An alternative hypothesis to the widely held view that renal excretion of sodium accounts for resistance to salt-induced hypertension

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It is widely held that in response to high salt diets, normal individuals are acutely and chronically resistant to salt-induced hypertension because they rapidly excrete salt and retain little of it so that their blood volume, and therefore blood pressure, does not increase. Conversely, it is also widely held that salt-sensitive individuals develop salt-induced hypertension because of an impaired renal capacity to excrete salt that causes greater salt retention and blood volume expansion than that which occurs in normal salt-resistant individuals. Here we review results of both acute and chronic salt-loading studies that have compared salt-induced changes in sodium retention and blood volume between normal subjects (salt-resistant normotensive control subjects) and salt-sensitive subjects. The results of properly controlled studies strongly support an alternative view: during acute or chronic increases in salt intake, normal salt-resistant subjects undergo substantial salt retention and do not excrete salt more rapidly, retain less sodium, or undergo lesser blood volume expansion than do salt-sensitive subjects. These observations: (i) directly conflict with the widely held view that renal excretion of sodium accounts for resistance to salt-induced hypertension, and (ii) have implications for contemporary understanding of how various genetic, immunologic, and other factors determine acute and chronic blood pressure responses to high salt diets.

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According to Hall,[1] raising salt intake in individuals with normal kidney function "usually does not increase arterial pressure much because the kidneys rapidly eliminate the excess salt and blood volume is hardly altered." This view holds that normal subjects are usually salt-resistant, that is, resistant to the pressor effects of both acute and chronic increases in salt intake, because they are able to rapidly eliminate excess salt and avoid substantial sodium retention and volume expansion. Furthermore, as recently stated by Crowley and Coffman,[2] "classic Guytonian models suggest that a defect in sodium excretion by the kidney is the basis for salt sensitivity, with impaired elimination of sodium during high-salt feeding leading directly to expanded extracellular fluid volume, which promotes increased blood pressure."

The widely held view[1–8] that normal salt-resistant subjects are protected from salt-induced increases in blood pressure because they rapidly excrete a salt load[9] and retain little sodium, is illustrated by the *hypothetical* study results presented in a recent review by Brands[8] (Figure 1). This view is incorporated, in full or in part, into many contemporary accounts of how various genetic, immunologic, and other factors determine acute or chronic blood pressure responses to a high salt intake.[1,2,6,8,10–15] In addition, Scholl and Lifton[12] have proposed that in the general population, genetic variants associated with decreased activity of sodium transporters in the renal tubule, contribute to resistance from hypertension by promoting increased salt excretion and decreased external salt balance.[16–18]

Recently, we[19] noted that the results of acute salt-loading studies in normotensive salt-resistant subjects seem to be at odds with the widely held view that normal subjects are usually salt-resistant because they excrete a salt load rapidly[9] and undergo very little blood volume expansion.[1] Here, we systematically review the results of studies that investigate whether normal subjects are usually resistant to the pressor effects of either acute or chronic salt loading because they rapidly excrete the excess salt and their blood volume is hardly altered.[1] Although many investigators have discussed salt-loading studies in salt-resistant *hypertensive* subjects, few if any investigators have systematically considered the results of both acute and chronic salt-loading studies in *normal* individuals (salt-resistant *normotensive* control subjects).

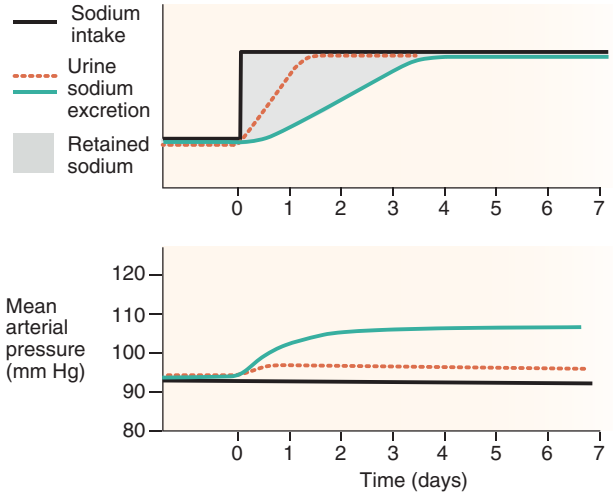

Figure 1 | Hypothetical experimental results reflecting the widely held view[1–4,6,8] that normal subjects excrete a salt load more rapidly and retain less sodium than salt-sensitive subjects. The figure shows presumed changes in sodium balance (i.e., changes in sodium balance envisioned to occur during salt-loading in normal subjects and salt-sensitive subjects).[8] Note that these hypothetical sodium balance results envisioned by Brands[8] differ from the actual sodium balance results generated in published salt-loading studies of normal subjects and salt-sensitive subjects (shown in Figures 2–6). In referring to the hypothetical results in the figure for salt-resistant normal subjects (depicted by the dotted, orange line), Brands states that the "line shows that sodium excretion normally rises rapidly to match an increase in sodium intake, such that blood pressure changes only minimally."[8] In referring to the hypothetical results in the figure for salt-sensitive subjects (depicted by the solid, light green line), Brands[8] notes that the line "shows that when renal sodium excretory capability is impaired, sodium balance takes longer to achieve. The result is an increase in extracellular fluid volume and blood pressure." Adapted from Brands MW. Chronic blood pressure control. *Compr Physiol.* 2012;2:2481–2494,[8] with permission from Wiley.

