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EDITORIAL

Cellular Sodium and Calcium in Experimental Hypertension

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There are no doubts that the alterations of sodium and calcium metabolism may participate in the pathogenesis of various forms of hypertension. In the last 15 years the attention was focused on the changes of cellular sodium and calcium handling in hypertensive humans and animals. Ion transport abnormalities due to intrinsic membrane defects and due to altered membrane regulation by numerous humoral factors were considered in both genetic and salt-dependent forms of experimental hypertension. The role of cell calcium which is directly involved in cellular mechanisms of vascular smooth muscle contraction (Heagerty and Ollerenshaw 1987, Furspan and Bohr 1988, Dominiczak and Bohr 1989) and in adrenergic neurotransmission (Tsuda *et al.* 1984, Raymond *et al.* 1990), was studied especially in spontaneously hypertensive rats (SHR). This article points out the necessity to search for detailed information about cellular aspects of calcium metabolism in various age-dependent forms of experimental salt hypertension.

1) Age-dependent salt hypertension

Young rats are more susceptible to various salt-dependent forms of experimental hypertension than the adults ones (Skelton and Guillebeau 1956, Musilová *et al.* 1966, Dahl *et al.* 1968, Kuneš and Jelínek 1984, Zicha *et al.* 1982, 1989). Contreras (1989) demonstrated that the perinatal NaCl exposure increased significantly not only blood pressure (BP) of adult rats but also their BP response to angiotensin II and isoproterenol. This work was stimulated by our recent review on the age-dependent BP response to high salt intake (Zicha *et al.* 1986) and its results are in good agreement with our observation that renin-angiotensin system was more suppressed and α_1-adrenergic contribution to BP maintenance more important in young than in adult DOCA-salt treated rats (Zicha *et al.* 1987a). Higher sensitivity of rats to hypertensive effects of increased salt intake seems to be limited to a relatively short age period (perinatal period, weaning and prepuberty) in which important maturation of haemodynamics, water and electrolyte metabolism and

neurohumoral regulation occurs. The blood pressure response of immature organism to high salt intake can only involve those regulatory mechanisms that are available at the particular stage of development. We have therefore proposed as a working hypothesis (Zicha *et al.* 1986) that a low natriuretic ability of weanling rats due to the insufficient action of atrial natriuretic factor (Bengele and Solomon 1974, Dlouhá and Křeček 1985) may augment a salt-induced secretion of other natriuretic agents. Endogenous inhibitors of Na^+,K^+-ATPase were the most likely candidates (Blaustein 1977, Haddy *et al.* 1979, De Wardener and Mac Gregor 1980, Gruber *et al.* 1980). Using a blockade of circulating digoxin-like factor by antidigoxin antibodies (ADA) according to Kojima *et al.* (1982) we observed a long-term decrease of blood pressure and systemic resistance only in young but not in adult DOCA-salt hypertensive rats (Zicha *et al.* 1984, 1985, Kuneš *et al.* 1985). The development of DOCA-salt hypertension in young rats in which elevated levels of the digoxin-like factor were reported (Kojima 1984), was attenuated by K^+-canrenoate, a digoxin antagonist (Vargas *et al.* 1989). The same was true in salt hypertension elicited in rats with reduced renal mass (De Mendonca *et al.* 1988, Pamnani *et al.* 1990). A similar age-dependent BP response to ADA injection was also found in salt hypertensive and 1K-1C renal hypertensive rats (Zicha *et al.* 1985, Pohlová *et al.* 1986) but not in SHR in which antidigoxin antibodies did not lower blood pressure prior to the age of 32 weeks (Pohlová *et al.* 1986). The latter finding agrees well with the age-dependent rise of the digoxin-like factor in SHR plasma (Wauquier *et al.* 1988). The ADA-induced haemodynamic changes were confirmed by Mann *et al.* (1987a) who discussed the specificity of the observed BP decrease in terms of a failure to elicit similar changes by the Fab ADA fragment. However, Zidek *et al.* (1989) demonstrated that the Fab fragment of antidigoxin antibodies completely blocked a humoral transmission of spontaneous hypertension in Münster rats. Furthermore, the Fab ADA fragments markedly enhanced rat renal and erythrocyte Na^+,K^+-ATPase activity (Wagener *et al.* 1989). The i.v. administration of a partially purified digoxin-like factor to anaesthetized rats substantially increased their urinary output and blood pressure (Shilo *et al.* 1989). The time course of these changes was comparable to that of ADA-induced BP fall (Zicha *et al.* 1985). Moreover, the *in vitro* treatment of digoxin-like material by antidigoxin antibody neutralized most of its biological effects (Shilo *et al.* 1989). Finally, Doris (1988) disclosed a major reduction of plasma digoxin-like activity in rats fed a high calcium diet that attenuated the development of several forms of experimental hypertension (McCarron *et al.* 1985, Peuler *et al.* 1987, DiPette *et al.* 1989).

