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REVIEW

Hemodynamic Mechanisms Initiating Salt-Sensitive Hypertension in Rat Model of Primary Aldosteronism

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Summary

Few studies have investigated the hemodynamic mechanism whereby primary hyperaldosteronism causes hypertension. The traditional view holds that hyperaldosteronism initiates hypertension by amplifying salt-dependent increases in cardiac output (CO) by promoting increases in sodium retention and blood volume. Systemic vascular resistance (SVR) is said to increase only as a secondary consequence of the increased CO and blood pressure. Recently, we investigated the primary hemodynamic mechanism whereby hyperaldosteronism promotes salt sensitivity and initiation of salt-dependent hypertension. In unilaterally nephrectomized male Sprague-Dawley rats given infusions of aldosterone or vehicle, we found that aldosterone promoted salt sensitivity and initiation of salt-dependent hypertension by amplifying salt-induced increases in SVR while decreasing CO. In addition, we validated mathematical models of human integrative physiology, derived from Guyton's classic 1972 model - Quantitative Cardiovascular Physiology-2005 and HumMod-3.0.4. Neither model accurately predicted the usual changes in sodium balance, CO, and SVR that normally occur in response to clinically realistic increases in salt intake. These results demonstrate significant limitations with the hypotheses inherent in the Guyton models. Together these findings challenge the traditional view of the hemodynamic mechanisms that cause salt-sensitive hypertension in primary aldosteronism.

Key words

Aldosterone • Blood pressure • Salt • Sodium • Rat

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Introduction

NaCl-dependent hypertension is a clinical disorder of major public health significance and is a leading cause of cardiovascular death and disability worldwide [1,2]. In most cases, the etiology of NaCl-dependent hypertension is unknown. However, it has been estimated that a significant percentage of hypertensive individuals have a NaCl-dependent form of hypertension caused by mineralocorticoid excess when primary aldosteronism is the most common secondary form of hypertension [3-5]. In addition, it has become increasingly recognized that mineralocorticoid excess or increased sensitivity to mineralocorticoids may frequently contribute to salt-sensitive forms of hypertension that are resistant to treatment with multiple antihypertensive drugs [3,6]. In this review, we describe current knowledge about hemodynamic abnormality through which mineralocorticoids enable increases in salt intake to almost always initiate hypertension and what are the mechanisms that mediate that hemodynamic abnormality.

The main controversy on the hemodynamic initiation of mineralocorticoid-NaCl dependent hypertension

The hemodynamic factors that ultimately determine mean arterial pressure (MAP) are cardiac output (CO) and systemic vascular resistance (SVR). The main controversy of mechanisms initiating hypertension is whether mineralocorticoids enable increases in salt intake to initiate hypertension by causing

a mineralocorticoid-dependent abnormality in the level of CO (as held by the "CO theory"), or in SVR (as held by the "SVR theory"), or both. Some investigators have contended that an abnormally high level of CO is responsible [7-9], others have reported that an abnormally high level of SVR is responsible [10-12], and others have reported that either an abnormal level of CO or SVR or both are responsible [13,14]. Here we summarize the main competing theories on the initiation of mineralocorticoid-NaCl hypertension, discuss why this controversy on mechanisms has persisted, and explain how the current research resolves this controversy.

The cardiac output (CO) theory for initiation of mineralocorticoid-NaCl hypertension

The prevailing theory of mineralocorticoid-NaCl hypertension holds that mineralocorticoids enable increases in salt intake to hemodynamically initiate hypertension by initially causing an abnormally high level of cardiac output (CO) as a consequence of their ability to cause abnormally high levels of salt retention and blood volume [7,15-17]. This CO theory (also known as Guyton's "volume loading" theory) is diagrammed in Fig. 1 and explicitly holds that systemic vascular resistance (SVR) is normal during initiation of the hypertension and becomes abnormal later, after the initial increases in BP and CO have occurred. As shown in the left panel of Fig. 1, the CO theory holds that in normal individuals, administration of a high salt diet does not initiate hypertension because it is believed that normal individuals rapidly excrete a salt load and therefore, have little or no initial increases in sodium retention and CO in response to salt loading. According to the Guyton and Hall Textbook of Medical Physiology: "raising salt intake in the absence of impaired kidney function or excessive formation of anti-natriuretic hormones usually does not increase arterial pressure much because the kidneys rapidly eliminate the excess salt and blood volume is hardly altered" [18]. It should be noted that the Guyton and Hall textbook provides no data or references supporting the contention that normal subjects excrete a salt load so rapidly that they have little or no increases in salt retention and blood volume. It should also be noted that there is no evidence that normal subjects excrete a salt load more rapidly than subjects with mineralocorticoid excess given the same salt load. The salt-induced increases in CO that initiate the increased BP are transient and the pressure-dependent and/or flow-dependent autoregulation in peripheral tissues causes a fall in CO back towards normal and an increase in SVR above normal that sustains the hypertension (Fig. 1, right panel).

