller rise in renal papillary blood flow in DS than in DR rats (Hirata *et al.* 1984) and there was also a reduced sensitivity of inner medullary collecting duct to ANP in terms of cGMP formation (Appel and Dunn 1987). This is in line with the decreased urinary cGMP excretion in salt hypertensive Dahl rats, although the attenuation of NO bioavailability might also contribute to this phenotype (Simchon *et al.* 1996, Trolliet *et al.* 2001).

Increased atrial content of ANP, enhanced ANP release and elevated plasma ANP levels were reported in adult salt-sensitive Dahl rats (Hirata *et al.* 1984, Snajdar and Rapp 1985, Snajdar and Rapp 1986, Tanaka and Inagami 1986, Gutkowska *et al.* 1986). It should be kept in mind that ANP content in the atria is increasing during postnatal development (Wilson *et al.* 1988) and ANP release from the atria is enhanced in adult hypertensive but not in prehypertensive SS/Jr rats (Onwochei *et al.* 1987, Onwochei and Rapp 1989). The development of hypertension in aging SS/Jr rats fed 1 % NaCl diet was associated with the increase of ANP content in both atria and ventricles (Dene and Rapp 1987). Chronic salt loading increased plasma ANP levels and brainstem ANP content in DS but not in DR rats (John and Morich 1990), whereas no significant changes of ANP content were induced by high salt intake in atria of young DS rats (Hirata *et al.* 1984, John and Morich 1990). Both preventive and therapeutic administration of L-VDCC blocker nisoldipine lowered blood pressure, attenuated cardiac hypertrophy and decreased plasma ANP levels in young salt hypertensive SS/Jr rats (Stasch *et al.* 1990). This suggests that ANP production is increasing with the progression of hypertensive cardiac dysfunction as a part of compensatory mechanisms. In fact, ANP gene delivery attenuated salt hypertension development, cardiac hypertrophy and renal injury in salt-sensitive Dahl rats (Lin *et al.* 1998).

The number of ANP binding sites detected in zona glomerulosa of adrenal gland, renal glomeruli and subfornical organ was increased in young SS/Jr rats compared to age-matched SR/Jr animals (Stewart *et al.* 1987, 1988). ANP receptor, which is coupled to guanylate cyclase (NPR-A), was considered to be a strong candidate gene for salt hypertension because it cosegregated with blood pressure in two sets of F_2 hybrids (SS/Jr x MNS and SS/Jr x WKY) fed a high-salt diet from the 5th week of age (Deng and Rapp 1992). Nagase *et al.* (1997) described the exaggerated reduction of NPR-C receptor expression induced by high salt intake in the kidneys of DIS rats and suggested that the abnormality of this "clearance" ANP receptor, which is, however, not coupled to guanylate cyclase, might be related to the impaired renal sodium excretion.

High-salt diet feeding of SS/Jr rats elevated plasma, cardiac and renal levels of adrenomedullin which is a hypotensive peptide (Shimokubo *et al.* 1996, Yoshihara *et al.* 2005). Chronic adrenomedullin infusion in salt hypertensive Dahl rats had partial preventive but

no therapeutic effects on salt hypertension, but in both cases the adrenomedullin infusion improved renal function, reduced proteinuria, restored renal NOS activity, lowered RAS activity in plasma and kidney and decreased TGF-β expression (Nishikimi *et al.* 2002, Yoshihara *et al.* 2005). Similar effects were achieved by a single delivery of human adrenomedullin gene to salt-loaded SS/Jr rats which increased cAMP levels, improved renal function, lowered blood pressure and ameliorated both renal injury and cardiac hypertrophy (Zhang *et al.* 2000). The effects of human adrenomedullin gene delivery resembled to those of human tissue kallikrein gene delivery except for the difference in cyclic nucleotides involved (cAMP for adrenomedullin vs. cGMP for kallikrein).