Purified digoxin-like factors (endogenous Na^+,K^+-pump inhibitors) were reported to elevate cytosolic free calcium concentration by increasing net Ca^{2+} influx and reducing Ca^{2+} efflux in cultured vascular smooth muscle cells (Goto *et al.* 1988, 1989). They also constrict isolated arterial smooth muscle by Ca^{2+}-dependent mechanisms as well as potentiate the vasoconstrictor effects of norepinephrine and angiotensin II as evidenced by a three- to fivefold leftward shift of the respective contraction dose-response curves (Weber *et al.* 1989).

2) Endogenous sodium pump inhibitors and cation transport

Most of the evidence for cellular effects of endogenous Na^+,K^+-pump inhibitors in salt-loaded animals was obtained by observations of increased

intracellular Na^+ concentration (Na^+_i) (Wauquier *et al.* 1986, De Mendonca *et al.* 1988), reduced ouabain-sensitive Na^+ extrusion or Rb^+ uptake (Pamnani *et al.* 1978, Huot *et al.* 1983, De Mendonca *et al.* 1988) and suppressed microsomal Na^+,K^+-ATPase activity (Clough *et al.* 1984, 1985a, Chen and Shiau 1989). Our recent studies on red cell ion transport kinetics (Duhm *et al.* 1989, Duhm and Zicha 1990, Zicha and Duhm 1990ab) revealed several problems concerning the evaluation of the above mentioned proofs for Na^+,K^+-pump inhibition. Increased red cell Na^+_i in DOCA-salt hypertensive rats as well as in salt hypertensive Dahl S (DS-HS) rats is not due to the Na^+,K^+-pump inhibition but due to an increased Na^+ leak (Duhm *et al.* 1983, Zicha and Duhm 1990a). A decreased rate of partial reactions of the Na^+,K^+-pump ($^{22}Na^+_i : Na^+_o$ and $^{(86)}Rb^+_o : K^+_i$ exchanges) can mimic a reduction of ouabain-sensitive ion transport rate mediated by the Na^+,K^+-pump operating in a normal $3Na^+_i : 2K^+_o(Rb^+_o)$ mode (Duhm 1989, Duhm and Zicha 1990). This was the case of red cell ion transport alterations found in salt hypertensive rats with reduced renal mass (Zicha *et al.* 1990). Numerous measurements of ion transport or Na^+,K^+-ATPase activity were carried out under non-physiological conditions including extreme Na^+_i elevation. Such values refer rather to the maximal velocity than to the actual transport rate. A typical example is the apparent discrepancy between increased ouabain-sensitive red cell ion transport and decreased Na^+,K^+-ATPase activity in renal and cardiac microsomes of young DS-HS rats (Zicha *et al.* 1977b). A careful kinetic analysis of red cell Na^+,K^+-pump in Dahl rats revealed a combined kinetic alteration – a reduction of maximal velocity associated with an increased affinity for Na^+_i (Zicha and Duhm 1990a). Consequently, the elevated ouabain-sensitive Rb^+ uptake in erythrocytes (Zicha *et al.* 1987b, Zicha and Duhm 1990a) or vascular smooth muscle cells of DS-HS rats (Pamnani *et al.* 1980, Overbeck *et al.* 1981, Vasdev *et al.* 1988a) can be explained by a higher affinity of the Na^+,K^+-pump for Na^+_i the concentration of which was far below saturating values in intact cells. On the other hand, a reduced Na^+,K^+-ATPase activity of microsomal preparations (McPartland and Rapp 1982, Clough *et al.* 1985b, Zicha *et al.* 1987b) was revealed when inner Na^+ binding sites of the Na^+,K^+-pump were exposed to saturating Na^+_i concentrations. Indeed, a decreased Na^+,K^+-ATPase activity in the aortic endothelium and smooth muscle (Manjeet and Sim 1987)) and a lower maximal Na^+,K^+-pump rate in erythrocytes (Rosati *et al.* 1988) were reported in adult SHR in which ouabain-sensitive red cell ion transport was not altered when intra- and extracellular cation concentrations were close to *in vivo* conditions (Duhm *et al.* 1983).