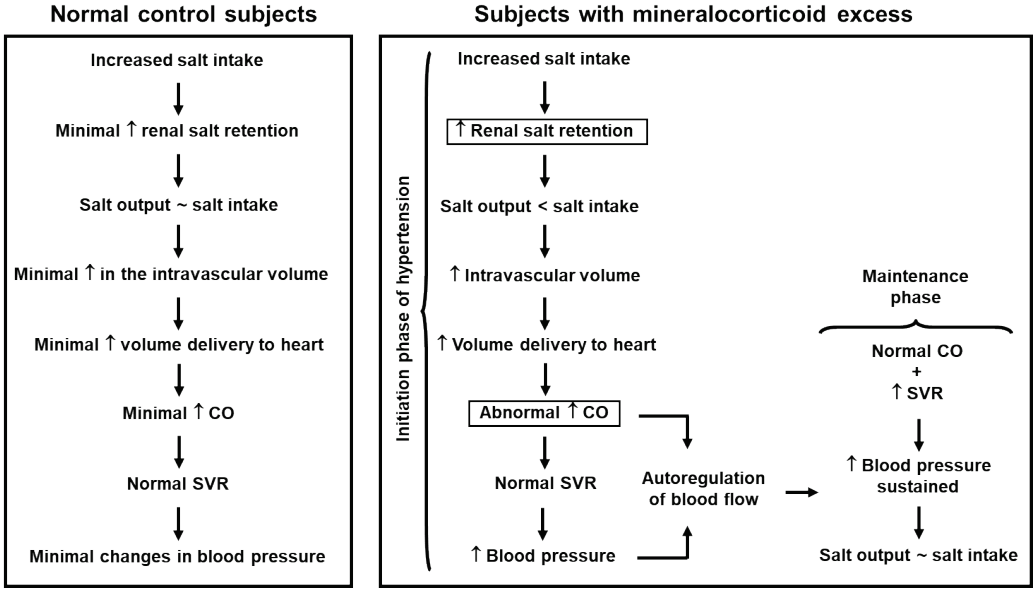

Fig. 1. The CO (Guyton's volume-loading) theory of the pathogenesis of NaCl-induced hypertension. Left panel. The mechanism held to mediate a normal, i.e., nonpressor, response to increases in salt intake (common pathway for salt resistance). Right panel. The mechanism held to mediate an abnormal, i.e., pressor, response to increases in salt intake (mechanism of salt sensitivity). According to the theory, an abnormal increase in the amount of renal salt reabsorption/retention is usually an early, critical abnormality that enables increased salt intake to initiate hypertension by increasing CO (boxes). Modified from [19].

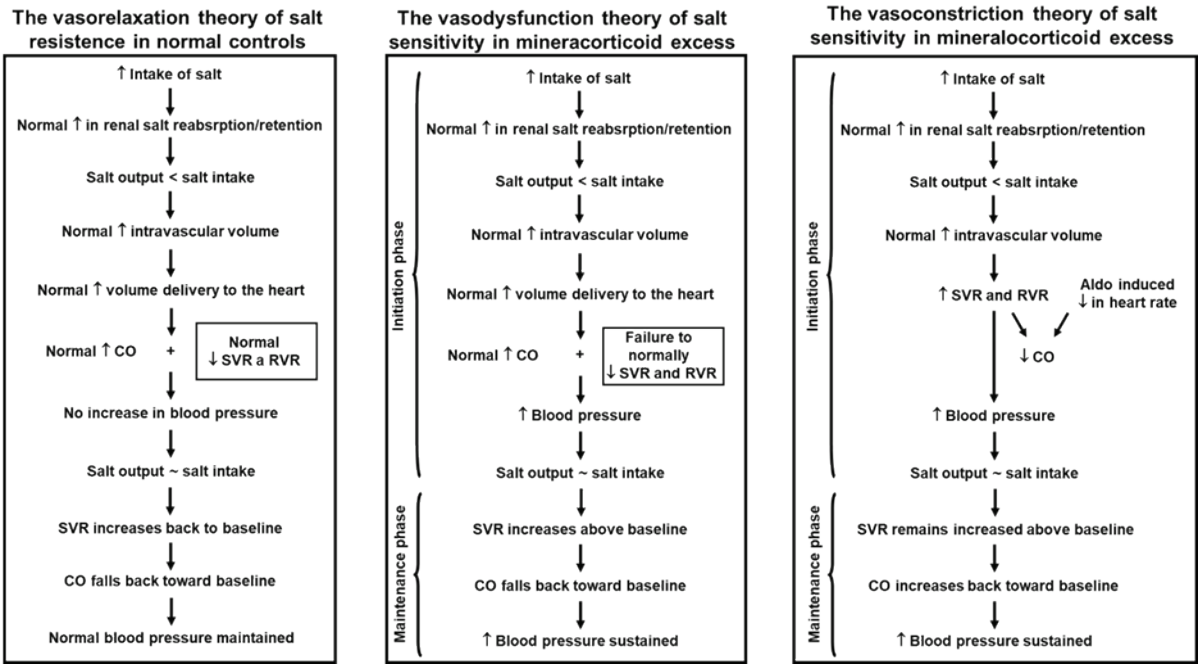

Fig. 2. The SVR theory of the pathogenesis of NaCl-induced hypertension. Left panel. Usual pathway yielding a normal (nonpressor) response to NaCl loading (mechanism of salt resistance, the vasorelaxation theory of salt resistance). This pathway depicts the initial sodium balance and hemodynamic responses to increases in salt intake usually observed in salt-resistant normotensive control subjects. Middle panel. Usual pathway yielding an abnormal (pressor) response to NaCl loading (mechanism of salt sensitivity, the vasodysfunction theory of salt sensitivity). Right panel. The vasoconstriction theory of salt sensitivity characterized by increased SVR and decreased CO. Reduced CO may be secondary to increased SVR and reduced heart rate.