The role of renal dopaminergic system in genetic and salt hypertension has been reviewed in details by Zeng *et al.* (2004). Earlier studies suggested increased dopamine levels in the adrenals (Saavedra *et al.* 1983) as well as lower renal dopamine content and reduced urinary dopamine excretion (Racz *et al.* 1987, Sakamoto *et al.* 1994) in salt hypertensive Dahl rats. However, the latter findings were not confirmed by DeFeo *et al.* (1987) or Grossman *et al.* (1991). The main defect of renal dopaminergic system in SS/Jr rats is the impaired ability of renal dopamine D_1-like receptors to stimulate cAMP production and to inhibit sodium transport in particular segments of the nephron (Nishi *et al.* 1993, Hansell 1995, Ohbu *et al.* 1995). This defect seems to be due to the uncoupling of D_1-like receptors from G protein/effector complex (José *et al.* 1996). One of the consequences of such a defect is the inability to inhibit the Na,K-ATPase activity in the thick ascending limb of loop of Henle and proximal tubule of SS/Jr rats (Nishi *et al.* 1993). This explains why high salt intake downregulated the Na,K-ATPase activity only in proximal tubule of SR/Jr but not SS/Jr rats (Nishi *et al.* 1992). Although D_1-like receptors were altered in SS/Jr rats, their natriuretic response to acute volume expansion was normal at least in prehypertensive animals fed a low-salt diet (Hansell 1995, Möller and Hansell 1995), indicating the replacement of the defective dopaminergic system by other natriuretic mechanisms. Besides the above mentioned alterations in the function of D_1-like receptors, Luippold *et al.* (2001) described a defect of renal dopamine D_3 receptors in SS/Jr rats and they succeeded to elicit considerable BP elevation in SR/Jr rats fed a high-salt diet if these animals were subjected to a chronic D_3 receptor blockade.

Less attention has been paid to prostacyclin (PGI_2) in Dahl rats. The initial studies reported impaired vascular PGI_2 generation in prehypertensive DIS rats but this was not the case of salt hypertensive animals (Uehara *et al.* 1987). Prostacyclin synthase activity and PGI_2 release from mesenteric artery were similar in DIS and DIR rats fed a low-salt diet, but these parameters were increased by high salt intake in DIS rats only (Uehara *et al.* 1990). A similar enhancement of PGI_2 formation by high salt intake was also observed in the aorta of DIS rats (Ishimitsu *et al.* 1991). On the contrary, Falardeau and Martineau (1983) reported that high salt intake increased PGI_2 production only in DR rats. Later study (Bayorh *et al.* 2004) disclosed higher plasma PGI_2 levels in SR/Jr than in SS/Jr rats, but high salt intake suppressed plasma PGI_2 levels only in SR/Jr but not in SS/Jr male rats. In fact, high salt intake had quite opposite effects on PGI_2 than on NO metabolism in SS/Jr rats because it lowered plasma NO levels but did not modify plasma PGI_2 levels in this rat strain (Bayorh *et al.* 2004). This is in line with the acute blockade of PGI_2 and/or NO formation by indomethacin and/or L-NAME administration which revealed greater suppression of NO-dependent vasodilatation than PGI_2-dependent vasodilatation in salt hypertensive SS/Jr rats (Behuliak *et al.* 2011).

Attenuated β-adrenergic vasodilatation in salt hypertensive DS rats was described by Soltis and Katovich (1991), who observed a reduction of isoprenaline-induced relaxation of the aortic smooth muscle from hypertensive rats, whereas the relaxation response to sodium nitrate was unaltered. Since contractile response to KCl and α_1- or α_2-adrenergic stimulation were also unchanged in aorta of salt hypertensive Dahl rats, the enhanced smooth muscle responsiveness to norepinephrine in hypertensive rats was ascribed to a decreased β-adrenergic responsiveness (Soltis and Katovich 1991). The desensitization of adenylyl cyclase in the heart of salt hypertensive SS/Jr rats seems to be caused by the upregulation of inhibitory G (Gi) proteins as well as by a decreased activity of adenylyl cyclase (Böhm *et al.* 1993). On the other hand, Gros *et al.* (2000) reported that the impaired β-adrenergic responsiveness in lymphocytes and vascular smooth muscle of hypertensive rats was due to a defect in receptor/Gs protein coupling which was related to the increased expression of G protein-coupled receptor kinase 2 (GRK-2). This abnormality was also found in aortas of salt hypertensive SS/Jr rats. Another reason for reduced β-adrenergic signaling in the kidney of salt

hypertensive SS/Jr rats might be the increased activity of renal phosphodiesterase 4B4 which lowers cAMP-induced relaxation of renal resistance vessels (Tawar *et al.* 2008).