Nevertheless, it is evident that salt hypertension can also occur without elevated red cell Na^+_i in young rats with reduced renal mass (Zicha *et al.* 1990) and blood pressure does not rise in old salt-loaded Dahl S animals in which red cell Na^+_i is increased (Zicha and Duhm 1990a). This suggests that more detailed information about cell free Ca^{2+} changes in tissues relevant to BP regulation (vascular smooth muscle, sympathetic neurons, etc.) is required.

The Na^+,K^+-pump inhibition causes cell membrane depolarization that alters not only Ca^{2+} influx through Ca^{2+} channels but also adrenergic tone. Thus Na^+,K^+-pump inhibitors (including endogenous factors) can rise blood pressure mainly by two Ca^{2+}-dependent mechanisms – the augmentation of vascular smooth muscle contraction caused by an increased level of cell free Ca^{2+} (Le Quan Sang *et al.* 1987, Mir *et al.* 1988, Goto *et al.* 1988, 1989) and the potentiation of vascular

noradrenergic transmission by an increased Ca^{2+}-dependent norepinephrine overflow and/or by its reduced reuptake (Oberfrank *et al.* 1988, Shima *et al.* 1988, Tsuda *et al.* 1988a, Pedrinelli *et al.* 1989). The latter action also increases cell free Ca^{2+} level mainly by opening of receptor-operated Ca^{2+} channels (Aqel *et al.* 1987ab).

3) Calcium and vascular contraction in spontaneous hypertension

Most information has been obtained in spontaneously hypertensive rats (SHR) that differ from normotensive Wistar-Kyoto rats (WKY) in both systemic and cellular Ca^{2+} metabolism (Young *et al.* 1988, Bohr and Webb 1988). Cytosolic free Ca^{2+} concentration, the rise of which plays a key role in vascular smooth muscle contraction, depends on Ca^{2+} entry through respective Ca^{2+} channels, internal Ca^{2+} mobilization and Ca^{2+} extrusion by either Ca^{2+} pump or Na^{+}-Ca^{2+} exchange (McCall 1987, Karaki and Weiss 1988, Shibata 1988).

A high resting tension of vascular smooth muscle from SHR results from an increased permeability of the cell membrane for Ca^{2+} (greater Ca^{2+} leakage) that is only partially compensated by the Ca^{2+} pump (Noon *et al.* 1978). Abnormal membrane Ca^{2+} permeability is also reflected by an augmented neurotransmitter release in sympathetic neurons (Tsuda *et al.* 1984, Yarowsky *et al.* 1985). Ca^{2+} influx in arterial smooth muscle of SHR occurs mainly *via* voltage-dependent Ca^{2+} channels (Lindner and Heinle 1987) but it is still not clear whether this abnormality concerns the number or kinetic properties of these channels or is due to an altered membrane potential. In contrast to WKY rats, a greater proportion of voltage-dependent Ca^{2+} currents is carried in neonatal SHR veins by L (long-lasting) than by T (transient) Ca^{2+} channels (Rusch and Hermsmeyer 1988, Hermsmeyer and Erne 1989). The L current seems to be the only calcium current yet identified that helps to maintain vascular smooth muscle tone by providing a continuous supply with external Ca^{2+} to sustain the vascular contraction and to replete internal Ca^{2+} stores (Bean *et al.* 1986, Sturek and Hermsmeyer 1986). Increased Ca^{2+} entry through verapamil-sensitive L channels explains a greater contraction of SHR aorta after Na^{+},K^{+}-pump inhibition (Lamb *et al.* 1988, Morita *et al.* 1988). This trait segregated with blood pressure in F_2 population of SHRxWKY hybrids (Bruner *et al.* 1986a). Vascular Ca^{2+} influx in SHR is also enhanced through "leak" and receptor-operated Ca^{2+} channels (Van Breemen *et al.* 1986). Increased Ca^{2+} entry by receptor-operated channels after a_1-adrenoceptor stimulation (Aqel *et al.* 1987a) is responsible for the increased Ca^{2+} sensitivity of SHR arteries to norepinephrine (NE) (Mulvany and Nyborg 1980, Aqel *et al.* 1986) that did not segregate with blood pressure (Mulvany 1988). SHR arteries seem to have an increased NE- and caffeine-sensitive intracellular Ca^{2+} pool (Aqel *et al.* 1987b) from which Ca^{2+} is released by inositoltriphosphate action. Phosphoinositide hydrolysis stimulated by pressor agonists is augmented in SHR vascular smooth muscle as evidenced by increased phospholipase C activity (Uehara *et al.* 1988, Remmal *et al.* 1988) leading to a greater inositoltriphosphate accumulation (Heagerty *et al.* 1986, Huzoor-Akbar *et al.* 1989, Resink *et al.* 1989) and to an increased diacylglycerol formation (Kato and Takenawa 1987). Diacylglycerol activates protein kinase C which controls Ca^{2+} influx through voltage-dependent Ca^{2+} channels. Recently Ek *et al.* (1989) suggested elevated basal protein kinase C levels in SHR arteries that are more

