

# Overview of dietary sodium effects on and interactions with cardiovascular and neuroendocrine functions<sup>1-3</sup>

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**ABSTRACT** The battle over salt has changed over the centuries from one of where to find salt sources to one of how much salt to use in a healthful manner. Many questions were answered by the INTERSALT Study across numerous countries and, yet, many questions persist. It is a love-hate relationship, an approach-avoidance paradigm. We need it but in excess it may cause harm. Questions that still remain are, Who is salt sensitive? What are the most appropriate and relevant models to study? What are the functional differences of the many salt effects? Can the data support a single public policy on dietary sodium recommendations? The following review examines some of these questions and the interaction of neural, neuroendocrine, renal, and social factors in the great salt debate. Dietary sodium can alter peripheral and central neurotransmitter concentrations, receptor density, and sensitivity. Low-sodium diets can produce acute neuroendocrine and neural compensations that are different from the chronic effects of low dietary sodium. Chronic high- or low-sodium diets may also cause trophic hormonal changes that can influence resistance vessel structure and, consequently, blood pressure. Both human and animal studies suggest a genetic basis for salt sensitivity. In some cases stress unmasks the salt sensitivity. For instance, the social context can modulate blood pressure responses to a high-sodium diet. Therefore, 24-h monitoring of blood pressure becomes important, especially in salt-sensitive persons. *Am J Clin Nutr* 1997;65(suppl):594S-605S.

**KEY WORDS** Salt, stress, hypertension, salt sensitivity, low-sodium effects, chronic effects, adaptations

## INTRODUCTION

The history of salt is long, covering thousands of years and encompassing religion, economics, wars, political battles, and now health and disease. Early civilization was concerned with finding and conserving salt. It was so precious that social bonds were formed over it. The Jews sealed covenants by exchanging salt and the Bedouins would not attack a man whose salt they had eaten. Cassiodorus, a Roman official and historian, proclaimed, "Mankind can live without gold but not without salt" (490-583 AD) (1). Roman Catholics used salt as a sign of purity and babies were baptized with salt. Through Moses, God enjoined the people of Israel to be faithful in their sacrificial offerings at the altar. "Season all your grain offerings with salt. Do not leave the salt of the covenant of your God out of your grain offerings; add salt to all your offerings" (Leviticus 2:13). Wisdom and pleasant speech was typified by salt. "Let your

conversation be always full of grace, seasoned with salt, so that you may know how to answer everyone" (Colossians 4:6).

Salaries were paid in salt (*salarius*: salt allowance) and battles were fought over salt and lost because of a lack of salt. Napoleon left 400 000 dead on his awful retreat from Moscow and attributed his men's inability to resist the hardship and cold of that ordeal to the lack of salt in their food (2). During the American Revolution there was a salt famine and bounties were given to salt makers: \$3 a bushel in Kentucky and \$16 a bushel in Ohio (3). The tax (12.5%) on salt helped to build the Erie Canal in 1825, which lowered the cost of 1 ton of merchandise from \$100 to \$5 (3). Salt was so precious that special containers were created to house and protect it. Salt cellars of the 15th century were beautifully ornate works of art, and the simple table salt shaker has hundreds of varieties that are collected as antiques and art objects (4) and are as varied as the scientists who study the effects of salt.

Today salt is plentiful thanks to efficient mining and recovery operations. Because salt is abundant in our diet and cannot always be tasted to warn of overindulgence, concern is focused on how much to consume rather than on availability. Most of our salt intake comes from processed food, where salt is used as a preservative and often is not tasted.

## BACKGROUND

Several excellent reviews of salt and cardiovascular function illustrate the complexity of this topic (5-10). The most comprehensive salt study, INTERSALT, has answered some of the questions, but others remain. The INTERSALT Study of > 10 000 subjects from 32 countries and 52 centers provided evidence of associations between salt consumption and blood pressure, but not of the magnitude expected (11). Some dietary studies showed significant blood pressure rises with large amounts of sodium (12-16); other studies showed no relation between blood pressure and salt (7, 17, 18). Because sodium is such a vital element for physiologic function and is not appreciably stored in the body, there is a complex set of integrated

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systems that regulate its balance. These control systems in animals and humans have a wide range with set points such that there is flexibility with minimal risk until extremes of sodium intake (either too low or too high) are reached. A consensus is needed to identify these extremes and to define the variables that influence sodium balance the most.