Recently, Toshiro Fujita and coworkers proposed that β-adrenergic mechanisms might be involved in the pathogenesis of salt hypertension through the modulation of WNK4 kinase pathway which plays a key role in the control of renal tubular sodium reabsorption (Mu *et al.* 2011). Thus the stimulation of β_2-adrenoceptors as a part of increased renal sympathetic activity in the hypertensive rats (DOCA-salt or DIS) downregulates WNK4 kinase expression which leads to the activation of Na^+-Cl^- cotransporter (NCC) and epithelial Na^+ channels (ENaC) resulting in enhanced renal tubular sodium reabsorption and salt hypertension development. On the contrary, chronic salt loading of normotensive rats (Sprague Dawley, DIR) reduced renal sympathetic nerve activity and renal norepinephrine turnover, which through a decreased β_2-adrenoceptor stimulation increased renal WNK4 kinase expression. These observations were further confirmed by the effects of renal denervation and/or β-adrenoceptor blockade (Mu *et al.* 2011).

Recent studies (Wang and Wang 2006, Gao and Wang 2010) disclosed the important role of transient receptor potential vanilloid type 1 and type 4 channels (TRPV1 and TRPV4) in salt hypertension of Dahl rats. These channels are upregulated by high salt intake in the kidneys and mesenteric arteries of salt-resistant rats, but they are suppressed by high salt intake in salt-sensitive rats. Consequently, this abnormality in salt hypertensive Dahl rats impairs their compensatory mechanisms facing salt load because BP-lowering effects of these channels are reduced. Of course, there is a considerable difference in the vasodilator action of these two TRPV channels because TRPV1-mediated vasodilatation is largely dependent on calcitonin gene-related peptide, whereas TRPV4-dependent vasodilatation is mediated by the activation of calcium-activated K^+ channels (Wang and Wang 2006, Gao and Wang 2010).

It is rather difficult to evaluate the complex role of numerous vasodilator and natriuretic systems in the pathogenesis of salt hypertension in Dahl rats because our conclusions will be highly dependent on the experimental approaches used. Some of these systems are enhanced in salt hypertensive rats (ANP, adrenomedullin, PGI_2), while the others (kallikrein, NO, dopamine, TRPV1 or TRPV4) seem to be absolutely or relatively downregulated. However, the ultimate impact of these systems on BP regulation depends on vascular and renal responsiveness to their mediators. Attenuated β-adrenergic vasodilatation and reduced natriuretic responses to ANP, NO or dopamine are characteristic examples of impaired action of these systems in salt hypertensive Dahl rats.

Cell calcium handling in salt hypertension – calcium influx and calcium sensitization

The altered influence of the above mentioned vasoconstrictor and vasodilator systems on BP regulation in salt hypertensive Dahl rats might result not only from the abnormal function of these systems but also from the alterations of cell signaling in resistance vessels. Cell calcium handling was therefore often studied in arterial smooth muscle of Dahl rats. It is always rather difficult to separate so-called primary defects of cell signaling from the changes induced by abnormal stimulation of vascular smooth muscle by various endogenous agents and/or from the consequences of high blood pressure.

Blood vessels of salt hypertensive Dahl rats were characterized by enhanced calcium uptake (Rapp *et al.* 1986, Vasdev *et al.* 1989) which was associated with augmented hypotensive response to acute nifedipine injection (Sharma *et al.* 1984). Increased vascular calcium uptake was reported to be mediated by a humoral factor present in the plasma of salt hypertensive Dahl rats (Vasdev *et al.* 1989). The relationship of this circulating factor to parathyroid hypertensive factor which is enhanced by high salt intake in plasma of salt-sensitive Dahl rats (Lewanczuk and Pang 1993) is still unclear. Vascular calcium uptake in salt-sensitive Dahl rats could be normalized by various interventions preventing the development of salt hypertension (Vasdev *et al.* 1990b, 1992).