susceptible to protein kinase C activation by phorbol esters (MacKay and Cheung 1987, Turla and Webb 1987, Bendhack *et al.* 1988). Ca^{2+} extrusion by Na^+-Ca^{2+} exchange is also greater in SHR than in WKY arteries (Ashida *et al.* 1989) but there is reduced Ca^{2+} pump activity in SHR vessels (Bhalla *et al.* 1978, Kwan *et al.* 1980). Altered activity of calmodulin-modulated Ca^{2+} pump and reduced Ca^{2+} binding to plasma membranes were also observed in erythrocytes and other tissues of SHR (Devynck *et al.* 1981ab, 1982, Postnov and Orlov 1984, David-Dufilho and Devynck 1985, Kowarski *et al.* 1986, Adeyoa *et al.* 1989).

Consequently, the above mentioned abnormalities of SHR Ca^{2+} handling in SHR result in the elevation of intracellular free Ca^{2+} ($Ca^{2+}{}_i$) levels in various blood cells (Bruschi *et al.* 1985, Le Quan Sang *et al.* 1985, Furspan and Bohr 1986, Orlov *et al.* 1988, Vasdev *et al.* 1988b) and vascular smooth muscle cells (Sugiyama *et al.* 1986, Jelicks and Gupta 1990). Increased $Ca^{2+}{}_i$ helps to explain the decreased plasma membrane fluidity found in SHR (Montenay-Garestier *et al.* 1981, Orlov *et al.* 1982, Tsuda *et al.* 1988bc). The activation of Ca^{2+}-dependent K^+ channel (Gardos effect) by elevated $Ca^{2+}{}_i$ is responsible for an increased K^+ efflux from arteries during norepinephrine stimulation (Smith and Jones 1985, Magliola and Jones 1987). This alteration of vascular smooth muscle ion transport in SHR arteries (Jones 1973) is a cause of NE-induced oscillatory contractile activity (Mulvany *et al.* 1980, Lamb *et al.* 1985, Bruner and Webb 1989) that segregated with blood pressure in the F_2 SHRxWKY population (Bruner *et al.* 1986b, Mulvany 1988). The elevation of Ca^{2+}-dependent K^+ efflux was also demonstrated in SHR erythrocytes (Orlov *et al.* 1989) and lymphocytes (Furspan and Bohr 1986). Lymphocyte K^+ efflux closely correlated with blood pressure of F_2 hybrids (Furspan *et al.* 1987).

Some of these effects can be related to the occurrence of endogenous factors that increase blood pressure through a modulation of Ca^{2+} uptake. A peptide that was isolated from SHR red cells causes a long-term BP elevation (McCumbee and Wright 1985, Wright *et al.* 1988) and increases Ca^{2+} uptake by aortic segments *in vitro* (McCumbee *et al.* 1987). A similarity of its effects to those of Bay K 8644 (Huang *et al.* 1988) suggests that it may act as an endogenous modulator of voltage-dependent Ca^{2+} channels (Simmons *et al.* 1989). The administration of antibodies directed against this peptide lowered blood pressure effectively in both SHR and normotensive Sprague-Dawley rats but BP reduction was more pronounced and persisted much longer in SHR animals (Todd *et al.* 1989).

