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Review

Role of the epithelial sodium channel in salt-sensitive hypertension

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The epithelial sodium channel (ENaC) is a heteromeric channel composed of three similar but distinct subunits, α, β and γ. This channel is an end-effector in the rennin-angiotensin-aldosterone system and resides in the apical plasma membrane of the renal cortical collecting ducts, where reabsorption of Na^+ through ENaC is the final renal adjustment step for Na^+ balance. Because of its regulation and function, the ENaC plays a critical role in modulating the homeostasis of Na^+ and thus chronic blood pressure. The development of most forms of hypertension requires an increase in Na^+ and water retention. The role of ENaC in developing high blood pressure is exemplified in the gain-of-function mutations in ENaC that cause Liddle's syndrome, a severe but rare form of inheritable hypertension. The evidence obtained from studies using animal models and in human patients indicates that improper Na^+ retention by the kidney elevates blood pressure and induces salt-sensitive hypertension.

Keywords: epithelial sodium channel; salt-sensitive hypertension; high-salt intake; oxidative stress; sympathetic nervous system

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Introduction

Several studies have classified humans who are suffering from hypertension as salt-sensitive or salt-resistant based upon blood pressure (BP) responses to differences in sodium balance[1, 2]. The increment in BP that is driven by a salt load is characteristic of salt-sensitive hypertension, a condition affecting more than two thirds of individuals with essential hypertension who are older than 60 years[3]. Salt-sensitive hypertension may exacerbate mortality rates and worsen the manifestations of target organ damage[1, 2]. The discovery of mutations in the β- and γ-subunits of epithelial sodium channel (ENaC) to understand Liddle's syndrome[4, 5], a severe form of low-renin hypertension[6], was followed by a search for common genetic variants in ENaC subunits. Several variants were identified[7]. Interestingly, these variants were almost universally more common in black individuals, which correlate nicely with higher prevalence of low-renin, salt-sensitive hypertension in black individuals. The questions and issues addressed in the current review are whether ENaC that resides in the renal distal nephron plays a role in the development of hypertension, particularly in salt-sensitive hypertension, how ENaC variants segregate with high BP, and whether high-salt intake induces oxidative stress and whether oxidative stress could activate ENaC, resulting in over reabsorption of Na^+. We also briefly discuss the role of ENaC expressed in vascular endothelia and the central nervous system in the development of hypertension.

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The topology and physiology of ENaC

Since 1994, when ENaC was initially cloned from the rat colon[8], the biophysical properties and molecular structure of ENaC have been extensively studied. ENaC consists of at least three subunits including α, β, and γ, each of which possesses two transmembrane domains, a large extracellular loop, a cytoplasmic C-terminal domain and a N-terminal domain. All three subunits are required to form a functional α-, β-, γ-ENaC channel complex (Figure 1)[8–15]. ENaC belongs to a member of the ENaC/Deg superfamily of ion channels that are responsible for sodium transport. The channel is typically located at the apical membrane of epithelial tissues throughout the body, including the colon, the sweat glands, the salivary duct, the airway, and the cortical collecting duct (CCD) of the kidney,

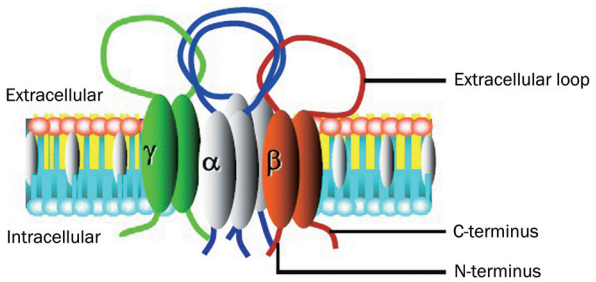

Figure 1. The topology of ENaC. ENaC consists of at least three subunits including α, β, and γ subunits, each of which possesses two transmembrane domains, a large extracellular loop, a cytoplasmic C-terminal domain and an N-terminal domain.

and this channel regulates sodium transport in tissues[16–20]. Recent studies have shown that ENaC subunits are also present in the endothelial cells of the artery and may function as a vascular mechanosensor[21–23].