Kazda *et al.* (1982, 1986), Fleckenstein *et al.* (1989) as well as McCaughran and Juno (1988) were the first to demonstrate the long-term beneficial effects of calcium antagonists (nifedipine, nitrendipine, amlodipine, verapamil) in salt hypertensive Dahl rats. Both preventive and therapeutic administration of these L-VDCC blockers was effective in salt-sensitive rats fed a high-salt diet, whereas no significant BP effects were induced in normotensive control groups (Kazda 1986). On the other hand, chronic administration of BAY K8644, which is a dihydropyridine agonist of L-VDCC channels, accelerated the development of fulminant salt

hypertension in SS/Jr rats, whereas no BP effects of BAY K8644 were observed in salt-loaded SR/Jr rats (Garthoff *et al.* 1984, Kazda *et al.* 1986).

Calcium antagonists (L-VDCC blockers) such as verapamil or nitrendipine increased glomerular filtration rate if the renal vascular resistance (RVR) was increased by norepinephrine pretreatment. This GFR rise was greater in the kidneys of DS rats, although RVR decrease elicited by calcium antagonists was similar in both rat strains. Nevertheless, GFR increase in DS kidney was not accompanied by the appropriate rise of Na^+ excretion which was observed in DR kidney (Steele and Challoner-Hue 1987). Similar results were obtained using *in situ* kidneys by Takenaka *et al.* (1994) who found that nicardipine enhanced renal plasma flow and GFR, improving thus the pressure-natriuresis relationship in salt hypertensive Dahl rats. The application of L-VDCC agonist BAY K-8644 increased RVR only in DS kidneys, irrespective of salt intake. This RVR increase was augmented by the 6-hydroxydopamine-induced sympathectomy of salt-loaded kidney donors, but the effect was greater in DS than in DR kidneys. L-VDCC agonist application reduced GFR in both DS and DR kidneys, but GFR decrease was most pronounced in the kidneys of salt hypertensive DS rats. This effect of BAY K-8644 was further enhanced under the conditions of chronic high salt intake (Steele and Challoner-Hue 1988b).

It is well known that membrane depolarization is responsible for L-VDCC opening, but Abel *et al.* (1981) reported that membrane potential was not altered in the caudal artery of adult salt hypertensive female DS rats and there were no changes in the contractile sensitivity to norepinephrine and serotonin. On the contrary, Fujii *et al.* (1997) demonstrated a depolarization of resting cell membrane in superior mesenteric artery of young salt hypertensive male DIS rats. Thus, L-VDCC channels in resistance vessels of these salt hypertensive rats were more available for opening near their altered resting potential (Ohya *et al.* 2000). Wellman *et al.* (2001) ascribed the membrane depolarization seen in the cerebral arteries of salt hypertensive Dahl rats to a decreased density of K^+ current mediated by voltage-dependent K^+ (K_V) channels.

The acute nifedipine administration lowered dose-dependently blood pressure of salt hypertensive SS/Jr rats and this BP reduction was proportional to basal BP level (Kuneš *et al.* 2004a, Pintérová *et al.* 2009, Zicha *et al.* 2011), suggesting a major contribution of calcium influx to the maintenance of high blood pressure in this form of experimental hypertension. However, vascular smooth muscle contraction is dependent not only on myosin light chain kinase (MLCK) pathway, which is stimulated by calcium entry through L-VDCC, but also on myosin light chain phosphatase (MLCP) pathway, which is dependent on Rho kinase activity stimulated by vasoconstrictors and atenuated by vasodilators (namely NO).