A "parathyroid hypertensive factor" (PHF) that was recently described in SHR plasma (Pang and Lewanczuk 1989) elicits a slow long-lasting pressor response, potentiates other vasoconstrictor agonists and stimulates Ca^{2+} uptake to the tail artery *in vitro* (Lewanczuk and Pang 1989, Lewanczuk *et al.* 1989). PHF levels were suppressed by high Ca^{2+} intake (Lewanczuk *et al.* 1990a) so that this peptide could mediate BP lowering effects of high calcium diet in SHR (Ayachi 1979, McCarron 1982, McCarron *et al.* 1985). Though chronic Ca^{2+} loading did not always decrease vascular reactivity in SHR (Kageyama *et al.* 1986, Bukoski and McCarron 1986, Stern *et al.* 1987, Bukoski *et al.* 1989), a high calcium diet lowered blood pressure, $Ca^{2+}{}_i$ and K^+ efflux in SHR lymphocytes (Furspan *et al.* 1989). A similar humoral factor increasing $Ca^{2+}{}_i$ in vascular smooth muscle was demonstrated in genetically hypertensive rats of the Münster strain (Losse *et al.* 1984, Zidek *et al.* 1986).

The importance of such humoral factors is underlined by the fact that circulating factors increasing $Ca^{2+}{}_i$ in platelets and neutrophils were also reported in essentially hypertensive patients (Banos *et al.* 1987, Lindner *et al.* 1987, Zidek *et al.* 1988). PHF levels were found to be elevated especially in low-renin and salt-sensitive hypertensive patients (Lewanczuk *et al.* 1990b, Resnick *et al.* 1990), in which increased lymphocyte $Ca^{2+}{}_i$ concentrations (Oshima *et al.* 1988ab) and high levels of a factor sensitizing to norepinephrine and angiotensin pressor effects (Mizukoshi and Michelakis 1972) were observed.

4) Calcium in salt-induced hypertension

The information on cellular Ca^{2+} metabolism in salt hypertension is less precise than that in SHR. Available data also indicate some important differences among particular hypertensive models.

In contrast to SHR neither the membrane potential nor norepinephrine sensitivity were altered in vascular smooth muscle of Dahl salt-sensitive (DS) rats with salt hypertension or DOCA-salt hypertensive rats (Abel *et al.* 1981, Hermsmeyer *et al.* 1982). Ca^{2+} pump activity was reduced only in vascular smooth muscles of DOCA-salt treated animals (Kwan *et al.* 1980) but not in salt hypertensive DS (DS-HS) rats (Kwan *et al.* 1986). On the other hand, the Ca^{2+} pump in non-vascular smooth muscle was lower only in DS-HS but not in DOCA-salt hypertensive rats (Kwan and Grover 1983, Kwan *et al.* 1986). Similarly to SHR Ca^{2+} uptake was also elevated in the aorta of DS rats due to an increased Ca^{2+} influx through both voltage-dependent and receptor-operated Ca^{2+} channels (Rapp *et al.* 1986). The difference to salt-resistant Dahl (DR) rats rose with the age and was augmented by high salt intake and renal mass reduction (Rapp *et al.* 1986). A higher Ca^{2+} influx through voltage-dependent Ca^{2+} channels in DS-HS rats can be documented by greater effects of dihydropyridine Ca^{2+} antagonists (Sharma *et al.* 1984, Kazda 1986, Garthoff and Bellemann 1987, Steele and Challoner-Hue 1987) and Ca^{2+} channel agonist Bay K 8644 (Garthoff *et al.* 1984, Steele and Challoner-Hue 1987) on blood pressure and renal vascular resistance of salt-loaded DS than DR rats. A higher Ca^{2+} influx is reflected by an elevation of $Ca^{2+}{}_i$ in platelets of DS-HS animals which is absent in DR-HS rats (Vasdev *et al.* 1988b). Though $Ca^{2+}{}_i$ elevation was not observed in platelets of DOCA-salt hypertensive rats (Murakawa *et al.* 1986, Baba *et al.* 1987), an increased sarcoplasmic Ca^{2+} content was detected in their aortas (Nickerson and Yang 1988). Ca^{2+} antagonists prevent DOCA-salt hypertension (Hall and Hungerford 1983, Otipka *et al.* 1987) by lowering of spontaneous vascular smooth muscle tone due to a blockade of Ca^{2+} influx through stretch-operated Ca^{2+} channels (Rinaldi and Bohr 1989). High Ca^{2+} influx is associated with an augmented phosphoinositide metabolism in blood vessels of mineralocorticoid-salt hypertensive rats (Eid and De Champlain 1988, Jones *et al.* 1988).

