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Regulation of sodium and body fluid homeostasis during development: Implications for the pathogenesis of hypertension

R. F. Kirby and A. K. Johnson

Departments of Psychology and Pharmacology, and the Cardiovascular Center, University of Iowa, Iowa City (Iowa 52242, USA)

Abstract. The spontaneously hypertensive rat (SHR) is an important animal model of human essential hypertension. During the first month of life, increased retention of sodium is present in the SHR which appears to be mediated by the renin-angiotensin system. The present review will discuss the role that increased activity of the renin-angiotensin system plays in sodium/body fluid regulation during early development. It is hypothesized that disordered regulation of sodium/body fluid homeostasis during this stage leads to pathological cardiovascular regulation in adulthood. Through an understanding of the relationship between sodium/body fluid balance in the young and cardiovascular function in the adult insights may be gained into both the pathological state of hypertension and the critical role played by early development in shaping homeostatic mechanisms in adulthood.
Key words. Renin-angiotensin; development; hypertension; SHR.

The present review will explore the role that activity of the renin-angiotensin system (RAS) during preweaning development may play in the etiology of high blood pressure in the spontaneously hypertensive rat (SHR). The period of early development has been shown to be a critical age for establishing set points of both humoral and neurotransmitter regulation in adulthood. Investigations by Ira Black and his associates on the development of the autonomic nervous system led to the proposal that preweaning development serves as a stage of 'modulation' in which activity of the system acts to determine adult function[2]. This hypothesis also appears to be appropriate for the influence of preweaning environmental variables upon adult cardiovascular homeostasis.

Manipulations limited to the preweaning period of development produce permanent reductions in arterial pressure in several animal models of high blood pressure, or hypertension. For example, rearing of genetically hypertensive rat pups by normotensive foster mothers results in 20–25% reductions in adult blood pressure[22]. Therefore, research on the role of developmental factors in hypertension is presently challenged to identify the physiological mechanisms that mediate permanent changes in arterial pressure. The results from such studies will first provide critical information on the pathological state of hypertension, and second, insights will be gained into the broader question of how early development can shape adult function.

Two systems that play critical roles in the maintenance of cardiovascular and body fluid homeostasis are the sympathetic nervous system and the renin-angiotensin system (RAS). In the adult animal, their influences have been well characterized and a wide variety of tools are available with which to selectively intervene in each system. This provides a valuable framework for investigations in the developing animal. In addition, previous studies[16, 17, 23, 24, 35, 37, 38] have demonstrated that the sympathetic nervous system and RAS begin to show adult-like characteristics of central neural control during the preweaning period of development. Thus, the role of

these systems in the regulation of cardiovascular function and body-fluid balance is in a dynamic state of change. Finally, experimental evidence supports the conclusion that the sympathetic nervous system and the RAS are involved in the maintenance of high blood pressure in adult SHR. Taken together this information leads to the question of how might the activity of these systems during preweaning development, either individually or together, contribute to the altered blood pressure regulation in adult life.

In the following section, a brief overview will be provided of the mechanisms by which the RAS and the sympathetic nervous system regulate sodium/body fluid balance to achieve cardiovascular homeostasis in the adult. With these mechanisms in mind, the focus will then turn to three specific developmental processes: a) sodium/volume regulation, b) the RAS, and c) sympathetic control of the RAS. We will then attempt a synthesis of these processes and discuss their possible role in the pathogenesis of high blood pressure in the SHR.

Sympathetic nervous system and RAS regulation of blood pressure in the normotensive adult rat

The extent of vasoconstriction in blood vessels is the result of the actions of many factors that act to establish the tone of the vascular smooth muscle[4]. The influences which determine vascular tone originate 1) locally from the vessel itself (e.g., endothelin; endothelial-derived relaxing factor), 2) from sympathetic nerves that innervate the vessels (e.g., norepinephrine; neuropeptide Y), or 3) from the systemic circulation (e.g., epinephrine; angiotensin II). Of the mechanisms discovered to promote vascular constriction, the sympathetic nervous system and the RAS are the most prominent.