The systemic vascular resistance (SVR) theory: The vasorelaxation theory of salt resistance, the vasodysfunction theory of salt sensitivity, and the vasoconstriction theory of salt sensitivity

- ***The vasorelaxation theory of salt resistance.*** In contrast to the CO theory, the SVR theory holds that during initiation of a high salt diet, the levels of systemic and renal vascular resistance (RVR) in response to salt loading, are abnormal, i.e., greater than those which occur during initiation of salt loading in normal controls, whereas the increases in sodium balance and CO are not abnormal, i.e., not greater than the increases in sodium balance and CO which occur during initiation of salt loading in normal controls. As shown in the left panel of Fig. 2 and contrary to popular belief, this theory holds that in normal controls, salt loading initially induces substantial increases in CO. However, BP does not increase because normal controls vasodilate and reduce SVR, thereby offsetting the pressor effects otherwise expected with NaCl-induced increases in CO.
- ***The vasodysfunction theory of salt sensitivity.*** The theory holds that in subjects with mineralocorticoid excess, salt loading induces similar increases in CO as in controls, i.e., increases in CO that are not greater than those induced by salt loading in controls, however, the subjects with mineralocorticoid excess fail to normally vasodilate and reduce vascular resistance like normal controls [20] (Fig. 2, middle panel).
- ***Vasoconstriction theory of salt sensitivity.*** It has been reported that in some cases of salt-induced hypertension with mineralocorticoid excess, increases in blood pressure are initiated by increases in vascular resistance in the absence of increases in CO or even with decreases in CO [11,21]. The induction of salt-dependent hypertension in these cases is better explained by a vasoconstriction theory of salt sensitivity (Fig. 2, right panel).

Why hasn't this controversy on hemodynamic initiation of mineralocorticoid hypertension been resolved?

There are three key reasons why previous studies have not resolved this controversy:

1. Surprisingly, all previous studies lacked necessary normal controls. None of the previous studies of this issue compared the changes in CO and SVR that occur during the initiation of salt loading in mineralocorticoid-treated subjects to those that occur during initiation of salt loading in normal controls not treated with mineralocorticoids [7-12,14]. Without the necessary normal controls, the previous studies could not determine whether the salt retention induced by giving a high salt diet and mineralocorticoids together, causes the initial CO or SVR responses to be abnormal or normal, i.e. different from the initial CO or SVR responses to salt retention induced by giving a high salt diet to normal controls alone (i.e., without mineralocorticoids). Without the use of adequate normal controls, previous investigators studying mineralocorticoid-NaCl hypertension [7-12,14] failed to recognize that the normal hemodynamic response to initiation of salt loading in control subjects not given mineralocorticoids involves substantial increases in salt retention, stroke volume, and CO together with substantial decreases in SVR that offset potential pressor effects of the increases in CO [22-25].

2. A mistaken assumption. Guyton and colleagues appear to have mistakenly assumed that normal subjects excrete a salt load very quickly and therefore, do not undergo substantial increases in salt retention, blood volume, and CO in response to substantial increases in salt intake [26-29]. In fact, it has never been demonstrated that normotensive salt-resistant subjects excrete a salt load faster than salt-sensitive subjects, with or without mineralocorticoid excess. In normal salt-resistant animals and humans, salt loading (increasing salt intake) induces substantial increases in salt retention, blood volume, stroke volume and cardiac output, similar to those induced by salt loading in salt-sensitive subjects [22-25]. The reason that salt does not increase BP in normal subjects is because normal subjects robustly vasodilate and reduce SVR in response to salt loading, not because normal subjects excrete a salt load faster than salt-sensitive subjects. The published data show that salt-sensitive subjects do not initially retain more of a salt load than true normal controls, i.e. salt-resistant subjects with normal blood pressure [22,24,25,30,31].

Because previous studies of mineralocorticoid hypertension were mainly correlational studies and lacked adequate normal controls (i.e., normal subjects studied during the initiation of salt retention induced by salt loading without mineralocorticoids), they were not capable of determining which of the observed hemodynamic changes (or lack thereof) were necessary or sufficient for initiation of the mineralocorticoid-NaCl hypertension. Interestingly, investigators who performed an intervention study found that preventing increases in CO with a beta adrenergic blocker did not prevent initiation of mineralocorticoid-NaCl hypertension. This indicated that an abnormally high level of CO was not necessary for initiation of the hypertension, and that an abnormality in SVR was involved in initiation of the hypertension [10,32]. However, these studies were largely ignored or dismissed based on questions raised about small sample sizes, experimental designs, and CO measurement methods [9,33].