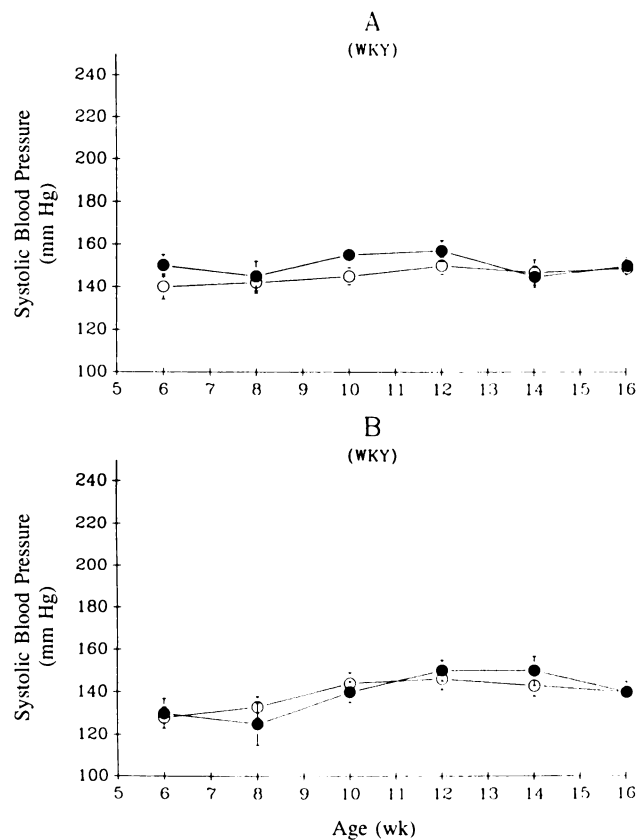
The following questions address some of the key issues. Which is the most appropriate animal model: the spontaneously hypertensive rat (SHR), the Dahl salt-sensitive rat, the Milan hypertensive rat, the stroke-prone SHR, or the kidney-clip rat model (19)? Which is the most appropriate human model: populations, patients, normotensive persons, or hypertensive persons? How long should studies last: 2, 4, or 8 wk or longer? What dosage should be studied? How do other electrolytes interact with salt? What are the effects of stress and sex differences on salt appetite? Who is truly salt sensitive? Are the markers for salt sensitivity reproducible over time and across age, sex, and obesity variables? Does a small change in blood pressure, heart rate, hormone concentration, or enzyme activity have functional significance? Some of these questions have been answered, some will be answered at this symposium, and still others will remain unanswered. In this chapter, I consider nervous system interactions, low-sodium effects, endocrine interactions, renal involvement, salt sensitivity, stress and salt appetite, and 24-h monitoring of blood pressure.

### SALT-NERVOUS SYSTEM INTERACTION

Several studies in rats showed that dietary sodium may alter central neurotransmitter and receptor concentrations and potentially modulate responses to stress. The responsiveness of central nervous system  $\alpha_2$ -adrenergic receptors and their role in the neural control of renal function were enhanced by a high sodium intake (3–4 wk of 1% NaCl) in conscious SHRs but not in normotensive Wistar Kyoto rats (WKYs) (20). Also, the brain renin-angiotensin system was shown to contribute to salt-induced enhancement of hypertension in SHRs (21).