The nerves of the sympathetic nervous system that innervate vascular smooth muscle arise from the thoracolumbar chain and run along the periphery of blood vessels until penetrating the vessel to terminate primarily at the adventitial-medial junction. Norepinephrine is released from the postganglionic sympathetic terminals to act on postsynaptic adrenoceptors. Second messenger mechanisms activated through postsynaptic alpha-1 adrenoceptors produce smooth muscle contraction through a process of second messenger-related events that involves the release of intracellular calcium.

The primary effector hormone of the RAS is the octapeptide angiotensin II. Circulating angiotensin II is generated as a result of renin being released from the kidney which is the rate-limiting step in a series of enzymatic cleavages that lead to formation of the effector peptide. Renin released from the juxtaglomerular cells of the kidney is under the control of three mechanisms. Two of these are local, intrarenal mechanisms, and the third is an extrarenal mechanism that depends upon activation of the sympathetic nervous system. The first intrarenal mechanism is activated by a reduction of sodium in the initial part of the distal tubule, and the second is related to a local baroreceptor mechanism that senses reduced renal perfusion. Extrarenal control derives from increased delivery of postganglionic sympathetic nerve norepinephrine and/or of circulating norepinephrine and epinephrine released from the adrenal medulla. The adrenoceptor subtype regulating renin release from the juxtaglomerular cells is the beta-1 receptor.

Exogenous angiotensin II delivered to the systemic circulation produces a marked pressor response due to a constriction of resistance vessels. On a molar basis, angiotensin is about 40 times more potent than norepinephrine as a pressor agent. The elevation of circulating angiotensin results in an increase in blood pressure within 10–15 s that can be maintained for days or weeks without signs of tachyphylaxis. In addition to its direct vascular action, angiotensin II enhances the release of norepinephrine from nerve terminals innervating various vascular beds[20] which reinforces its role as a potent vasoconstrictor. This type of facilitative interaction between the RAS and the sympathetic nervous system is a biologically appropriate response as both of these systems are activated under many of the same physiological states or environmental conditions. For example, hypovolemia, hypotension and hypoglycemia as well as various external stressors (psychosocial stressors such as threat or conflict) have been demonstrated to be effective stimuli for simultaneous sympathetic activation and renin release.

In addition to the acute pressor actions of the RAS and the sympathetic nervous system, as a result of their actions on vascular smooth muscle, both of these systems play important roles in the determination of extracellular fluid volume, a component of body fluid homeostasis that has been extensively implicated in the long-term regulation of blood pressure and in hypertension[13]. Angiotensin II promotes several actions that are consistent with fluid retention in the interstitial and vascular spaces. Specific examples of control systems responsible for maintaining fluid balance that may be activated by angiotensin II in physiological or pathophysiological states are: 1) sodium retention through the release of aldosterone and through a direct action of angiotensin II in the kidney, 2) water retention as a result of the stimulation of antidiuretic hormone release, 3) increased water intake (thirst) due to an action of angiotensin II on the subfornical organ and 4) enhanced sodium appetite which is, in all likelihood, due to an action of the peptide on the brain. At the present time, the sympathetic nervous system has not been directly implicated in as many effector mechanisms for the expansion of extracellular volume as the RAS. However, the demonstrated role of renal sympathetic activation which stimulates renin release and promotes sodium and water reabsorption from the distal tubule are important determinants of body fluid homeostasis.

In summary, the RAS and sympathetic nervous system act through a wide variety of ways to maintain cardiovas-

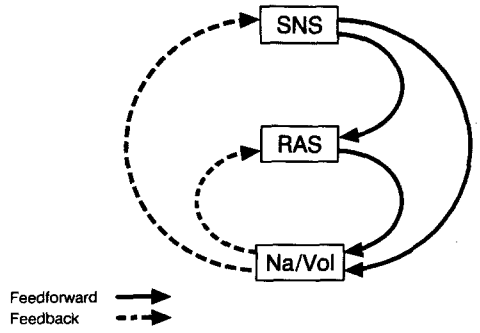

Figure 1. The role of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) in the regulation of sodium/volume balance. The SNS and RAS act in a feedforward manner to increase the amount of sodium/volume maintained by the animal through both independent and interactive mechanisms. The activity of these systems is then inhibited by feedback mechanisms from sodium/volume sensors to maintain the appropriate balance.