ENaC α, β, and γ subunits share approximately 30% homology at the amino acid level, and each subunit corresponds to a molecular mass of 70–85 kDa. The three ENaC subunits are inserted into the plasma membrane with a proposed stoichiometry of 2:1:1[24] or 3:3:3[25, 26]. The α-subunit is critical to the formation of the ion permeating pore, whereas the β and γ subunits are required for the maximal channel activity and may play regulatory role. While α-ENaC is knocked out in mice, the mice would die within 40 h of birth because failure of pulmonary fluid clearance. This result clearly demonstrates the pivotal role of α-ENaC in forming a functional Na^+ channel complex *in vivo*[27]. Moreover, decreased α-ENaC expression in mice causes a respiratory distress syndrome, whereas the β and γ have only a modest effect on pulmonary fluid clearance[28]. The α-, β-, γ-ENaC channel complex is highly selective for Na^+ and mediates Na^+ entry through the apical membrane of distal renal epithelial cells with a slope single-channel conductance of approximately 5 pS. ENaC accounts for a small proportion of distal renal sodium reabsorption (<5%). However, there appears to be no further downstream sodium transport system beyond CCD, which places ENaC in a very critical position for the regulation (or homeostasis) of the extracellular fluid volume, electrolyte balance and long term BP[7]. The factors such as high-salt intake that affect ENaC activity and the ENaC expression level at the apical membrane of CCD may constitute the critical role of ENaC in Na^+ over reabsorption and water retention.

The experiments assessed in animal models reveal the role of ENaC in developing salt-sensitive hypertension

The strains of rats were bred by Dr Lewis K Dahl for sensitivity or resistance to the hypertensive effect of a high-salt diet in the 1960s and were named Dahl salt-sensitive (DS) or Dahl salt-resistance (DR)[29, 30]. When DS rats were placed on a high-salt (8% NaCl) diet at 21–23 d of age, they rapidly developed hypertension. All of the DS rats died by the 16th week of salt feeding. With similarly treated DR rats, the BP remained in the normotensive range, and 80% of animals survived to the 48th week on a high-salt diet[30]. Since then the kidney has been the focus of considerable attention in DS and DR rats because of the results obtained from the renal cross-transplantation assays, which involve the transplantation of a kidney from a DS rat into a DR rat that had the original kidneys removed, the results suggest that the DR rats develop a higher BP than DR rats with transplanted DR kidneys or DR rats with a unilateral nephrectomy. Conversely, a DR kidney that was transplanted into a DS rat ameliorated the increase in the BP that was seen in DR rats with transplanted DS kidneys or DS rats with a unilateral nephrectomy[31–33]. Later studies revealed that the plasma renin and aldosterone concentrations were normal or lower in DS rats compared with that in control rats[34, 35]. Aoi *et al* investigated the mechanisms by which quercetin, a plant extract, exerted an anti-hypertensive effect, and they found that quercetin diminished the αENaC mRNA expression in the kidney, which was associated with the reduction of the systolic BP that was elevated by a high-salt diet in DS rats. These results suggest a role for ENaC in salt-sensitive hypertension[36]. The same group attempted to determine whether a high-salt diet in DR rats stimulated the expression level of ENaC. These investigators divided the DS and DR rats into several salt diet groups as follows: DS and DR rats that were fed with a low-sodium diet (0.005% NaCl), a normal-sodium diet (0.3% NaCl), or a high-sodium diet (8% NaCl). Four weeks after the high-salt diet in DS rats, an increase in the systolic BP was observed. However, the BP was not altered in any of the other groups. Subsequently, these investigators examined the expression level of α-ENaC mRNA and serum and glucocorticoid-regulated kinase 1 (SGK1) mRNA. They found that the expression level of α-, β-, γ-ENaC, and the SGK1 mRNAs was significantly enhanced by the high-sodium diet in DS rats. Interestingly, the expression of SGK1 mRNA was down-regulated in DR rats that were fed a high sodium diet. These observations suggest that the expression of ENaC and SGK1 mRNAs is abnormally regulated by the dietary sodium in salt-sensitively hypertensive rats and that this abnormal expression may be a factor that causes salt-sensitive hypertension[37]. Convincing evidence indicates that the aldosterone activated mineralocorticoid receptor increases SGK1 gene transcription in the CCD, and consequently, SGK1 strongly stimulates the activity and expression of the ENaC and renal Na^+/H^+ exchanger (NHE)[38-43]. High-salt intake may up-regulate both ENaC and SGK1 in DS rats. However, functional studies that examine ENaC activity are required to evaluate the role of ENaC and SGK1 in salt-sensitive hypertension in DS rats and the mechanisms by which the high-salt intake regulates ENaC and SGK1.