Studies from Oparil's lab showed that hypothalamic norepinephrine concentrations are altered by sodium in SHRs (22, 23). In prehypertensive SHRs (age 2 wk) high dietary sodium intake (8% NaCl) specifically decreased norepinephrine concentrations in the anterior and posterior hypothalamus (22, 23). In Dahl salt-sensitive rats, specific brain regions, such as the paraventricular and suprachiasmatic areas, were shown to be involved (24). Sodium depletion (5  $\mu$ mol Na/g food, or 0.5 mmol/100 g) altered the release of norepinephrine from central and peripheral tissue in SHRs (25). These results suggest that the direction of central nervous system norepinephrine changes in response to dietary sodium may depend on the role of the specific brain area involved in blood pressure regulation, how each variable influences the neurotransmitter, and whether the changes are primary or secondary.

Numerous studies show that both high- and low-sodium diets can alter sympathetic nervous system (SNS) activity in animals and humans (8, 26–38). Data on the effects of dietary sodium on systolic blood pressure in WKYs, borderline hypertensive rats, and SHRs between 6 and 18 wk of age under low-stress (standard lab cage) and high-stress (territorial conflict) conditions are presented in **Figures 1–3**. In WKYs, a high sodium intake (1.2 mmol Na/g food, or 120 mmol/100 g) did not

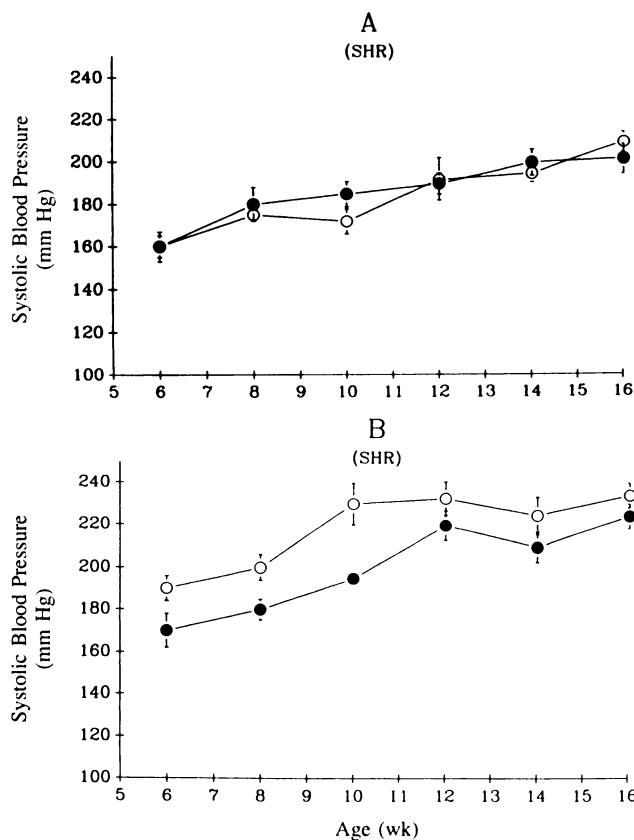


**FIGURE 1.** Blood pressure responses to (A) low-stress conditions (laboratory cage) and (B) high-stress conditions (territorial stress) in male Wistar Kyoto rats (WKYs) fed a control-sodium diet (0.12 mmol Na/g food, ●) or a high-sodium diet (1.2 mmol Na/g food, ○).  $n = 10/\text{group}$ .  $\bar{x} \pm \text{SE}$ .

significantly raise blood pressure in low- or high-stress conditions (Figure 1). In SHRs and borderline hypertensive rats (Figures 2 and 3), a high sodium intake did not significantly increase blood pressure under low-stress conditions, but when territorial stress was present, the high-sodium groups showed a significant rise in blood pressure over respective controls with standard sodium intake (0.12 mmol Na/g food, or 12 mmol/100 g). These data show that a high sodium intake (10 times greater than normal) did not raise blood pressure in SHRs or borderline hypertensive rats unless a certain level of social stress was present.

Recent work in my laboratory has attempted to evaluate the degree of participation of the SNS in raising blood pressure in SHRs subjected to territorial social stress and a high-sodium diet through use of drugs that interfere with the pathway from the central nervous system to arteriolar smooth muscle. When a vascular smooth muscle relaxant was administered (hydralazine, 0.08 g/L in drinking water), blood pressure was lowered to normotensive values (**Figure 4**). To show that the rise in blood pressure associated with the combination of stress and a high-sodium diet was not due to an increase in blood volume, a diuretic (hydrochlorothiazide, 0.1 g/L in drinking water) was administered to high-sodium, high-stress SHRs; blood pressure was not significantly lowered (Figure 4).