3. Previous studies used inadequate hemodynamic monitoring techniques. Inconsistency in the hemodynamic findings reported by different investigators could be due to the questionable approaches that were used to monitor the hemodynamic variables. In previous studies, suboptimal techniques were used to monitor CO, SVR, and BP and the variables were not continuously measured beat to beat, 24 hours/day throughout the experiments. Two groups [7,12] indicated that they continuously sampled the hemodynamic variables for at least 20 hours per day yet, in fact, the sampling was intermittent and the sampling time in those studies actually totaled no more than 4 hours per day; these two studies gave conflicting results [7,12]. Furthermore, neither group examined changes in CO and SVR induced by salt loading in normal controls not given mineralocorticoids. Other studies were even less reliable because they did not even monitor CO and SVR daily and were not capable of detecting early events occurring during initiation of the salt retention and hypertension [8,9].

Testing computer models predicting human responses to a high salt diet

Guyton and colleagues pioneered the use of large-scale computer models to investigate potential physiologic abnormalities involved in the initiation and maintenance of salt-induced hypertension [34,35]. The original Guyton model was revised and expanded by Guyton and colleagues over decades. The most evolved derivative of the 1972 Guyton model is a large, multi-scale model called “HumMod” that includes a Windows-based graphical user interface [36].

In reviewing the literature on the 1972 Guyton model and the most evolved derivatives of the Guyton model, we could not find validation studies testing the capacity of the models to accurately predict sodium balance, cardiac output, and vascular resistance responses of normal subjects to increases in dietary salt within the real life range of salt intake in humans. Accurate quantitative characterization of the physiologic responses to salt loading in normal control subjects is a prerequisite for accurately determining which physiologic responses to salt loading are abnormal in salt sensitive subjects.

The lack of published validation studies of the historical Guyton model, or of its contemporary derivatives, HumMod and QCP models with respect to predicting normal sodium balance and hemodynamic responses to salt loading is surprising and prompted our recent investigation [37,38]. For validation testing, the predictions of the computer models were plotted against the human experimental data [25]. A model was considered to fail validation testing when the salt-induced change predicted by the model fell outside the 95 % confidence limits of the mean of the salt-induced changes observed in human studies. As can be seen in Fig. 3A, both model simulations vastly underestimated the cumulative amount of sodium that is usually retained in response to switching from a very low NaCl intake to a high salt intake in normal subjects (normotensive salt-resistant subjects). As can be seen in Fig. 3B, both computer models accurately predicted that in normal subjects, switching from a very low-salt diet to a high salt diet for 5 to 7 days causes minimal increases in blood pressure above baseline. On the other hand, contemporary computer models fail to accurately predict cardiac output (Fig. 3C) and systemic vascular resistance (Fig. 3D) responses to short-term salt loading in normal humans.