Fenton and co-authors found that none of the ENaC subunits was increased in abundance in the inner medullas of DS rats compared with that of DR rats[44]. In fact, the α-subunit was strongly down regulated, which may be a consequence of the marked increase in 11β-HSD2 expression in the cells of the inner medulla. Consistent with this view, the protein abundance of α-ENaC was markedly elevated following the

carbenoxolone-induced inhibition of the 11β-HSD2 activity. These investigators also examined whether the ENaC subunits may be upregulated by a high-salt diet in DS rats. However, Husted and co-workers showed that the ENaC activity is doubled in the IMCD cells of DS rats *versus* in that of DR rats[40, 45]. The reasons for this variability in ENaC activity and/or expression level in DS *versus* DR rats are poorly understood at the present time. Shehata and co-workers examined the complete coding sequences of three ENaC subunits and showed that there were no genetic differences within the 5′ and 3′ flanking regions in DS *vs* DR rats[46]. The alternative splicing of α-ENaC may regulate α-ENaC by formation of coding RNA species (α-ENaC-a and -b) and non-coding RNA species (α-ENaC-c and -d). The α-ENaC-a and -b mRNA levels are significantly higher in DR *versus D*S rats. After 4 weeks of the high-salt intake, the level of α-ENaC-b was dramatically elevated compared to that in DR rats fed a normal-salt diet. These results suggest that α-ENaC-b is a salt-sensitive transcript. Furthermore, among the four α-ENaC transcripts (-a, -b, -c, and -d), α-ENaC-b is a predominant transcript that exceeds α-ENaC-wt abundance by approximately 32 fold. α-ENaC-b may potentially act as a dominant negative protein for ENaC activity and rescue DR rats from developing salt-sensitive hypertension on a high-salt diet[47].

The molecular variations in ENaC and the risk for developing hypertension in humans

The search for common genetic variants in ENaC subunits that affect the susceptibility in less rare forms of hypertension took place soon after the discovery of mutations in α-, β-, and γ-ENaC that cause Liddle's syndrome (Table 1). The first variant that was associated with hypertension was T594M in the C-terminus of β-ENaC in black individuals. This variant was found in approximately 8% of hypertensive individuals, whereas the variant was detected in only approximately 2% of normotensive individuals[48]. In another study, seven variants in β-ENaC, including G589S, T594M, R597H, R624C, E632G (last exon), G442V, and V434M (exon 8) were identified and almost found in black individuals[49]. The functional properties of the variants were evaluated in *Xenopus* oocytes expressing these mutants. Interestingly, small but not significant differences were detected between the variants and wild-type ENaC. The clinical evaluation of the family bearing the G589S variant, which provided the highest relative ENaC activity, did not show any cosegregation between the mutation and hypertension[49]. However, the lack of a significant increase in the Na^+ current that was observed in *Xenopus* oocytes that overexpressed these variants cannot completely rule out any functional impact of the ENaC mutants in developing hypertension[49]. One possibility to explain why the association studies of ENaC variants are often inconclusive is that many factors influence the ENaC activity. Therefore, a variant that affects ENaC function *in vitro* may not necessarily cause Na^+ retention, unless at the same time, the regulatory factors do not adjust accordingly. The variants identified in the β- and γ-subunits of ENaC were almost exclusively identified in individuals of African origin. However, the physiological significance of the β- and γ-subunit polymorphisms may partially explain the high incidence of salt-sensitive hypertension in African Americans. Among the black hypertensive population, approximately 75% is salt-sensitive, characterized by a BP increase after dietary salt intake[2].