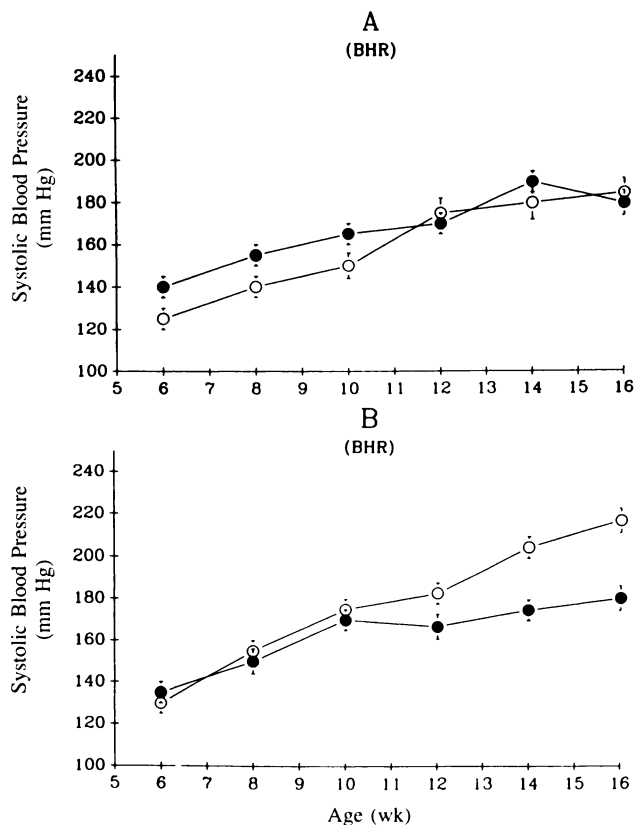
To eliminate the effects of  $\beta$ -adrenergic receptor involvement in accelerated salt-stress hypertension, a nonselective



**FIGURE 2.** Blood pressure responses to (A) low-stress conditions (laboratory cage) and (B) high-stress conditions (territorial stress) in male spontaneously hypertensive rats (SHRs) fed a control-sodium diet (0.12 mmol Na/g food, ●) or a high-sodium diet (1.2 mmol Na/g food, ○).  $n = 10/\text{group}$ .  $\bar{x} \pm \text{SE}$ . The high-sodium group under high-stress (B) had significantly higher pressures than did the control-sodium group,  $P < 0.01$  (ANOVA).

$\beta$ -adrenergic receptor blocker was given (propranolol, 0.5 mg/L in drinking water) to another group of high-sodium, high-stress SHRs. There was no change in blood pressure (Figure 4), suggesting that  $\beta$ -adrenergic receptor stimulation was not directly involved. However, when the  $\alpha_2$ -adrenergic receptor agonist clonidine was given (100  $\mu\text{g}/\text{kg}$ , intraperitoneally twice a week) to block SNS outflow, the blood pressure of the high-sodium, high-stress group was maintained at control values (Figure 4). This suggests that for chronic mild social stress to elevate blood pressure in the SHRs consuming a high-sodium diet, enhanced SNS activity with consequent constriction of resistance vessels was required. Recently, Ando et al (39) showed that salt loading (8%) accelerated the development of hypertension in young SHRs and that cicletanine (potential mechanism to block sympathetic nerve activity) decreased the blood pressure rise and plasma norepinephrine concentrations, consistent with an SNS mechanism.

