

ENaC isn't ASIC

**A Study of Various Activating Mutations and Conditions of the
Epithelial Sodium Channel**

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Frontmatter

Acknowledgements

We'll get here.

Part I.

Introduction

1. ENaC in the Body

1.1. ENaC in the kidney

Blood pressure must be maintained within a narrow window of acceptable values. Too low, and vital organs do not receive sufficient oxygen and nutrients to function, but too high and blood vessels sustain damage. It is not surprising, then, that the human body has evolved several mechanisms for responding to changes in blood pressure, each with their own timescale¹. ENaC is the essential mechanism of the longest-term control, kidney excretion.

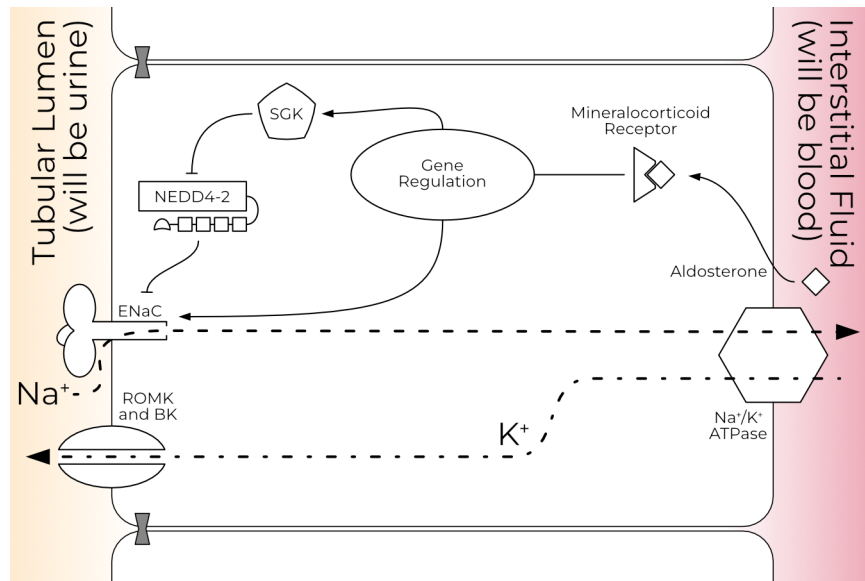


Figure 1.1.: Simplified model of ENaC regulation in a principal cell of the distal nephron in the kidney.

When the kidney is not receiving enough salt, it initiates a cascade which ends with the mineralocorticoid hormone aldosterone augmenting the activity of ENaC in the distal nephron (Figure 1.1). Apical sodium permeability is

1. ENaC in the Body

Of note: Asher and colleagues report an aldosterone mediated increase in expression of the β and γ , but not α , subunits. A trend of subunit-specific regulation is widely observed in the literature, but poorly understood.

increased both by synthesis of new channels as well as trafficking of an existing pool of channels to the cell surface^{2,3}. Despite its expression relatively late in the nephron, ENaC is the rate-limiting step of sodium reabsorption in the kidney. Sodium in the principal cells is transported across the basolateral membrane by the Na^+/K^+ ATPase, and therefore induces retention of extra water to maintain the tightly-controlled plasma sodium level. Thus, ENaC controls three essential functions of kidney filtration: first, the amount of sodium reabsorbed by the kidney; second, blood volume (and therefore pressure); third, the amount of potassium passed from the plasma into the urine.

A variety of ENaC mutations have dramatic effects on patients' blood pressure. One of the earliest described is Liddle syndrome⁴. Liddle syndrome (also called pseudoaldosteronism) results from an autosomal dominant gain-of-function mutation in ENaC. Severe hypertension, low potassium, high blood pH, low renin activity, and low aldosterone are hallmarks of the disease⁵. It is a rare disorder, with only 72 families described as of 2018⁶. However, after excluding patients with other clear causes (primary aldosteronism, kidney or heart diseases, and obstructive sleep apnea), approximately one in one hundred hypertensive patients had Liddle syndrome, indicating that the prevalence may be higher than is currently thought^{7,8}. All but one of the described cases involve mutation of the β or γ subunits^{6,8}.

A majority of the mutations in the β and γ subunits disrupt or remove entirely a proline-rich PY motif at the C-terminus of those channels⁹. This PY motif is the binding site for the E3 ubiquitin ligase NEDD4-2 (see section). Study of ENaC surface dwell time is complicated by a reserve pool maintained by the cells to be cycled up to the membrane, but there is a consensus that ENaC is recycled quickly; surface half life estimates range from fifteen minutes to three hours, with the low end having more support¹⁰. ENaC lacking the PY motif cannot be pulled back in from the membrane, thus increasing sodium permeability by increasing N rather than the conductivity or P_O of the channels¹¹⁻¹³. The α subunit does have a PY motif, but no Liddle syndrome mutation of the α PY has been described. This is discussed further in]{.aside} The remaining minority of described Liddle syndrome mutations (including the sole ENaC _{α} mutation) which do not affect PY-motif binding instead directly augment channel P_O ⁶. Liddle syndrome is typically treated with small molecules that block ENaC (amiloride or triamterene) and a low-salt diet.

Loss-of-function mutations also cause severe phenotypes. Type 1 pseudohypoaldosteronism (PHA1) was first described in a severely dehydrated infant who did not respond to aldosterone treatment¹⁴. There are two forms of

1.1. ENaC in the kidney

PHA1: renal PHA1, which is milder and involves a mutation in the mineralocorticoid receptor; and systemic PHA1, which involves a mutation in a gene for ENaC α , β , or γ ^{15,16}. Patients with systemic PHA1 are unable to retain any salt, and so become severely dehydrated and have high potassium, low sodium, and increased acidity in their blood⁵. This makes the disease particularly deadly to newborns, and requires life-long supplementation with sodium and the potassium elimination drug Kayexalate¹⁷. Contrary to the pattern observed for Liddle Syndrome, most systemic PHA1 mutations occur in the gene encoding ENaC α ¹⁷. The majority of described PHA1 mutations are nonsense mutations, although three missense mutations have been described¹⁶⁻⁻¹⁸. One of these mutations occurs in the palm domain, one in the transmembrane domain, and one likely in the intracellular domain.

Although the genes for the β and γ subunits are both on chromosome 16 and the gene for ENaC α is on chromosome 12, no difference in the rates of mutation for the affected genes are seen between patients and control groups¹⁷.

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