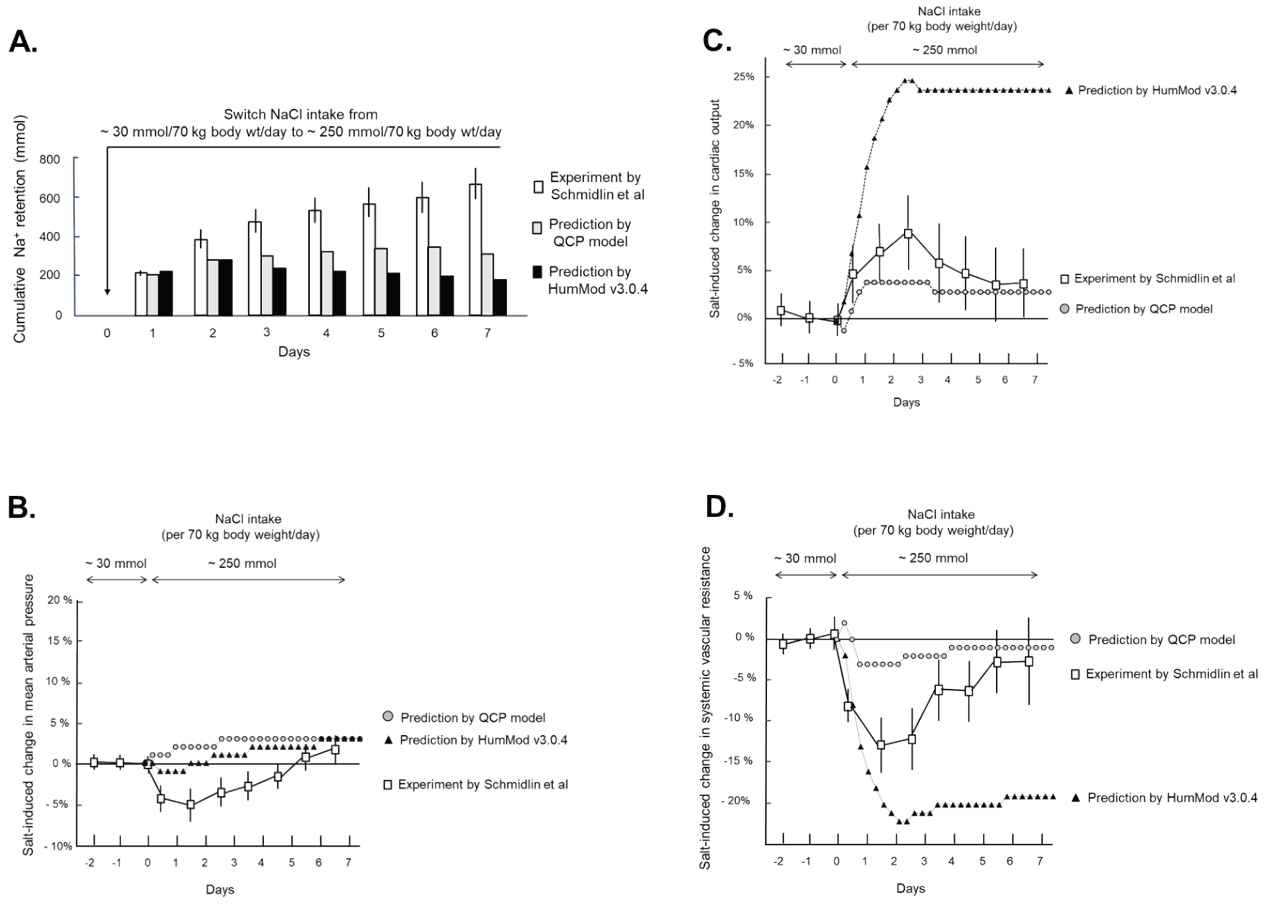

Fig. 3. Experimental and predicted short-term changes in cumulative sodium retention (**A**), mean arterial pressure (**B**), cardiac output (**C**), and systemic vascular resistance (**D**) induced by switching from a very low-salt diet to a high-salt diet. This figure shows percentage changes induced by switching NaCl intake from ≈30 mmol NaCl per 70 kg body weight per day to ≈250 mmol per 70 kg body weight per day according to the studies of Schmidlin *et al.* [25] in normotensive salt-resistant humans and according to the predictions of HumMod 3.0.4 and Quantitative Cardiovascular Physiology (QCP)-2005. Results of human studies are presented as means and 95 % CIs. Modified from [36].

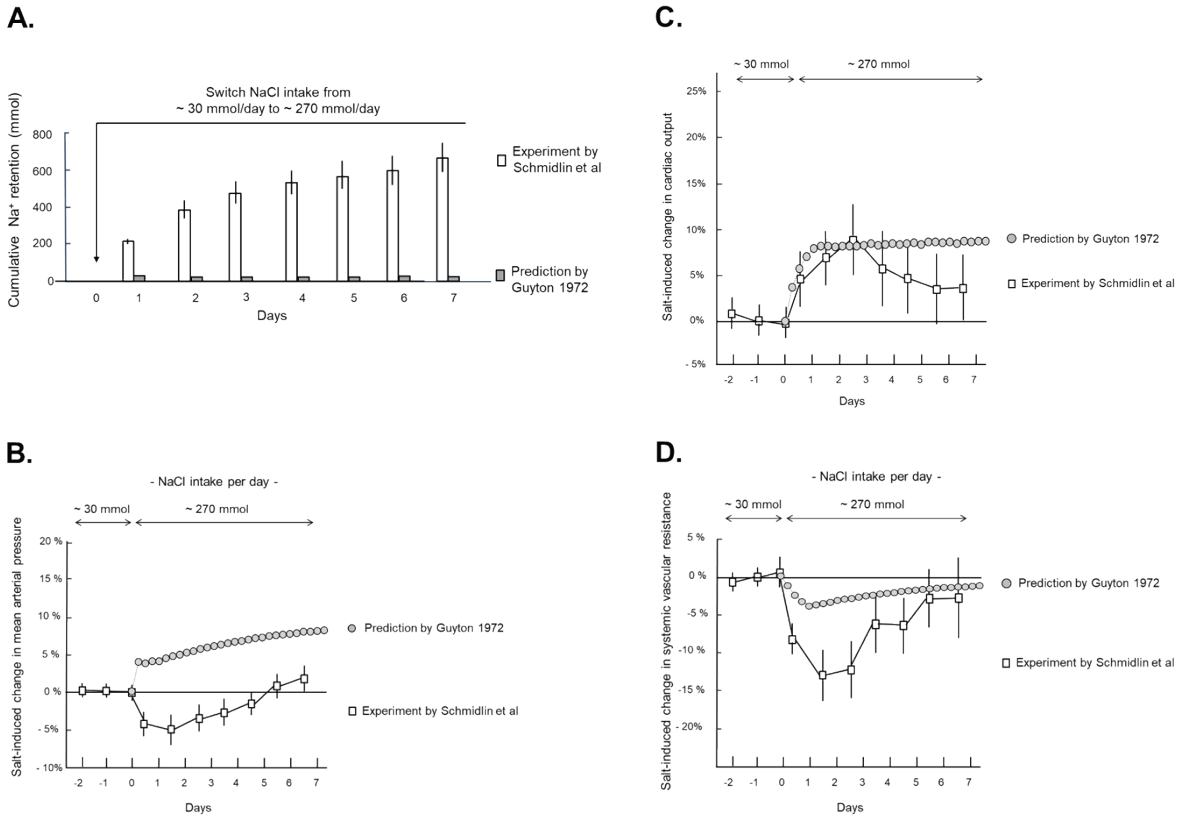

Fig. 4. Comparison of predictions from the 1972 Guyton model to the results from human studies [25]. This figure shows the percentage changes in cumulative sodium retention (**A**), mean arterial pressure (**B**), cardiac output (**C**), and systemic vascular resistance (**D**) predicted to occur in response to switching from a very low NaCl intake of 30 mmol/day to a high NaCl intake of 270 mmol/day for 7 days. Modified from [37].