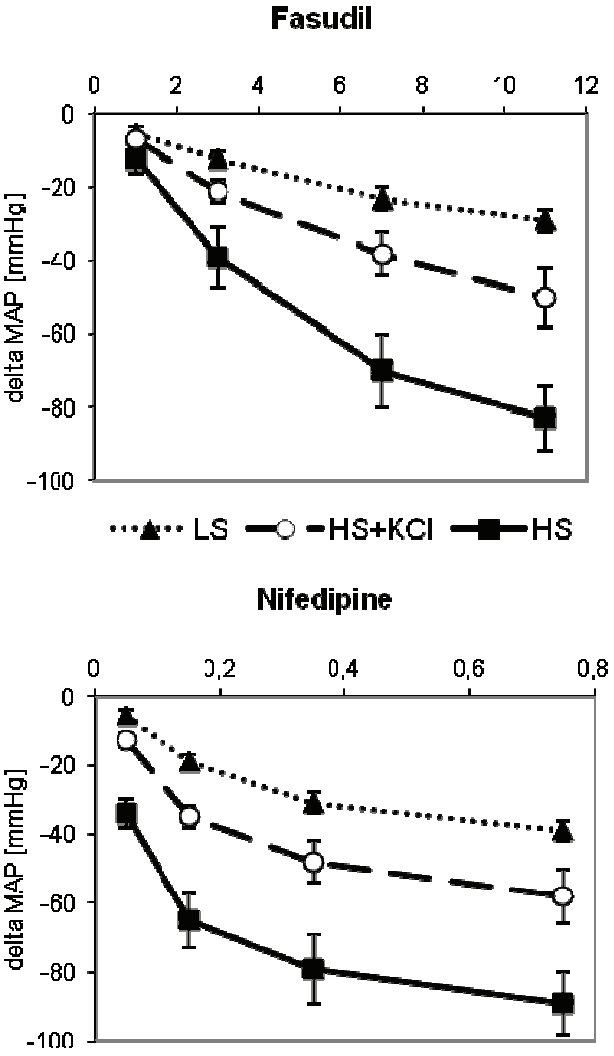

Fig. 6. A comparison of dose-dependent MAP response of young SS/Jr female rats to acute blockade of Rho kinase by fasudil (top panel) or L-VDCC by nifedipine (bottom panel). Animals fed a low-salt diet (LS, 0.3 % NaCl) were compared with those fed either high-salt diet (HS, 5 % NaCl) or potassium-supplemented high-salt diet (HS+KCl, 5 % NaCl plus 3 % KCl). Data are means ± S.E.M.

To our surprise, the same was true for the acute inhibition of Rho kinase by fasudil (Fig. 6), indicating the important role of calcium sensitization in salt hypertension. A detailed comparison of dose-dependent BP changes induced by fasudil or nifedipine (Fig. 6) revealed a more pronounced BP reduction at low

nifedipine doses. Our current explanation is that fasudil-induced BP changes could be attenuated by a compensatory increase of Ca^{2+} influx. This explanation might also be pertinent for minimal BP effects elicited by chronic administration of various Rho kinase inhibitors in salt hypertensive Dahl rats (fasudil – Nishikimi *et al.* 2004, Fukui *et al.* 2008, Takeshima *et al.* 2012; Y-27632 – Kobayashi *et al.* 2002, Satoh *et al.* 2003, Mita *et al.* 2005), although such treatments attenuated cardiac hypertrophy, heart failure or renal damage in these animals.

Further abnormalities of cell Ca^{2+} handling in vascular smooth muscle of young male salt hypertensive DIS rats were the reduction of Ca^{2+} extrusion mediated by the plasma Ca^{2+} pump and the acceleration of Ca^{2+} extrusion mediated by the Na^+/Ca^{2+} exchanger. Both parameters correlated with blood pressure – Ca^{2+} pump negatively and Na^+/Ca^{2+} exchanger positively (Ashida *et al.* 1996). Increased Ca^{2+} extrusion mediated by the Na^+/Ca^{2+} exchanger might be a compensation mechanism for increased $[Ca^{2+}]_i$ resulting from the attenuated Ca^{2+} pump activity and/or enhanced Ca^{2+} entry through L-VDCC or non-selective cationic channels. In contrast to the acceleration of Na^+/Ca^{2+} exchanger in the aorta, the activity of this transport system was attenuated in afferent but not in efferent arterioles of young salt hypertensive SS/Jr rats (Nelson *et al.* 1999), which seems to be related to a defect in protein kinase C regulation of Na^+/Ca^{2+} exchanger in mesangial cells of hypertensive animals (Mashburn *et al.* 1999).