To determine whether SCNN1B or SCNN1G, which encode β and γ subunits, respectively, were present in a patient who was clinically suspected to have Liddle's syndrome with no familial history of hypertension, Wang and coworkers identified a mutation causing Liddle's syndrome. They demonstrated that a frameshift mutation of the γ subunit resulted in a new termination site at the 585 codon of the γ subunit and the deletion of its PY motif. Moreover, the parents of the patient, the other 50 randomly selected hypertensive patients, and 50 controls did not have the mutation that causes Liddle's syndrome. These results suggest that this frameshift mutation is a *de novo* mutation and not a common genetic variant[50].

Several α-ENaC variants at the residues 334, 618 and 663 are possibly associated with the abnormal Na^+ handling by the kidney and the salt-sensitive hypertension that is prevalent in black populations[51-54]. Several groups have studied whether these variants segregate with BP, and the outcomes are controversial[51, 53]. Ambrosius and coworkers reported that the allele of T663A was twice as common in whites and that T663A was associated with being normotensive in black and white populations[51]. The expression of T663A did not alter the basal Na^+ current[51]. Kleyman's group used *Xenopus* oocytes expressing a mouse/human chimera (m(1-678)/h(650-669)/T663A), which was generated by the replacement of the distal C terminus of the mouse α-subunit with the distal C terminus of the human α-subunit, and determined that the human αT663βγ ENaC has increased activity in *Xenopus* oocytes when compared with human αT663Aβγ ENaC. The increase in the channel activity in human αT663βγ reflected an increase in surface expression[55]. Stockand's group has reported that the polymorphic C618F and A663T ENaCs had greater activity compared with the wild-type channels in the excised patches with activity of channels increased 3.8- and 2.6-fold, respectively[56]. This increase in the channel activity is associated with an increase in the surface expression of the polymorphisms. The results obtained by these studies are consistent with the C618F and A663T polymorphisms leading to an elevated ENaC activity with the possibility that these polymorphisms facilitate the altered Na^+ handling by the kidney[55, 56]. Iwai *et al* reported that a polymorphism in the promoter region of the α-ENaC gene G2139A is associated with BP status and that the G2139 allele significantly increased the risk of hypertension in the general Japanese population[57].

Does oxidative stress induced by high-salt intake activate ENaC?

ENaC activity depends upon the number of channels in the apical membrane, the permeation properties, and the open probability of the channel (P_o). One of the best examples is the salt-sensitive hypertension of Liddle's syndrome, in which

Table 1. Genetic variants of ENaC and risk for hypertension.

Genetic variation	Genetic variant location	Genetic variant frequency	Mutant gene function/ENaC activity	Risk for hypertension	Ref
G589S	Exon 12 of β-ENaC	1/475 W hypertension	↑	NS	[49]
		8/347 hypertension, 2/175 normotension	NS	OR=2.4	[106]
i12-17CT	Intron 12 of β-ENaC	16/347 hypertension, 2/175 normotension	–	OR=4.6	[106]
T594M	Exon 12 of β-ENaC	3/50 B hypertension	NS	NS	[49]
		17/206 hypertension, 3/142 normotension	–	OR=4.17	[48]
		7/126 B hypertension, 7/105 B normotension; 0/192 W hypertension	NS	NS	[107]
R597H	Exon 12 of β-ENaC	1/475 W hypertension	NS	NS	[49]
R624C	Exon 12 of β-ENaC	1/50 B hypertension	NS	NS	[49]
E632G	Exon 12 of β-ENaC	1/475 W hyptertension	NS	NS	[49]
G442V	Exon 8 of β-ENaC	1/475 W hyptertension, 18/50 B hypertension	NS	NS	[49]
		0.002 W, 0.083 B normotension	NS	NS	[51]
V434M	Exon 8 of β-ENaC	1/475 W hyptertension	NS	NS	[49]
V546I	Exon 13 of γ-ENaC	8/347 hypertension, 1/175 normotension	NS	OR=2.4	[106]
T387C	Exon 3 of γ-ENaC	Similar frequencies in hypertension and normotension, similar frequencies in B and W	–	NS	[108]
T474C	Exon 3 of γ-ENaC	Similar frequencies in hypertension and normotension, similar frequencies in B and W	–	NS	[108]
C549C	Exon 3 of γ-ENaC	Similar frequencies in hypertension and normotension, similar frequencies in B and W	–	NS	[108]
C1990G	Last Exon of γ-ENaC	Similar frequencies in hypertension and normotension, similar frequencies in B and W	–	NS	[108]
594insP	Rare mutant located outside the PY motif of γ-ENaC	One case of mild hypertension	NS	–	[108]
R631H	Rare mutant located 39 to the PY motif of γ-ENaC	Two severe cases of severe hypertension	NS	–	[108]
A334T	Exon 6 of α-ENaC	0.031 W, 0.442 B normotension	–	NS	[51]
C618F	Exon 13 of α-ENaC	0.002 W, 0.080 B normotension	–	NS	[51]
			↑ 3.8-fold	–	[56]
T663A	Exon 13 of α-ENaC	0.293 W, 0.146 B normotension	NS	Aassociates with normotension	[51]
			↑	–	[55]
			↑ 2.6-fold	–	[56]
G2139A	Promoter region of α-ENaC	1719/3989 J hypertension	Promoter activity↑	OR_{total}=1.31 $OR_{<60\,y}$=1.77	[57]