However, both models appropriately reflect the general trends in these variables that normally occur in response to physiologic salt loading. Specifically, both models show that in normal subjects, non-extreme salt loading induces relatively little or no increase in blood pressure because normal subjects usually undergo robust vasodilation and reduce systemic vascular resistance sufficiently to offset the potential pressor effects of substantial salt-induced increases in cardiac output. These observations are consistent with the results of salt loading studies in normal salt-resistant humans and in animals [20,25]. These observations are also consistent with the vasodysfunction theory of salt sensitivity [19,20] which holds that in response to salt loading, normal subjects undergo substantial decreases in systemic vascular resistance that offset potential pressor effects of salt-induced increases in cardiac output whereas salt-sensitive subjects do not.

We also performed validation testing of the original 1972 Guyton model against the human experimental data [34]. As can be seen in Fig. 4A, Guyton model underestimated the cumulative amount of sodium that is usually retained in response to a high salt intake in normal subjects. In addition, the original 1972 Guyton model clearly overestimates the extent to which arterial pressure increases in response to salt loading in normal humans (Fig. 4B). Thus, the default subject with normal renal function simulated by the 1972 Guyton model is not normal and is salt sensitive according to criteria recommended for identifying salt sensitivity by the expert panel of the American Heart Association, and by other scientists with experience investigating salt sensitivity in humans [39]. The greater salt sensitivity in the 1972 Guyton model is not initiated by greater levels of sodium retention and cardiac output, but rather by greater levels of systemic vascular resistance due to a failure to vasodilate after salt loading (Fig. 4D).

It can be concluded that the results of testing computer models demonstrate significant limitations with the hypotheses inherent in Guyton models regarding the usual regulation of sodium balance, cardiac output and vascular resistance in response to increased salt intake in normal salt-resistant humans. Accurate understanding of the normal responses to salt loading is a prerequisite for accurately establishing abnormal responses to salt loading. Accordingly, the present results raise concerns

about the interpretation of studies of salt sensitivity with the various Guyton models.

Experimental testing hemodynamic mechanisms initiating salt-sensitive increases in blood pressure in a rat model of primary aldosteronism

In recent studies in a widely used rat model of primary aldosteronism, we directly tested the hemodynamic mechanism whereby hyperaldosteronism enhances salt sensitivity and initiation of salt-induced hypertension [21]. We continuously monitored mean arterial pressure (MAP), cardiac output (CO), and systemic vascular resistance (SVR), 24-hrs/day, 7 days/week using implanted arterial pressure probes and Doppler ultrasonic flow probes in unrestrained, unilaterally nephrectomized, male Sprague-Dawley rats receiving constant infusions of aldosterone or vehicle on low-salt diet and during transition to high-salt diet. We found that in aldosterone-treated animals, CO decreased during initiation of salt-induced increases in blood pressure and remained below control during the high-salt period. Thus, in hyperaldosteronism, initiation of salt-dependent hypertension was caused by primary increases in SVR, with reductions in CO.

Figure 5 shows the absolute values for 24-hr average MAP, CO, and SVR on the last 7 days of the low-salt diet (0.26 % NaCl) and on each day of the high-salt diet (4 % NaCl). In vehicle treated controls, switching from the low-salt to the high-salt diet initiated modest increases in MAP by increasing SVR while simultaneously decreasing CO. In aldosterone-treated rats compared with control rats, switching from a low-salt diet to a high-salt diet caused greater increases in MAP and SVR while simultaneously decreasing CO. Mean CO did not increase at any time during initiation of salt-induced increases in blood pressure in either the control rats or rats infused with aldosterone (Fig. 5). The results show that aldosterone enhances salt sensitivity and augments salt-induced hypertension by amplifying salt-dependent increases in SVR. Salt-dependent hypertension is initiated during decreases in CO, not increases in CO. CO decreased presumably as a consequence of increases in SVR, decreases in heart rate, and potentially increases in afterload.

