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Implication of ENaC in salt-sensitive hypertension ☆

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Abstract

Arterial blood pressure is critically dependent on sodium balance. The kidney is the key player in maintaining sodium homeostasis. Aldosterone-dependent epithelial sodium transport in the distal nephron is mediated by the highly selective, amiloride-sensitive epithelial sodium channel (ENaC). Direct evidence that dysfunction of ENaC participates in blood pressure regulation has come from the molecular analysis of two human genetic diseases, Liddle's syndrome and pseudohypoaldosteronism type 1 (PHA-1). Both, increased sodium reabsorption despite low aldosterone levels in Liddle's patients and decreased sodium reabsorption despite high aldosterone levels in PHA-1 patients, demonstrated that ENaC is an effector for aldosterone action. Gene-targeting and classical transgenic technology enable the generation of mouse models for these diseases and the analysis of the involvement of the epithelial sodium channel (ENaC) in the progress of these diseases. A first mouse model using αENaC transgenic knockout mice [αENaC(−/−)Tg] mimicked several clinical features of PHA-1, like salt-wasting, metabolic acidosis, high aldosterone levels, growth retardation and increased early mortality. Such mouse models will be necessary in testing the involvement of genetic and/or environmental factors like salt-intake in hypertension.

Keywords: ENaC; Gene targeting; Hypertension; Sodium homeostasis; Sodium channel

1. Introduction

Hypertension is a multifactorial vascular disorder which affects 15–20% of adults in industrialised countries. It is one of the risk factors for stroke, myocardial infarction, and end-stage renal disease. Genetic and environmental factors also contribute to blood pressure variation in the human population. There are direct and indirect relationships between sodium balance, the extracellular fluid volume and blood pressure. Guyton and colleagues have argued that hypertension cannot be sustained without the active participation of the kidney, because elevated renal perfusion pressure leads to salt and water diuresis, returning blood pressure to normal levels [1]. Inhibition of the adrenal-renal axis as first shown by Addison (1855) causes hypotension and proved to be lethal, confirming a critical role of the adrenal gland and the kidney function [2]. Stimulation of the adrenal renal axis caused high blood pressure as established by Cushing in 1932 and later by Conn in 1955 [2].

Several epidemiological and experimental studies have provided evidence for a relationship between salt intake and the incidence of hypertension [3,4]. Derangement in function of proteins that transport Na^+ and of those regulating the activity of these sodium-transporting proteins are therefore likely to be responsible for a number of clinical disorders of fluid and electrolyte homeostasis. For example, mutations within the Na^+Cl^--transporter causing Gitelman's syndrome reduce blood pressure by diminishing renal salt reabsorption [5]. Within the human population, genes might exist which do confer salt-sensitivity, defined as an increase in blood pressure in response to high salt intake or, conversely, salt-resistance in response to high salt intake in the human population. Molecular genetic analysis of these genes might then

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provide insight into the physiologic mechanisms underlying common forms of hypertension.

2. Renin-angiotensin system and salt transport

In humans, all genes examined so far, and being proven for a potential causative role in hypertension, mediate or regulate renal sodium reabsorption. Unequal crossing over between the aldosterone synthase and the steroid 11β-hydroxylase genes causing glucocorticoid-remediable aldosteronism (GRA) [5], loss-of-function mutations in 11β-hydroxysteroid dehydrogenase (syndrome of apparent mineralocorticoid excess; AME; [6]), and mutations in the β and γ subunit of ENaC causing Liddle's syndrome, result in constitutively increased renal sodium reabsorption and hypertension. In contrast, mutations within the α, β, and γ subunit of ENaC causing pseudohypoaldosteronism (PHA-1) reduce blood pressure by diminishing renal salt reabsorption [7]. Nucleotide substitution in the promoter of human angiotensinogen gene was shown to be associated with essential hypertension by affecting basal transcription [8]. Patients with steroid 11β-hydroxylase deficiency [9,10] and steroid 17α-hydroxylase deficiency [11] commonly develop hypertension as a consequence of overproduction of steroid metabolites with mineralocorticoid activity. Hypertension in patients with glucocorticoid resistance and Cushing's syndrome is likely to be due in part to saturation of 11β-hydroxysteroid dehydrogenase, with cortisol as potent minerocorticoid [12]. All of these disorders share altered activity of the extended renin-angiotensin system and affect renal handling of salt in the kidney.