Higher $Ca^{2+}{}_i$ in vascular smooth muscle of hypertensive rats (as a consequence of greater Ca^{2+} influx through voltage-dependent Ca^{2+} channels) elevates basal K^+ and Cl^- efflux as well as Na^+ influx through the respective Ca^{2+}-dependent channels. These alterations which are manifested as an increased turnover of the above mentioned ions can be abolished by Ca^{2+} antagonists (Smith and Jones 1990, Smith *et al.* 1989). An early increase of Na^+ permeability observed

in arteries of DOCA-salt treated rats seems to be related to the onset of the hypertensive process (Friedman and Tanaka 1987, Friedman *et al.* 1988). A characteristic increase of the steady-state K^+ turnover was observed in arteries of SHR (Jones 1973), DOCA-salt and aldosterone-salt hypertensive rats (Jones *et al.* 1977, Garwitz and Jones 1982) as well as in salt hypertensive rats with reduced renal mass (Chi *et al.* 1986). Agonist stimulation of vascular smooth muscle causes an additional Ca^{2+} entry *via* receptor-operated Ca^{2+} channels which further augments K^+ efflux. An increased stimulation of aortic K^+ turnover by norepinephrine was demonstrated in all the above mentioned hypertensive models as compared to respective controls (Jones 1973, Jones *et al.* 1977, Garwitz and Jones 1982, Chi *et al.* 1986). Surprisingly, no significant changes in K^+ turnover or its stimulation by norepinephrine were found in salt hypertensive DS rats (Smith and Jones 1983). There is an interesting age-dependent decrease of NE-activated $K^+(Rb^+)$ efflux in rat arteries until the age of 6 months (Cox and Tulenko 1989), at which high salt intake fails to elicit hypertension in rats with reduced renal mass or in DS rats (Zicha and Duhm 1990a, Zicha *et al.* 1990).

A high calcium diet that was reported to decrease parathyroid hypertensive factor (PHF) levels in SHR (Lewanczuk *et al.* 1990a), lowers blood pressure in both DOCA-salt (Kageyama *et al.* 1987, DiPette *et al.* 1989, Yang *et al.* 1989) and DS-HS rats (Peuler *et al.* 1987, Kuneš *et al.* 1988). Increased PHF levels were disclosed in DOCA-salt hypertension (Lewanczuk and Pang 1990) but at present there are no direct data concerning the presence of PHF in DS-HS rats in which humoral hypertensive factors were described earlier (Dahl *et al.* 1969, Tobian *et al.* 1979, 1982). However, the serum of salt hypertensive Sprague-Dawley and Dahl S rats (Self *et al.* 1976, Hirata *et al.* 1984) potentiated norepinephrine pressor action similarly to the effects exerted by SHR serum (Battarbee *et al.* 1981, Wright 1981, Lewanczuk and Pang 1989). Parathyreoidectomy decreases blood pressure and vascular norepinephrine hypersensitivity not only in SHR (Gairard *et al.* 1982, Schleiffer *et al.* 1986, Mann *et al.* 1987b, Pang and Lewanczuk 1989) but also in DOCA-salt rats (Berthelot and Gairard 1978, Gairard *et al.* 1982) and rats with reduced renal mass (Zimlichman *et al.* 1984).

As shown above, the most detailed information on cellular Ca^{2+} metabolism was derived from a simple comparison of SHR and WKY rats although much more sophisticated genetic analysis is required to prove the association of observed Ca^{2+} abnormalities with blood pressure (Rapp 1987). The use of inbred Dahl salt-sensitive (DS) and salt-resistant rats with age-dependent salt hypertension offers a possibility to study the role of both genetic predisposition and NaCl intake under the conditions in which high salt diet induces fulminant (young), moderate (adult) or negligible BP response (old animals). The age-dependent response of DS rats to a high salt intake might indicate profound differences in blood pressure regulating mechanisms. Indeed, blood pressure reduction induced by chronic Ca^{2+} supplementation was observed only in young but not in adult Dahl salt-sensitive rats (Kuneš *et al.* 1988). The present information on cellular Ca^{2+} metabolism in salt-dependent hypertension is relatively modest and should be completed before further conclusions about the role of Ca^{2+} in experimental hypertension will be drawn.

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