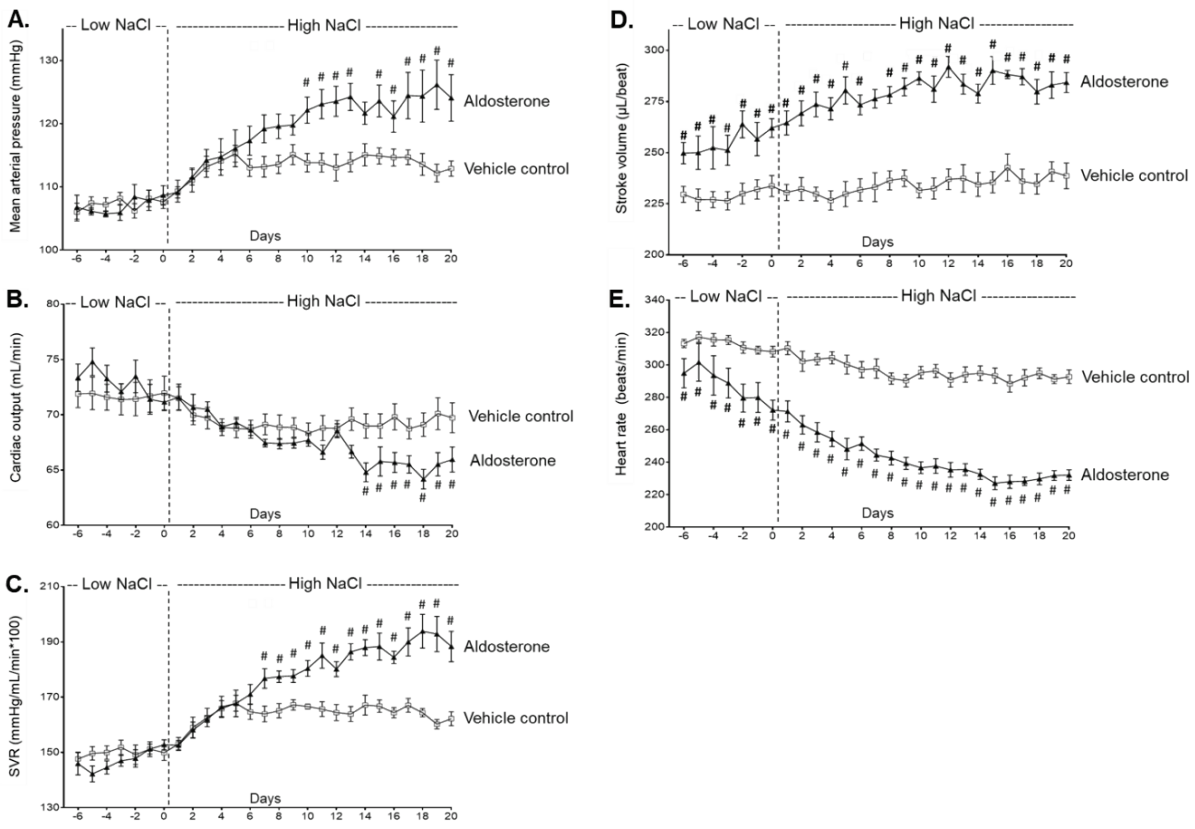

Fig. 5. Daily 24-hour averages (mean±SEM) of mean arterial pressure (MAP) (**A**), cardiac output (CO) (**B**), systemic vascular resistance (SVR) (**C**), stroke volume (**D**), and heart rate (**E**) during administration of a low-NaCl diet (0.26 % NaCl) and a high-NaCl diet (4 % NaCl) in control rats infused with vehicle and in rats infused with aldosterone. Modified from [21].

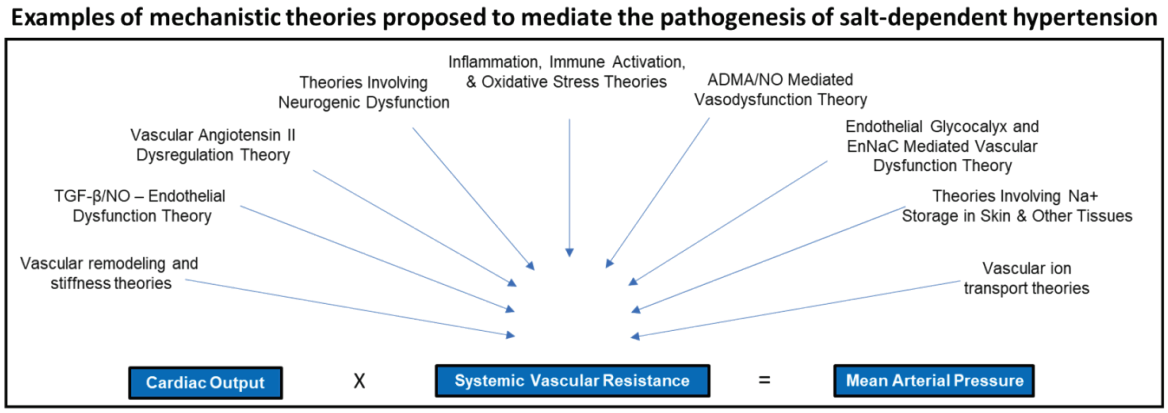

Fig. 6. Examples of mechanistic theories proposed to mediate the pathogenesis of salt-dependent hypertension. Some of these mechanistic theories might explain how the combination of excess aldosterone and salt promotes the increases in systemic vascular resistance that hemodynamically initiate salt-dependent hypertension in primary aldosteronism. ADMA indicates asymmetrical dimethylarginine; EnNaC, endothelial sodium channel; and TGF-β, transforming growth factor beta. Modified from [47].