cular homeostasis in the adult animal. The two systems may act independently, although in a synergistic manner, to increase the bodily stores of sodium and water. In addition, sympathetic nerves innervating the kidney act as a principal regulator of the RAS. The activity of both of these systems then is regulated to maintain sodium/volume homeostasis in a feedback loop as depicted in figure 1. We propose that it is the process of adjusting this setpoint early in development that may be critical for determining whether cardiovascular homeostasis is maintained within normal or pathological (i.e., hypertensive) ranges in the adult animal.

Sodium and volume regulation in young WKY and SHR

During the preweaning period of development, SHR pups are suckled on milk that contains a greater amount of sodium, or a greater sodium/potassium ratio, than that ingested by WKY[5] or Sprague-Dawley pups[10]. Cross-fostering SHR offspring to either of these normotensive strains during the preweaning period leads to a reduction in adult pressure[1,5,25], and the maternal environment can also influence cardiovascular sensitivity to alterations in dietary sodium in later life[3]. However, WKY or Sprague-Dawley pups reared by SHR do not have increased blood pressures in adulthood[5,25], indicating that the increased blood pressure of SHR raised by SHR dams involves an interaction between altered maternal care/diet and genetic predisposition. An important factor in this regard may be the diminished natriuretic capacity of young SHR. Total body sodium of SHR is elevated from the first postnatal week through adulthood compared to WKY[15]. Young SHR (age 4–5 weeks) retain four-fold more sodium than WKY despite similar intakes and absorption. The most extensive metabolic studies on developing WKY and SHR were performed by Beierwaltes and colleagues[1] beginning at 3 weeks of age and continuing to adulthood. Despite similar intakes, sodium excretion and fractional sodium excretion were less in SHR throughout the second postnatal month of life, leading to an elevated sodium balance during this time. These differences diminished as the animals matured, and no differences in sodium balance were found between the strains from postnatal week 9 through adulthood, i.e., at the time frank hypertension became evident in the SHR. In addition to the differences in daily sodium balance, natriuretic and diuretic responses to an acute challenge, such as volume loading, are also diminished in young SHR[31,32]. Sodium and water excretion of 4–5-week-old SHR were only 50% of the response of WKY to an oral isotonic volume load during the acute testing period. However, by 10 weeks of age the response of SHR and WKY was equivalent. Thus, in the prehypertensive stage SHR both receive and retain more sodium than WKY. It is possible that the increased level of total body sodium or the increased rate of sodium turnover in prehypertensive SHR may establish a higher set point for total body sodium/fluid volume in SHR that persists into adulthood and is responsible for the hypertension that is characteristic of this strain.

The RAS in young WKY and SHR

Increased activity of the RAS in the kidney may play a major role in the retention of sodium in young SHR. Sinaiko and Mirkin[33] were the first to report that renal renin activity was greatly elevated in SHR relative to WKY during the preweaning period. This difference was not present during the fetal period, but was first found to be significantly elevated at the time of birth and through the preweaning period. By the fourth postnatal week, renal renin levels decreased for SHR and were again equal for the two strains. The greater levels of renal renin in SHR, and their decrease with maturation, has recently been replicated by Gomez and co-workers[12], who also found that expression of mRNA for angiotensinogen, the renin substrate, was elevated on postnatal day 2 in SHR compared to WKY. In addition to elevated angiotensinogen and renal renin, levels of angiotensin I and II, and angiotensin II binding sites on brush border membranes in the kidney are increased in prehypertensive SHR compared to WKY[21].