3. ENaC as target for aldosterone action

The mineralocorticoid aldosterone is the primary hormone responsible for maintaining salt and water balance in the kidney [13,14]. Its major effect is to stimulate Na^+ absorption in the distal renal tubules and the distal colon. ENaC constitutes the limiting step for sodium reabsorption in epithelial cells that line the distal nephron, distal colon, ducts of several exocrine glands and lung airways [15]. In the kidney, mRNA transcripts and proteins from all three subunits (α, β and γ) are detected in the renal distal convoluted tubule, connecting tubule, cortical collecting duct and outer medullary collecting duct [16]. In these cells, the Na,K-ATPase on the basolateral side provides the driving force for transepithelial Na^+ transport [2]. Several studies demonstrated that ENaC is strongly affected by aldosterone as shown in short circuit current (Isc) measurements, current fluctuation analysis, microelectrode impalements, and patch-clamp recordings (see for review [14]). Upon stimulation, aldosterone binds to its intracellular receptor, the mineralocorticoid receptor (MR), and the active hormone-receptor complex interacts with hormone-responsive elements in the promoter of genes, like for example the β2 subunit of the Na,K-ATPase to modulate transcription [17]. Thus, increase in sodium reabsorption in epithelial cells is achieved by activating such genes directly and/or indirectly via aldosterone-induced proteins. Recent data using the A6 kidney cell line from *Xenopus laevis* showed that in the early phase of its action, aldosterone has a major effect on the translation of the α subunit of ENaC. During the late phase of its action, aldosterone induces accumulation of all three mRNA transcripts (α, β, and γENaC) leading to a further increase in channel protein synthesis [18].

Table 1
Identified mutations in human ENaC subunits causing Liddle's syndrome and pseudohypoaldosteronism type 1[a]

Phenotype	Subunit	Mutation	Reference
Liddle	β	R564stop	Shimkets et al., 1994 [21]
			Melander et al, 1998 [39]
	β	Q589stop	Shimkets et al., 1994 [21]
	β	T592fr	Shimkets et al., 1994 [21]
	β	A593fr	Jackson et al., 1998 [40]
	β	R595L	Shimkets et al., 1994 [21]
	β	P615	Inoue et al., 1998 [41]
	β	P616L	Hansson et al., 1995 [22]
	β	Y618H	Tamura et al., 1996 [42]
	β	579del32	Jeunemaitre et al., 1997 [43]
	γ	W574stop	Hansson et al., 1995 [22]
Polymorphism	β	T594 M	Su et al., 1996 [44]
			Baker et al., 1998 [45]
PHA-1	α	I68fr	Chang et al., 1996 [32]
	α	R508stop	Chang et al., 1996 [32]
	β	G37 S	Chang et al., 1996 [32]
	γ	KYS106-108- > N[b]	Strautnieks et al., 1996 [46]

[a] stop = stop codon; fr = frameshift; del = deletion.
[b] Splice site mutation.

4. Liddle's syndrome and pseudohypoaldosteronism

First evidence that ENaC is involved in salt-sensitive hypertension came from molecular analysis of two human genetic diseases, Liddle's syndrome (or pseudoaldosteronism) and pseudohypoaldosteronism type 1 (PHA-1). Liddle's syndrome is a rare disorder with severe and early onset of hypertension [19]. Urinary excretion of aldosterone was low, and spironolactone, a mineralocorticoid receptor antagonist, had no effect on blood pressure. In contrast, administration of a sodium channel blocker (triamterene) together with restriction of salt intake normalised blood pressure.