Abbreviations and symbols: B, black; W, white; J, Japanese; NS, not significant; OR, odd ratio; ↑, increase; –, not determined.

a gain of function ENaC mutant enhances its trafficking to the plasma membrane and thereby increases its cell surface expression[4–6, 58–61], which leads to over reabsorption of Na^+ and water.

Evidence obtained in rats and humans suggest that high-salt diets also cause oxidative stress. This high-salt intake induced increase in oxidative stress is more obvious in salt-sensitive hypertension[62, 63]. Furthermore, high-salt intake may also target the tissues and organs independent of hypertension via a mechanism of elevating reactive oxygen species (ROS)[64]. In the absence of the prominent elevations of BP after salt-loading, salt sensitivity may be revealed by the structural and functional injuries of the targeting organs such as the heart and kidney[65]. Recent studies have shown that hydrogen peroxide (H_2O_2), an isoform of ROS, stimulates ENaC and that high NaCl elevates ROS in CCD cells[66]. However, the mechanism by which a high-salt diet induces an increase in ROS to stimulate ENaC is not known. A high-salt intake is known to induce the compensatory natriuresis to maintain sodium homeostasis. Reduced plasma aldosterone causes a decrease in α-ENaC mRNA level, which suggests an important role in the compensatory natriuresis[40]. Previous electrophysiological experiments assessed in renal CCD have indicated that dietary sodium intake and variations in aldosterone plasma levels regulates the abundance of functional ENaC in the apical plasma membrane[39]. A high or low Na^+ diet for three weeks also influenced the distribution pattern of ENaC in the mouse kidney. The regulation of ENaC function *in vivo* involves shifting the β- and γ-subunits from the cytoplasm to the apical plasma membrane and *vice versa*, respectively[12]. The insertion of these subunits into the apical plasma membrane coincides with the upregulation of the α-subunit and its insertion into the apical plasma membrane[67]. These studies together suggest that dietary salt modulates the expression pattern of ENaC subunits in the kidney and may stimulate its activity via enhanced ROS level, which in turn leading to an increase in Na^+ reabsorption.

Several studies have demonstrated that there is increased oxidative stress in animals with high-salt intake[68–71]. In experimental models of salt-sensitive hypertension, high-salt intake increased the markers of vascular and systemic oxidative stress[1]. Studies in essential hypertensive patients have suggested that high-salt intake and/or salt sensitivity is associated with impaired endothelial function[72–75]. Miyoshi *et al*[76] reported a decrease in acetylcholine-induced forearm vasodilation in salt-sensitive hypertensive subjects regardless of the level of salt intake. Increased ROS have a critical role in the initiation of hypertension and may be generated by the hypertension itself, suggesting a positive-feedback mechanism. In addition to the systemic effects of ROS, recent evidence demonstrated that oxidative stress within the kidney plays a central role in the pathophysiology of sodium retention by inducing the tubulointerstitial accumulation of Ang II-positive cells. The prohypertensive role of intrarenal ROS is suggested by the strong correlation between the renal superoxide-positive cells and the severity of hypertension in the spontaneously hypertensive rats (SHR)[77]. However, there is a lack of information at the present time regarding whether oxidative stress induced by high-salt intake affects the BP via influencing ENaC activity. In our preliminary studies, we found that the high-salt intake decreased the expression level of α-ENaC in the CCD cells of DR rats, but not that in DS rats (unpublished observations). When cultured CCD cells are treated with high NaCl, ROS accumulated within these cells. Using patch-clamp experiments, we found that H_2O_2 stimulates ENaC activity. These results suggest that high-salt intake may activate ENaC through an elevation of ROS [unpublished observations].