For purposes of discussion, we refer to "acute" (short-term) salt-loading studies as those in which the salt-loading is carried out for a matter of days to no more than a week or 2. We define "chronic" (long-term) salt-loading studies as those in which the salt-loading is carried out for ≥3weeks, and in some cases up to a year. Because we are focused here on mechanisms that mediate resistance to salt-induced hypertension, we review studies of the effects of increasing salt intake rather than studies of dietary salt restriction or diuretic-induced salt depletion. We emphasize the results of clinical studies in which the levels of salt intake tested are within ranges observed to be consumed by humans in non-research environments. We begin by discussing the effects of acute and chronic salt-loading on external sodium balance, and then we discuss the effects of acute and chronic salt-loading on blood volume.

During acute salt loading, normal salt-resistant subjects usually retain large amounts of sodium and do not rapidly excrete it

In humans and in animals, the results of sodium balance studies consistently demonstrate that in response to short-term salt-loading over approximately 1 week, normal salt-resistant subjects retain substantial amounts of sodium,[20–34] just as much and sometimes more than the amounts of sodium retained by either normotensive or hypertensive salt-sensitive subjects (Figures 2–5).[21,23–25,29–32] Yet, blood pressure increases little if at all in normal salt-resistant subjects (Figures 2–5). This observation, that normal salt-resistant subjects acutely retain large amounts of sodium like salt-sensitive subjects do, has been made not only in salt-loading studies in which normal salt-resistant control subjects have been compared with humans or animals with spontaneous forms of salt-sensitivity (Figures 2–4),[21,23–25,29–31] but also in salt-loading studies in which normal control subjects have been compared with animals rendered salt-sensitive by surgical reduction of renal mass (Figure 5).[32] During acute salt-loading sufficient to raise blood pressure in salt-sensitive subjects, normal salt-resistant individuals undergo large increases in

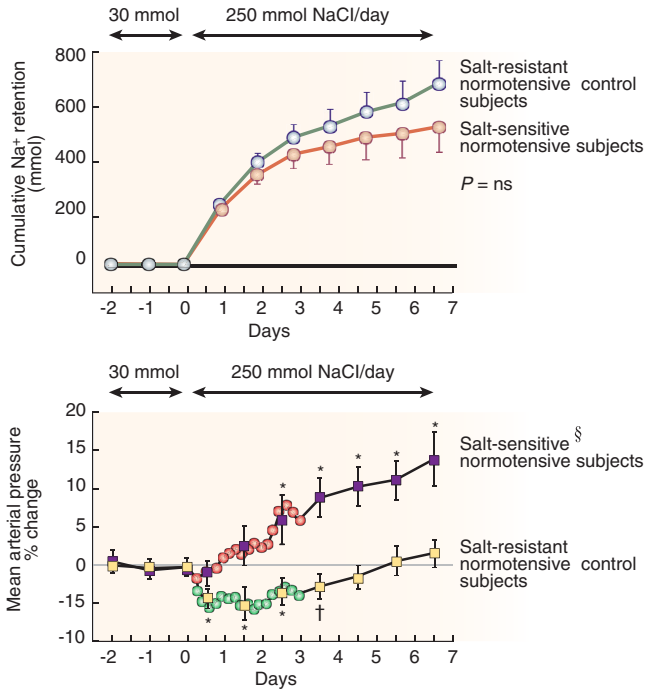

Figure 2 | Results of studies in normotensive African Americans in which Schmidlin *et al.*[25] measured cumulative sodium retention and mean arterial pressure before and after increasing dietary intake of NaCl from 30 mmol/day to 250 mmol/day. During the last 3 days of the low NaCl diet, the salt-resistant normotensive control subjects ($n = 18$) did not differ from the salt-sensitive normotensive subjects ($n = 19$) with respect to mean arterial pressure or cumulative sodium balance. § denotes significant difference between the salt-induced change in arterial pressure in salt-sensitive subjects versus salt-resistant normal control subjects on day 1 of high NaCl intake ($P < 0.05$) and on days 2 to 7 of high NaCl intake ($P < 0.001$). There was no significant (ns) difference in cumulative sodium balance between salt-sensitive subjects and salt-resistant normal control subjects throughout the 7-day period of salt-loading. Significant difference compared with period of low NaCl intake denoted by †$P < 0.05$; *$P < 0.01$. Changes in blood pressure are shown at 4-hour intervals for the first 72 hours and then at 24-hour intervals thereafter. Results are displayed as means and 95% confidence intervals. Adapted with permission from Schmidlin O, Forman A, Leone A, et al. Salt sensitivity in blacks: evidence that the initial pressor effect of NaCl involves inhibition of vasodilatation by asymmetrical dimethylarginine. *Hypertension.* 2011;58:380–385.[25]