Mesenteric arteries isolated from salt hypertensive DIS rats exhibited increased spontaneous electrical activity which was inhibited not only by Ca^{2+}-free medium or L-VDCC blocker nicardipine but also by cyclooxygenase inhibitor indomethacin or PGH_2/TXA_2 receptor antagonist. The latter two drugs did not modify membrane potential or Ca^{2+} entry through L-VDCC because PGH_2 seems to activate non-selective cationic channels in arterial smooth muscle cells of DIS rats (Fujii *et al.* 1997, Ohya *et al.* 1997). It should be kept in mind that PGH_2 acts as endothelium-derived contracting factor (EDCF) in large conduit arteries but not in small resistance arteries (Paulis *et al.* 2008) and its potentiation of vasoconstrictor effects of norepinephrine is enhanced with age and in hypertension (Líšková *et al.* 2011).

Acetylcholine-induced release of EDCF was demonstrated in the carotid and renal arteries (Zhou *et al.* 1999b, Zhou *et al.* 2001) but not in the aorta (Lüscher *et al.* 1987) of salt hypertensive Dahl rats in which it contributed to endothelium dysfunction. EDCF action can be blocked not only by indomethacin but also by the pretreatment of vessels with thromboxane synthase inhibitor OKY-046 or PGH_2/TXA_2 receptor antagonist ONO-3708 (Zhou *et al.* 1999b). Dietary L-arginine supplementation, which attenuated BP rise in salt-sensitive Dahl rats exposed to high salt intake, also abolished EDCF-mediated contraction of their renal arteries (Zhou *et al.* 2001). However, chronic administration of orally active PGH_2/TXA_2 receptor antagonist ONO-8809 neither reduced blood pressure nor improved acetylcholine-induced arterial relaxation in salt hypertensive rats (Zhou *et al.* 1999b, 2001). On the other hand, acetylcholine-induced EDCF-mediated contraction of renal arteries was also abolished by chronic ET_A receptor blockade by LU132252, which attenuated not only salt hypertension development in Dahl rats but also improved NO-dependent vasorelaxation and enhanced renal NOS activity (Barton *et al.* 2001).

It is evident that vascular smooth muscle contraction in salt hypertensive Dahl rats is enhanced due to the alterations in cell calcium handling and/or intracellular signaling. Although the increased Ca^{2+} entry through L-VDCC seems to be a dominant abnormality in this hypertensive model, further attention should be paid to possible alterations in membrane potential regulation, Ca^{2+} mobilization from internal stores, Ca^{2+} entry through other channels and Ca^{2+} extrusion from VSMC as well as to intracellular signaling *via* myosin light chain kinase or Rho kinase/myosin light chain phosphatase.

Conclusions and perspectives

Salt-sensitive Dahl rats are not only a useful model for salt hypertension research, but they also represent a challenge for the scientific mind. There are many unresolved contradictory issues which expect a future scientific effort, although a lot has already been done.

Salt hypertension is a “low-renin” form of hypertension because peripheral activity of the renin-angiotensin-aldosterone system (RAAS) is suppressed by high salt intake. Nevertheless, this is not the case of central nervous system in which the enhancement of RAAS system plays a critical role in the pathogenesis of salt hypertension (for review see Leenen 2010, Huang and Leenen 2011, Oki *et al.* 2012). Although renal epithelial sodium channels (ENaC) contribute to a greater sodium retention in salt-loaded SS/Jr rats (Husted *et al.*

1997, Amin *et al.* 2011) and brain ENaC are the integral part of central pathogenetic mechanisms responsible for sympathoexcitation and high blood pressure in salt hypertensive SS/Jr rats (Wang and Leenen 2002, Wang *et al.* 2003), the comprehensive sequence analysis of ENaC genes did not reveal any differences between SS/Jr and SR/Jr rats (Shehata *et al.* 2007). Both renal tubules and choroid plexus utilize ENaC for Na^+ influx into the cells and the Na,K-pump for Na^+ extrusion from the cells. The increased renal Na^+ reabsorption in salt hypertensive SS/Jr rats is due to the enhanced permeability of the apical membrane for Na^+, which is mediated by ENaC (Husted *et al.* 1997). In contrast, the increased Na^+ concentration in cerebrospinal fluid of these rats does not result from the enhanced Na^+ influx through ENaC, but it is caused by the failure to inhibit ouabain-sensitive Na^+ transport in the choroid plexus of salt hypertensive Dahl rats (Amin *et al.* 2009), although the increased levels of endogenous brain ouabain (OLC) were observed in both plasma and hypothalamus of salt hypertensive Dahl rats (Leenen *et al.* 1994).