One explanation for the increased sodium retention of young SHR may be the influence of the kidney RAS on renal hemodynamics. Increased activity of the RAS during early development leads to altered renal function in 4-week-old SHR[31]. Renal vascular resistance is increased and renal blood flow and glomerular filtration rate are decreased in SHR compared to WKY at this age. Treatment with the angiotensin converting enzyme inhibitor, MK421, causes renal vascular resistance to decrease and renal blood flow to increase to a greater degree in SHR than WKY[31]. Together, the increased kidney levels of angiotensin II, increased number of angiotensin II binding sites, and diminished renal blood flow and glomerular filtration rate would be expected to

lead to greater sodium retention in young SHR than WKY. The increased retention of sodium would be especially deleterious for blood pressure regulation in SHR because of the increased sodium content and sodium to potassium ratio in the milk of their mothers.

Recently, we have begun to address two specific questions concerning the RAS during the postnatal period in SHR. First, is there an altered sensitivity of the RAS in SHR to variations in dietary sodium? This question stems from the increased activity of the RAS during early development in SHR in the face of elevated sodium in their dams milk and a sodium retention. Second, does activity of the RAS during the postnatal period lead to increased blood pressure in adulthood? Studies related to this question explain the long-term consequences of the elevated RAS activity in SHR during preweaning development on adult blood pressure.

The increased activity of the RAS evidenced by young SHR while retaining sodium and receiving increased dietary sodium from their dam's milk indicates an altered sensitivity of control mechanisms for the RAS. To investigate the responsiveness of the RAS in the preweaning WKY and SHR, alterations in dietary sodium chloride were made during the preweaning period [19]. To manipulate dietary sodium, the technique of artificial rearing by gastrostomy [14, 26] is used to allow rearing of isolated rat pups with complete control over their dietary intake between 6 and 18 postnatal days of age. A probe for the renin gene is then used to assess activity of the RAS. Using these techniques, artificially reared WKY pups are found to make appropriate corrections in the expression of the renin gene in response to altered dietary sodium. However, no increases or decreases in renin gene expression have been found to alterations in dietary sodium in artificially reared SHR compared to their normally reared controls. These data indicate that in the preweaning stage of development, SHR pups may be unable to suppress activity of the RAS to appropriately correct for the elevated sodium which they receive in the milk from their dams.

To address the long-term consequences of increased activity of the RAS during preweaning development on adult blood pressure in the SHR, animals were administered a selective antagonist of the RAS (DuP 753; 10 mg/kg) or a vehicle injection daily on postnatal days 10 through 20. Direct measures of arterial pressure were then recorded at 90 days of age and the arterial pressure response to bolus doses of angiotensin II tested. Animals administered the angiotensin receptor antagonist during early development had significantly lower arterial pressure in adulthood when compared to their vehicle-injected littermate controls (fig. 2). However, there was no difference in the blood pressure response of these animals to the administration of angiotensin II. Consistent with a decreased fluid retention, preweaning body weight was significantly decreased in animals receiving the antagonist. However, by 90 days of age weights were equivalent between the groups. These results are the first to indicate that activity of the RAS during a limited period in postnatal development can determine adult pressure in SHR.

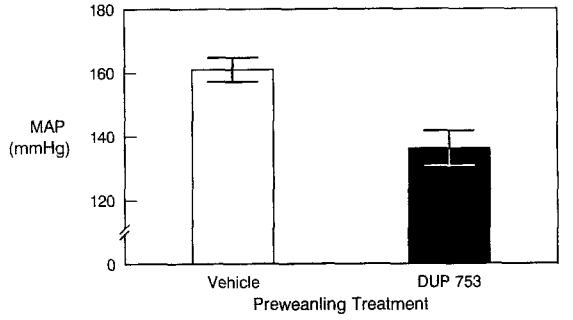

Figure 2. Adult blood pressures of spontaneously hypertensive rats (SHR) administered vehicle or the selective angiotensin II receptor antagonist DuP 753 during preweaning development. Blockade of angiotensin II receptors limited to the preweaning period produced a long-term decrease in mean arterial pressure (MAP) in SHR. (Kirby, Nanda, Henry and Johnson; unpublished observations).