The above described studies call into question the traditional theory of Guyton, Hall, and others [7, 16, 29,40-44] that in hyperaldosteronism, the salt-dependent hypertension is initiated by "a primary increase in cardiac output followed by a secondary vasoconstriction" [7]. Our findings demonstrate that in hyperaldosteronism, increases in CO are not necessary for initiation of the salt-dependent hypertension. In hyperaldosteronism, primary increases in SVR can drive increases in blood pressure and decreases in CO during initiation of salt-dependent hypertension. Although it is widely accepted that hyperaldosteronism can promote increases in sodium balance and fluid retention, it should not be assumed that the increases in sodium balance and fluid retention translate to increases in CO.

During administration of the low-salt diet and throughout administration of the high-salt diet, stroke volume was greater, and heart rate lower in the aldosterone-treated group than in the control group (Fig. 5). In the aldosterone-treated group, stroke volume trended upwards and heart rate trended downwards during administration of the low-salt diet and during transition to the high-salt diet. In vehicle-treated controls, stroke volume trended slightly upwards and heart rate trended slightly downwards during transition from the low-salt diet to the high-salt diet (Fig. 5).

It should be noted that a significant reduction in heart rate and increases in stroke volume occurred in aldosterone-treated rats even on the low-salt diet, that is, before initiation of salt-induced elevations in blood pressure. The heart rate changes are consistent with studies showing that aldosterone binds to GPERs (G-protein–coupled estrogen receptors) and decreases heart rate by activating GPER in cardiac vagal neurons of nucleus ambiguous [45]. Other investigators using continuous telemetry recordings have shown similar reductions in heart rate during initiation of hypertension induced by deoxycorticosterone (DOC) and salt [46].

A variety of mechanistic theories have been proposed to account for the pathogenesis of salt-dependent hypertension [21]. Figure 6 shows some examples of mechanistic theories that may explain how the combination of excess aldosterone and salt promotes increases in SVR that hemodynamically initiate hypertension.

Mechanism-based strategies to prevent salt sensitivity and salt-induced hypertension

Understanding of the responsible hemodynamic mechanisms will enable the design of new approaches to prevent salt-sensitive hypertension. According to the vasodysfunction theory, the induction of salt-induced hypertension involves the combination of normal salt-induced increases in sodium balance and cardiac output together with subnormal vasodilation and abnormal levels of vascular resistance (Fig. 2, middle panel). In such cases, initiation of salt-induced hypertension could be prevented by either (1) reducing the normal increases in sodium balance and cardiac output induced by increases in salt intake (i.e. reducing salt consumption) or, (2) preventing the abnormal vascular resistance responses to increases in salt intake (i.e. preventing vasodysfunction).

(Ad 1) Food salt reduction programs to decrease the risk for salt-induced increases in blood pressure and

cardiovascular events are based on the assumption that reducing the salt concentration of processed foods will substantially reduce mean salt intake in the general population. However, contrary to expectations, reducing the sodium density of nearly all foods consumed in England by 21 % had little or no effect on salt intake in the general population [47,48]. One way to effectively reduce sodium consumption is to use salt substitutes that are often prepared by mixing potassium chloride with sodium chloride. It is reported that most individuals cannot distinguish between regular salt and salt substitutes containing no more than 30 % potassium chloride. In March 2023, the United States Food and Drug Administration (FDA) announced plan to permit potassium-containing salt substitutes (75 % NaCl, 25 % KCl) in food manufacturing [49,50].

(Ad 2) We suggest that interventions to prevent salt-induced hypertension primarily focus on preventing the abnormal physiologic mechanisms that appear to commonly mediate salt sensitivity, i.e., preventing the abnormal vascular resistance responses to salt loading that are usually required for initiation of salt-induced increases in blood pressure. It is for instance possible to promote salt resistance by non-pharmacologic manipulation of nitric oxide (NO) activity by fortifying salty foods with nitrate-rich vegetable extracts. Recently, we have found that tiny amounts of inorganic nitrate in the form of sodium nitrate or beetroot juice can protect against initiation of salt-induced increases in blood pressure [51] (Morris *et al.* 2019). In the most widely used animal model of spontaneous salt sensitivity, the Dahl salt-sensitive rat, we found that providing a molar ratio of added nitrate in the form of beetroot juice to added salt of <1:100 conferred substantial protection against salt-induced increases in blood pressure [51].

Conclusions

The above described results provide evidence for the role of vasoconstriction theory in the pathogenesis of salt-dependent hypertension in hyperaldosteronism. Aldosterone promotes salt sensitivity and initiation of salt-dependent hypertension by amplifying salt-induced increases in SVR while decreasing CO. Increases in CO are not required for initiation or maintenance of hypertension. These findings challenge the traditional Guyton's volume-loading theory of the hemodynamic mechanisms that cause salt sensitive hypertension in primary aldosteronism.

Potassium-enriched salt substitutes and fortification of salty foods with nitrate-rich vegetable extracts are examples of mechanism-based methods for preventing salt-induced hypertension that do not depend on restricting salt intake to levels recommended by various regulatory authorities.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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