Does altered activity of ENaC affect the function of the vascular endothelium and sympathetic nervous system to influence BP?

Although ENaC was known as the typical sodium channel in the kidney, the colon and the lung, vascular endothelial cells were also shown to express ENaC and mineralocorticoid receptors[21, 78, 79]. Endothelial cells are targets for aldosterone, which activates the apically located ENaC, and its activity modifies the biomechanical properties of the endothelium. Therefore, ENaC is proposed as the key mediator of aldosterone-dependent BP control in the endothelium[80]. Several studies, in different cell types including CCD and endothelial cells, have suggested that ENaC may function as a mechanosensor and that mechanical stimuli may activate ENaC[22, 81, 82]. Because endothelial ENaC inhibition may activate nitric oxide (NO) synthase[83], it is completely possible that altered blood flow (shear stress), which is caused by over reabsorption of Na^+ via ENaC located at distal nephron, may affect the NO production in endothelia. High-salt intake may cause an increase in plasma [Na^+], which may or may not be detectable depending upon the extent of water intake and the timing of blood sampling relative to high-salt intake. Fang and coworkers showed that four days after 8% high-salt diet exposure, plasma [Na^+] increased by 3–4 mmol/L in SHR and Wistar Kyoto rats[84]. In normotensive rats, when salt intake increased from 10 to 250 mmol/d over 5 d, the plasma [Na^+] increased by 3 mmol/L. In addition, reducing the salt intake from 350 to 12–20 mmol/d lowered the plasma [Na^+] to a similar extent by 3–4 mmol/L[85]. Huang and coworkers showed that high-salt intake increased [Na^+] in the cerebrospinal fluid (CSF) up to 5 mmol/L in DS rats and SHR rats but not in DR rats[86]. Similar to the results obtained from the animal models, [Na^+] in CSF was increased by 2–3 mmol/L in patients with both salt-sensitive and non-salt-sensitive hypertension after a 7-d high-salt diet (16–18 g/d) compared to those given a low-salt diet (1–3 g/d)[87]. Nevertheless, high-salt diets elevated the arterial pressure in salt-sensitive individuals. These results suggest that increases in plasma [Na^+] may trigger this effect[84] via a mechanism that has not been elucidated.

Previous studies have suggested that DS rats have abnormalities in the sympathetic nervous system (SNS)[88, 89] and endothelial function[90, 91], which causes significant vascular resistance. In addition, there is evidence that supports the hypothesis that abnormal modulation of SNS is involved in