Sympathetic control of the RAS in the developing rat

One possible mediating mechanism that could act to stimulate activity of the RAS during early development in the SHR would be increased sympathetic nervous system activity. Increased sympathetic drive to the kidney during the preweaning period would stimulate renin release to increase sodium retention, directly increase sodium reabsorption, and indirectly increase sodium retention by interacting with non-neural mechanisms that regulate sodium excretion.

Renal norepinephrine content, which serves as an index of sympathetic neural innervation, increases from the time of birth until 3–4 months of age. However, norepinephrine concentration remains fairly constant in the first two postnatal weeks, then doubles to reach adult levels during the third postnatal week [34, 36]. At the time of birth, fine fluorescent fibers may be identified about the large arteries in the cortex. Innervation then surrounds the vessels as the animals mature to reach a 'fully developed pattern' during postnatal week 2. The increase in sympathetic terminals and norepinephrine content during the second and third postnatal weeks is accompanied by a four-fold increase in renal norepinephrine turnover, which reaches adult levels at this time. These findings indicate a shift to adult-like sympathetic innervation of the kidneys during the second to third postnatal week in the normotensive rat.

A recent report by Gattone and coworkers [11] indicates that sympathetic innervation of the kidneys is accelerated in SHR during development. Renal norepinephrine content was significantly greater in SHR than in WKY at 1, 2 and 3 weeks of age. The use of histofluorescence to demonstrate the anatomical localization of sympathetic nerves revealed that the nerves were present throughout the renal cortex by 2 weeks of age in both strains. How-

ever, the innervation spread throughout the kidneys more rapidly during development in SHR. These data indicate that sympathetic nerves could begin to influence renal function prior to 2 weeks of age in SHR.

The development of renal adrenoceptors provides an indication of when sympathetic innervation may begin to affect specific renal functions. Binding sites for the alpha-2 adrenoceptor, which has been proposed to influence sodium reabsorbtion, develop into two subpopulations during the postnatal period [36]. High affinity binding sites are present prior to the time of birth. However, low affinity binding sites are not present until postnatal day 3. Both binding sites increased in density from postnatal days 7 to 21, but their affinity remained unchanged. In contrast, the major developmental increase in renal beta adrenoceptors occurs during a more limited period slightly later in development. Beta-adrenoceptor concentration increases four-fold between postnatal days 10 and 20 [34]. The increase in receptor number occurs without a change in affinity between birth and adulthood. The large increase in beta-adrenoceptors, at the time that renal noradrenergic stores undergo their greatest increase, may play an important role in the ability of sympathetic innervation to stimulate renin release.

To investigate developmental aspects of sympathetic control of renin release from the kidney in the normotensive rat, we have used a pharmacological approach to increase sympathetic drive to the kidney [17]. Stimulation of sympathetic nervous system activity led to an age-dependent stimulation of plasma renin activity during the preweaning period. Sympathetic activation produced limited increases in plasma renin activity in 5- and 10-day-old animals, and marked increases by 15 and 20 days of age. Figure 3 depicts the plasma renin activity response to a beta-1 adrenoceptor agonist, prenalterol, during the preweaning period. A dose response relationship to prenalterol treatment was not found in 5- and 10-day-old rats, with minimal stimulation of plasma renin activity even at the highest drug doses used. As the animals matured to 15 and 20 postnatal days of age, the ability of direct beta-1 adrenoceptor activation to stimulate plasma renin activity increased and a dose response relationship was established, consistent with the rapid increase in beta adrenoceptor binding reported by Slotkin and coworkers [34]. These data indicate that the ability of sympathetic drive to the kidney to influence renin release is limited during early preweaning development in the normotensive rat.