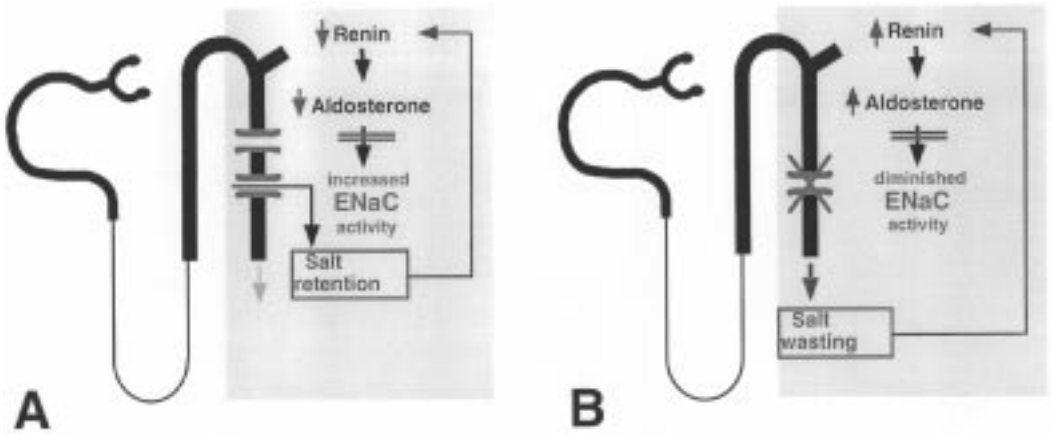

Fig. 1. ENaC as an effector for aldosterone action. (A) In patients with Liddle's syndrome, constitutive activation of ENaC leads to salt retension. As a consequence, the renin-angiotensin system is suppressed but cannot downregulate ENaC since it is defective. (B) In patients with pseudohypoaldosteronism, mutations within ENaC subunits lead to diminished ENaC activity which results in urinary salt-wasting. The renin-angiotensin system is stimulated, but without effect on the target of aldosterone action, ENaC.

Renal transplantation corrected the defect in a Liddle's sydrome patient which suggests that the defect in these patients is intrinsic to the kidney [20]. In 1994, Lifton's group demonstrated complete linkage of the gene encoding the β subunit of ENaC to Liddle's syndrome [21]. More recent analyses revealed further mutations in both the β and γ subunits of ENaC [22,23] (Table 1). Expression of these ENaC gene variants in Xenopus oocytes produced a marked increase of whole-cell Na^+ current [24]. This activation might be caused by impaired interactions of a short proline-rich segment (PPP × Y motif) in the C-terminal part of ENaC subunits with a homologue of Nedd4 protein that likely acts as a regulator of channel activity [25–27]. The precise mechanims by which Nedd4 modulates channel activity remains to be elucidated. Interference with the normal degradation pathway of the channel has been discussed [26,28]. In Xenopus oocytes, increased intracellular Na^+ normally induces downregulation of wild-type ENaC activity, but not of Liddle mutants [29]. In summary, despite low activity of the renin-angiotensin system, salt reabsorption cannot be controlled, since ENaC is constitutively active (Fig. 1A) [27,30].

Pseudohypoaldosteronism type 1 (PHA-1) is an inherited recessive disease characterised by a life-threatening dehydration in the neonatal period, marked hypotension, salt wasting, high serum potassium level, metabolic acidosis, and marked elevation in plasma renin acitvity and aldosterone levels [31]. Examination of the ENaC subunit genes in families with PHA-1 revealed mutations that result in a decreased ENaC function [32,33]. Contrary to the mutations identified in Liddle's patients, where they seem to be clustered to the C-terminus of β and γENaC, mutations in PHA-1