salt-inducd hypertension. Salt loading has been shown to augment the sympathetic activity in DS rats but not in DR rats[92–94]. The intracerebroventricular (ICV) infusion of sodium caused sympathoexcitatory and pressor responses to a greater degree in DS rats than in DR rats[85, 95]. The strict regulation of [Na^+] in the CSF is crucial for the normal function of neurons. An increase in CSF [Na^+] by as little as 2 mmol/L can increase the firing rate of neurons. A chronic 5 mmol/L increase in CSF [Na^+] causes sympathetic hyperactivity and hypertension[96–98]. Increases in CSF [Cl^-] or the osmolarity of CSF did not cause such sympathoexcitation and hypertension[99]. Because the role of ENaC in regulating sodium transport across the epithelia is important, investigators started to study whether ENaC in neural components also plays a role in salt-sensitive hypertension. Stoichiometrically different populations of ENaC may be present in both epithelial and neural components in the brain, which may contribute to the regulation of CSF and interstitial Na^+ concentrations and neuronal excitation[90, 97]. ENaC subunits are also expressed in sensory nerve endings in the rat foot pad[100] and in the trigeminal mechanosensory neurons[101]. However, the function of the ENaC subunits in these tissues has not yet been elucidated. Functional studies have suggested the presence of specific Na^+ channels, presumably ENaC, in the brain that are activated by aldosterone or a high-salt diet and blocked by amiloride or benzamil. In Wistar rats, ICV infusion of aldosterone or Na^+-rich artificial CSF increased BP and renal sympathetic nerve activity. In DS rats but not DR rats, a high-salt diet or ICV infusion of aldosterone caused sympathoexcitation and hypertension. The blood-brain barrier in DS rats is five to eight times more permeable to Na^+ than that in DR rats[102]. Increases in CSF [Na^+] are observed in DS rats but not DR rats on a high-salt diet and precede changes in BP by 1–2 d[86]. Importantly, the responses to aldosterone or Na^+-rich artificial CSF in Wistar rats and to aldosterone or a high-salt diet in DS rats can be prevented by ICV infusion of benzamil or spironolactone[103–105]. These findings suggest that the mineralocorticoid receptor (MR)-mediated activation of sodium channels in the brain is responsible for the mechanisms leading to increased sympathetic outflow and hypertension.

Conclusion

We present evidence that places ENaC in a central position for Na^+ retention, which is necessary to achieve a state of high BP in the salt-sensitive population. The Na^+ reabsorptive site (ENaC) does not act alone in the mechanisms for developing hypertension. The emerging evidence is compelling for the consideration of ENaC as the additional requisite participant in endothelia and SNS (Figure 2). However, the mechanisms by which the activation of ENaC to induce Na^+ retention and the consequences in the vascular compartment and SNS require further investigation.

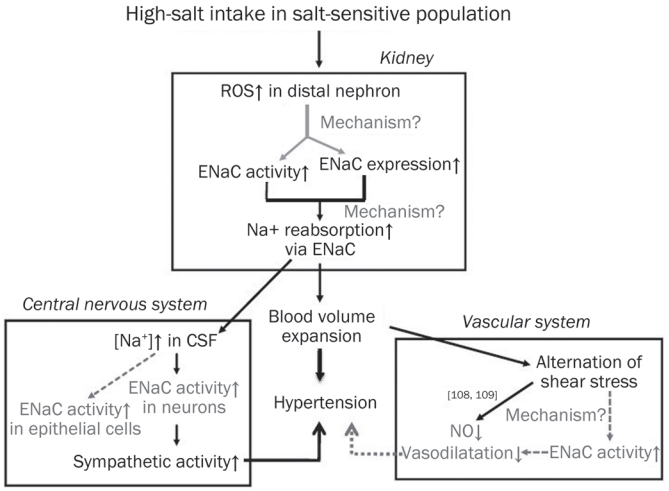

Figure 2. A schematic that illustrates the central role of ENaC in the development of salt-sensitive hypertension after the loss of compensatory natriuresis. High-salt intake in the salt-sensitive population induces oxidative stress in the kidney, which enhances the apical membrane expression of ENaC and ENaC activity with an unknown mechanism at the present time. This increased activity eventually causes Na^+ over-reabsorption in CCD followed by water retention and elevation of BP. The volume expansion in the vascular compartment alters blood flow (shear stress) and directly affects endothelial function by reducing the synthesis of NO[109, 110]. ENaC may act as a mechanosensor in endothelial cells and may sense changes in shear stress. Alterations in shear stress may activate ENaC residing at the apical membrane of endothelial cells and may affect the regulation of vasoactive substances. Na^+ over-reabsorption in CCD elevates [Na^+] in CSF, which in turn triggers sympathetic activity in neurons and contributes to hypertension. Stoichiometrically different populations of ENaC may be present in epithelial cells and neurons in the brain, which may contribute to the regulation of CSF and interstitial [Na^+] as well as neuronal excitation. CCD: cortical collecting duct; CSF: cerebrospinal fluid; and NO: nitric oxide. Black solid lines with arrows: already known; grey dash lines with arrows and words in gray: open questions.

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