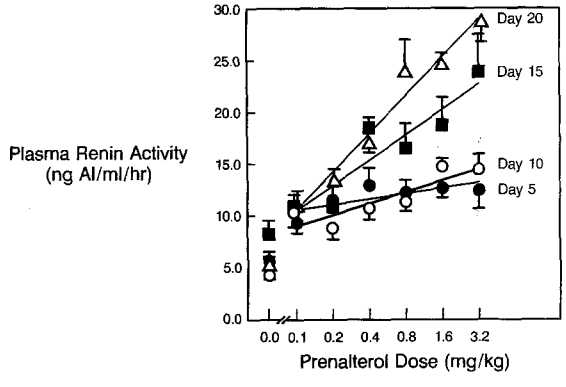

Figure 3. The effects of beta-1 adrenoceptor stimulation with prenalterol on plasma renin activity during preweaning development in normotensive rat pups. As the animals matured to 15 and 20 postnatal days of age, there were greater increases in plasma renin activity following administration of the beta-1 adrenoceptor agonist. These data indicate that the ability of the sympathetic nervous system to stimulate the renin angiotensin system is limited during early development, but matures rapidly during the second and third postnatal weeks of life. (Data redrawn from Kirby and Johnson, J. Pharmac. exp. Ther. *253* (1990) 152–157).

Sympathetic control of the RAS in the developing WKY and SHR has not specifically been addressed. However, a wide number of studies have demonstrated altered sympathetic development in SHR. The ontogeny of sympathetic innervation to peripheral target tissues regulating cardiovascular function, such as the kidneys [11] and the heart [23] is accelerated. The level of tonic sympathetic drive regulating cardiovascular function is elevated in SHR beginning in the first postnatal week, as evidenced by an increased sympathetic contribution to resting heart rate [38] and blood pressure [35]. Phasic increases in sympathetic drive to the periphery are greater in the preweaning SHR [24, 29]. Each of these alterations in sympathetic development could have important implications towards renal function in the preweaning SHR.

The cardiovascular response to suckling in preweaning WKY and SHR serves as an example of how increased sympathetic drive would stimulate the RAS to increase sodium retention. During suckling, there are rapid and pronounced increases in blood pressure mediated by the sympathetic nervous system that are greater in SHR than WKY [29, 30]. This increase in blood pressure should lead to pressure-induced natriuresis/diuresis [8, 9]. However, the greater increase in efferent renal sympathetic nerve activity of SHR would blunt the natriuretic/diuretic response and would produce greater activation of the RAS. Together, these responses would lead to increased sodium retention in the face of increased dietary sodium in SHR milk.

Summary and working hypothesis: Role of the RAS and sympathetic nervous system in hypertension in SHR

In this review, the following evidence has been presented: 1) The sodium content and sodium to potassium ratio is elevated in the milk of SHR dams. 2) Sodium retention and total body sodium are elevated in young SHR. 3) Activity of the renal RAS is elevated in prehypertensive SHR. 4) Sympathetic drive to peripheral target tissues is elevated in SHR during preweaning development and renal innervation matures earlier in SHR. 5) Blockade of the RAS between postnatal days 10 and 20 reduces adult blood pressure in SHR. Taken together, these findings suggest that increased activity of the sympathetic

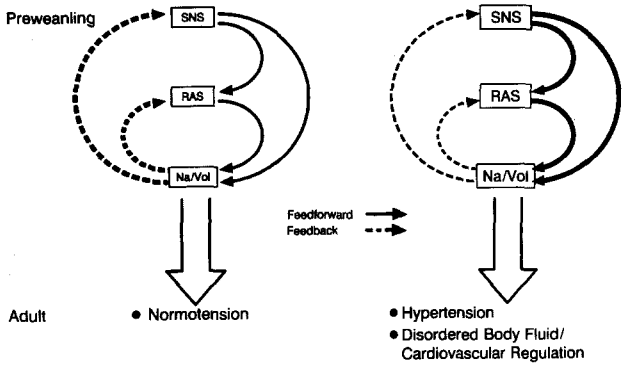

Figure 4. A proposed model of the influences of increased activity of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) during preweaning development on adult cardiovascular control. On the left side of the figure, appropriate sodium/volume levels are maintained early in development through a balance in the activity of the SNS and RAS and feedback from receptors sensitive to sodium/volume. This would lead to the maintenance of a normal setpoint for sodium/volume and normotension in adulthood. In contrast, the right side represents that of the spontaneously hypertensive rat. Increased activity of the SNS and RAS (depicted by the heavier solid feedforward lines) are present during development. Furthermore, a diminished sensitivity (depicted by the thinner hatched feedback lines) to elevated sodium/volume may be present during early development. This combination of events is hypothesized to act as an initiating event leading to hypertension in the adult animal by establishing an elevated set point for sodium/volume regulation.

nervous system and RAS act together to increase sodium retention, in the face of increased dietary sodium of SHR milk, and predispose the animal towards hypertension.