Another example of such a contradiction is the fact that the acute systemic inhibition of Rho kinase by fasudil elicits similar BP effects as the acute systemic blockade of L-VDCC by nifedipine (Fig. 6). Both fasudil and nifedipine reduce blood pressure dose-dependently and proportionally to the initial BP level. The onset of BP reduction after intravenous administration is similar for both drugs, but the duration of fasudil-induced BP reduction seems to be considerably shorter. Thus high blood pressure in salt hypertensive Dahl rats can be lowered either by the normalization of calcium sensitization of the contractile apparatus by fasudil or by the reduction of calcium influx by nifedipine. Nevertheless, long-term BP reduction can be easily achieved in salt hypertensive Dahl rats by a chronic administration of L-VDCC antagonists but not by a chronic inhibition of Rho kinase. The questions arise whether the increase of Ca^{2+}entry can compensate for decreased Ca^{2+} sensitization and why there is no compensation for diminished Ca^{2+}entry. The interrelationships of MLCK and MLCP in chronic regulation of vascular tone are still not fully resolved.

Further puzzle in hypertension research is the gender difference in the severity of salt hypertension which is less expressed in salt-sensitive female Dahl rats (Dahl *et al.* 1975, Hinojosa-Laborde *et al.* 2000, Bayorh *et al.* 2001, Mazancová *et al.* 2003b). The influence of gonadal hormones (both testosterone and estradiol) is evident (Dahl *et al.* 1975, Rowland and Fregly 1992), but sex differences in the involvement of mineralocorticoids and glucocorticoids should also be considered (Gomez-Sanchez and Gomez-Sanchez 1988, Mazancová *et al.* 2003b). Female sex hormones do not exert their protective effects through renal excretory mechanisms (Hinojosa-Laborde *et al.* 2000), but they downregulated renal AT_1 receptors (Harrison-Bernard *et al.* 2003), whereas testosterone aggravates salt hypertension development through the upregulation of intrarenal RAS (Yanes *et al.* 2009). There are only very scarce data on sex differences in the hemodynamics and in the participation of particular vasoactive systems in salt hypertension of Dahl rats. Interestingly, Bayorh *et al.* (2001) reported much smaller increase of systemic resistance in female than in male salt hypertensive Dahl rats. Surprisingly, renal vascular resistance was increased in male but decreased in female hypertensive rats. As far as vasoconstrictor and vasodilator systems were concerned, the involvement of SNS was augmented in male rats compared to female ones, while no major sex differences were demonstrated in circulating levels of NO metabolites or vasodilator prostaglandins (PGI_2 or PGE_2) (Bayorh *et al.* 2001).

These are only three of many questions (local vs. systemic effects of humoral factors, detailed description of abnormalities in intracellular signaling, involvement of local RAAS in the end-organ damage etc.) which must be solved before we shall fully understand the complex pathogenesis of salt hypertension. The possibility to apply the hypertensive stimulus (increased salt intake) as well as the nutritional or pharmacological interventions in different age periods is a great advantage but also a major complication of the use of Dahl rats for hypertension research. The effects and/or consequences of particular stimuli applied within critical periods of development (developmental windows) might considerably differ from those elicited by the same interventions applied in adulthood. The detection of such differences together with the detailed knowledge on the developmental processes might provide desirable clues for better understanding of pathophysiological mechanisms underlying salt hypertension and/or its complications.

Conflict of Interest

There is no conflict of interest.