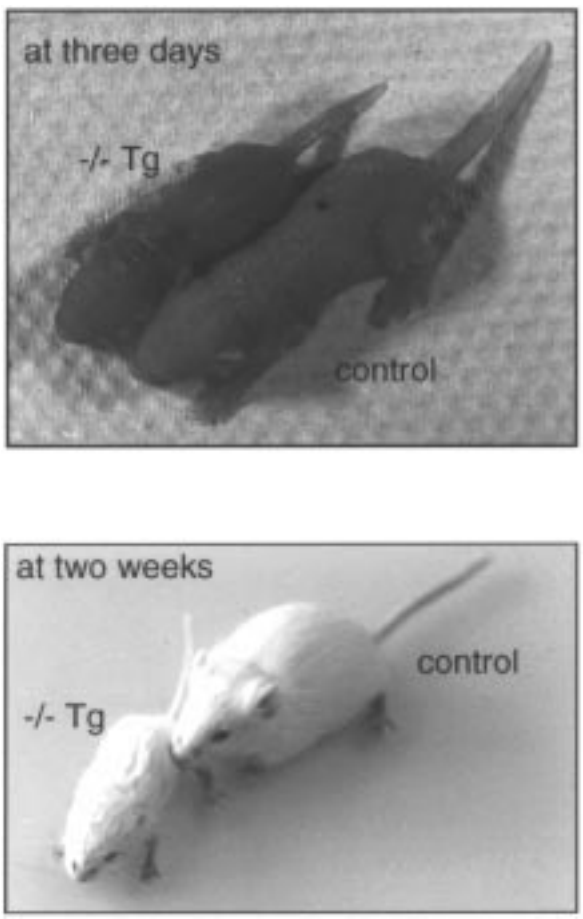

Fig. 2. Development of an animal model for PHA-1. Transgenic knockout [αENaC − / − Tg] mice show clinical symptoms characteristic of PHA-1 phenotype, e.g. weight loss. Already at 3 days after birth (above), smaller-sized animals can be detected and easily followed (below). These animals exhibit urinary salt wasting and metabolic acidosis and die within the first 2 weeks after birth.

patients are more widely distributed over the three ENaC subunits (α, β, γ), thus affecting various functional domains, e.g. the gating domain of the channel pore [33]. This leads to primary salt wasting from the kidney tubules, accompanied by a secondary defect in the secretion of potassium and hydrogen ions. Despite stimulated activity of the renin-angiotensin system, salt reabsorption cannot be augmented because the effector, ENaC, is defective (Fig. 1B).

5. ENaC mouse models for salt-sensitive hypertension

In humans, all of the PHA-1 mutations identified so far are characterised by a partial loss of ENaC function leading to diminished, but still detectable channel activity in a heterologous Xenopus expression system. Using the gene knockout approach in mouse embryonic stem cells, we expected to generate a salt-wasting syndrome. However, inactivation of the α subunit of ENaC led to early respiratory distress and death due to failure of the lung to clear liquid [34]. Low expression of an αENaC transgene on the αENaC knockout background resulted in a mouse model for PHA-1 [35]. These transgenic knockout [αENaC −/− Tg] mice exhibited sufficient basal Na^+ absorptive capacity to clear lung liquid but developed clinical symptoms characteristic for PHA-1 phenotype. During the first 2 weeks after birth (day 3–14), metabolic factors appear to be important determinants of survival. Half of the [αENaC −/− Tg] mice died with metabolic acidosis and 2-fold elevated urinary Na^+ loss. There was a correlation between size of the pups and postnatal lethality, since, shortly after birth, we could easily distinguish the transgenic knockout survivors from the non-survivors, being generally smaller (Fig. 2). The adult surviving [αENaC −/− Tg] mice showed compensation of these acid/base imbalances and electrolyte disturbances, thus suggesting that there was spontaneous improvement in renal Na^+ absorption with age. They had normal blood gases and normal serum and urinary electrolyte concentrations despite elevated aldosterone levels [35]. In PHA-1 patients, supplemental Na^+ requirements diminish over time, but the mechanism of this apparent change in renal Na^+ handling is not yet well understood [36]. In colon, adult transgenic knockout mice exhibited lower Na^+ transport and loss of cyclic variation of ENaC-mediated Na^+ transport, measured as amiloride-sensitive rectal potential difference, despite elevated aldosterone levels [35]. According to our model, salt reabsorption in kidney and colon cannot be augmented because the effector, ENaC is 'defective' and does not respond to elevated aldosterone levels in these animals. Low expression of the transgene and/or lack of corresponding regulatory elements in our transgenic heterologous promoter render ENaC-mediated transport aldosterone-insensitive. It will be interesting to study whether reduced ENaC-mediated sodium transport in these mice confers salt-sensitivity to high salt-intake paralleled with lower blood pressure levels. Polymorphisms, like the mutation T594 M (human βENaC) might be of relevance in essential hypertension confering salt resistance or salt sensitivity to the human population [37].

Characterisation of mutant mouse models will contribute to understand the pathophysiology of these diseases and to design rational therapies. The design of new models, based on mutations identified in human studies, will provide opportunities to examine the effects of these mutations under different defined environmental conditions, e.g. higher salt-intake. Using the Cre-loxP-mediated recombination, we introduced the Liddle's mutation (R566stop; βENaC subunit; [21]) into mice which are currently analysed [38]. Physiologic consequences of different combinations of mutant genes involved in salt-sensitive hypertension can then subsequently be analysed. Mice deficient for the β or γENaC gene locus die shortly after birth due to metabolic dysfunction [47,48]. In mice expressing low levels of βENaC, salt restriction induces pseudohypoaldosteronism type 1 [49].

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