A possible model of the regulation of high blood pressure in SHR based on the alterations in sympathetic and RAS activity is depicted graphically in figure 4. In the developing normotensive rat, represented on the left side of the figure, appropriate levels of sodium/volume are maintained by the activity of the sympathetic nervous system and RAS through feedback from sodium/volume signals. This balance would lead to normotension in the adult animal.

In contrast, activity of the sympathetic nervous system and RAS is elevated in the preweaning SHR (depicted on the right side of the figure). These would stimulate sodium/volume retention through their direct actions and also by the indirect action of sympathetic nerves driving the RAS. The increased sodium/volume load should feed back to decrease activity of these systems. However, the effectiveness (or sensitivity) of these feedback mechanisms appears to be altered in the preweaning SHR since activity of these systems is elevated and sodium retention is present while the pups receive an increased dietary sodium load. Together, these alterations in sodium handling due to increased activity of the RAS and sympathetic nervous system in preweaning SHR may act as important initiating events in SHR hypertension.

The current working hypothesis proposes that alterations in sodium and body fluid balance in early life produce long-term alterations in the set points for control systems affecting sodium/volume regulation and cardiovascular homeostasis. Therefore the central nervous system, which receives afferent information on sodium/volume from the body and orchestrates the corrective mechanisms for their maintenance [16], must be the site at which the set points become established. Evidence from studies manipulating dietary sodium during preweaning development in the normotensive rat support the role of the central nervous system in maintaining altered sodium and cardiovascular regulation [6, 7, 28] and have also provided a possible mechanism. Dietary sodium manipulations, limited to preweaning development, produce alterations in both angiotensin receptor density and affinity in adult animals in central regions intimately linked to sodium/volume regulation and cardiovascular control [27]. These long-term alterations in the central RAS could, in turn, influence sympathetic outflow and other effector systems (e.g. vasopressin) regulating sodium/volume balance. It is currently unknown if the central RAS is altered during development in the SHR. However, the central RAS acts to maintain sodium/volume balance in the adult animal and is mutable to early environmental influences. These characteristics will be necessary for any system to account for the pathogenesis of hypertension in the SHR.

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Reviews

The ATP synthase (F_0-F_1) complex in oxidative phosphorylation

J. P. Issartel, A. Dupuis, J. Garin, J. Lunardi, L. Michel and P. V. Vignais

Laboratoire de Biochimie (URA 1130 du CNRS), Département de Biologie Moléculaire et Structurale, Centre d'Etudes Nucléaires 85X, F-38041 Grenoble cedex (France)

Abstract. The transmembrane electrochemical proton gradient generated by the redox systems of the respiratory chain in mitochondria and aerobic bacteria is utilized by proton translocating ATP synthases to catalyze the synthesis of ATP from ADP and P_i. The bacterial and mitochondrial H^+-ATP synthases both consist of a membranous sector, F_0, which forms a H^+-channel, and an extramembranous sector, F_1, which is responsible for catalysis. When detached from the membrane, the purified F_1 sector functions mainly as an ATPase. In chloroplasts, the synthesis of ATP is also driven by a proton motive force, and the enzyme complex responsible for this synthesis is similar to the mitochondrial and bacterial ATP synthases. The synthesis of ATP by H^+-ATP synthases proceeds without the formation of a phosphorylated enzyme intermediate, and involves co-operative interactions between the catalytic subunits.

Key words. ATP synthase; oxidative phosphorylation; mitochondrial ATPase; bacterial ATPase; F_0-F_1-ATPase.