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Abreviations

$[Ca^{2+}]_i$ – cytosolic calcium level; 11β-HSD 1 – 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD 2 – 11β-hydroxysteroid dehydrogenase type 2; 20-HETE – 20-hydroxyeicosa-tetraenoic acid; ACE angiotensin converting enzyme; ACTH – adrenocorticotropic hormone; Akt – protein kinase B (serine/threonine-specific protein kinase); Ang II – angiotensin II; ANP – atrial natriuretic peptide; AT_1 – angiotensin type 1 receptor; BK_{Ca} – large conductance Ca^{2+}-activated K^+ channel; BN – Brown Norway rats; BP – blood pressure; cAMP – cyclic adenosine monophosphate; cGMP – cyclic guanosine monophosphate; CSF – cerebrospinal fluid; CYP4A – cytochrome P450-4A; DIS, DIR – Dahl/Iwai salt-sensitive and salt-resistant rats; DLF – digoxin-like factor; DOCA – deoxycorticosterone acetate; DPH – diphenylhexatriene; DS, DR – Dahl salt-sensitive and salt-resistant rats; EDCF – endothelium-derived contracting factor; EDHF – endothelium-derived hyperpolarizing factor; EETs – epoxyeicosatrienoic acids; ENaC – epithelial Na^+ channels; eNOS – endothelial NO synthase (NOS 3); ET-1 – endothelin-1; ET_A receptor – endothelin type A receptor; FE_{Na} – fractional sodium excretion; GFR – glomerular filtration rate; G_i – inhibitory G proteins; GRK-2 – G protein-coupled receptor kinase 2; G_s – stimulatory G proteins; GTP – guanosine triphosphate; HO – heme oxygenase; IMCD – inner medullary collecting duct; iNOS – inducible NO synthase (NOS 2); LEW – Lewis rats; L-NAME –N^{ω}-nitro-L-arginine methyl ester; L-NMMA – N^G-monomethyl-L-arginine; LOX-1 – lectin-like oxidized LDL receptor-1; L-VDCC – L-type voltage-dependent calcium channel; MAPK – mitogen-activated protein kinase; MBG – marinobufagenin; MCHC – mean cell hemoglobin content; MCP-1 – monocyte chemoattractant protein-1; MLCK – myosin light chain kinase; MLCP – myosin light chain phosphatase; MNS – Milan normotensive rats; MR – mineralocorticoid receptors; Na,K-ATPase – sodium, potassium adenosine triphosphatase; NADPH oxidase – nicotineamide adenine dinucleotide phosphate oxidase; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; nNOS – neuronal NO synthase (NOS 1); NO – nitric oxide; NOS – nitric oxide synthase; NPR-A – natriuretic peptide receptor A; NPR-C – natriuretic peptide receptor C (clearance receptor); OLC – ouabain-like compound; OS – ouabain-sensitive; PGE_2 – prostaglandin E_2; PGH_2 – prostaglandin H_2; PGI_2 – prostacyclin; PHF – parathyroid hypertensive factor; PI3K – phosphatidylinositol 3-kinase; PKCε – protein kinase C epsilon; PPARγ – peroxisome proliferator-activated receptor gamma; PRA – plasma renin activity; RAAS – renin-angiotensin-aldosterone system; Rac1 – Ras-related C3 botulinum toxin substrate 1 (G protein); RAS – renin-angiotensin system; RBF – renal blood flow; Rho kinase – Rho-associated protein kinase (ROCK); ROS – reactive oxygen species; RSK – ribosomal S6 kinase; RVLM – rostral ventrolateral medulla; RVR – renal vascular resistance; SERCA – sarco/endoplasmic reticulum Ca^{2+} ATPase; SGK1 – serum- and glucocorticoid-induced serine/threonine kinase 1; SHR – spontaneously hypertensive rats; SNS – sympathetic nervous system; SS/Jr, SR/Jr – Dahl/Rapp salt-sensitive and salt-resistant rats; TALH – thick ascending limb of loop of Henle; TGF – tubuloglomerular feedback; TGF-β – transforming growth factor beta; TNF-α – tumor necrosis factor alpha; TRPV1, TRPV4 – transient receptor potential vanilloid type 1 and type 4 channels; TXA_2 – thromboxane A_2; WKY – Wistar-Kyoto rats; WNK4 kinase – serine/threonine protein kinase WNK4.

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