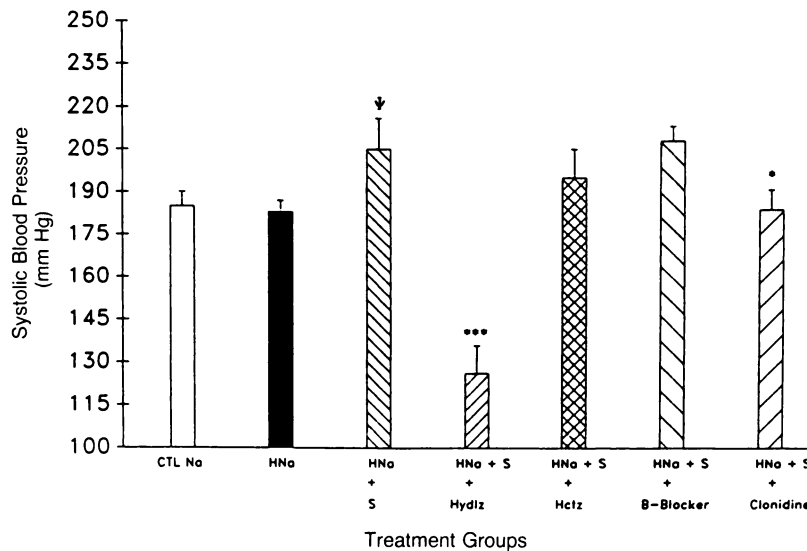
To explore in more detail the mechanism of interaction between salt and the SNS, Nilsson et al (40, 41) analyzed neuroeffector function in SHR and WKY mesenteric resistance vessels during graded vasoconstrictor fiber activation using paired experiments in Mulvany-Halpern micromyographs. Smooth muscle sensitivity and dose-response curves to exogenous norepinephrine were unaffected by dietary sodium con-



**FIGURE 3.** Blood pressure responses to (A) low-stress conditions (laboratory cage) and (B) high-stress conditions (territorial stress) in male borderline hypertensive rats (BHRs; WKY  $\delta \times$  SHR  $\text{f}$ ) fed a control-sodium diet (0.12 mmol Na/g food, ●) or a high-sodium diet (1.2 mmol Na/g food, ○).  $n = 10/\text{group}$ .  $\bar{x} \pm \text{SE}$ . The high-sodium group under high-stress (B) had significantly higher pressures than did the control-sodium group,  $P < 0.01$  (ANOVA).

tent in preparations from both WKYs and SHRs. Structural vascular adaptation occurred only when mean arterial pressure had become modestly lowered in low-sodium SHRs with a corresponding "downward structural autoregulation." However, mesenteric resistance vessels from both low-sodium SHR and WKY groups showed attenuated responses to nerve stimulation. In contrast, the curves of the very-high-sodium rats showed enhanced neurogenic responses. Further, when vessels from low-sodium and very-high-sodium animals were studied in pairs, the very-high-sodium effector responses to physiologic discharge rates were about twice those of the low-sodium effector responses, whereas the median effective dose and the dose-response curves for exogenous norepinephrine were the same. These data suggest that norepinephrine release from sympathetic postganglionic nerve terminals was modulated by dietary sodium.

Altered intracellular sodium concentrations can modify norepinephrine release by affecting the neurotransmitter reuptake mechanism. Studies on chromaffin granules and synaptosomes showed that their active amine accumulation depends on the transmembrane ionic gradients (42). Accordingly, a low-sodium diet would decrease norepinephrine reuptake. However, interference with the norepinephrine reuptake pump by means of specific pump blockers considerably modified the resistance



**FIGURE 4.** Blood pressure response in male spontaneously hypertensive rats (aged 22–23 wk) under territorial stress and consuming a high-sodium diet from 4 to 23 wk (1.2 mmol Na/g food) in different drug treatment groups (dosages in text,  $n = 8$ –12/group) compared with a control-sodium group (0.12 mmol Na/g food) or a high-sodium and stress group. CTL Na, control sodium; HNa, high sodium; HNa+S, high sodium and territorial stress; Hydiz, hydralazine treatment; Hctz, hydrochlorothiazide;  $\beta$ -blocker = propranolol.  $\bar{x} \pm SE$ . \*\*\*\*Significantly different from HNa+S; \* $P < 0.05$ , \*\*\* $P < 0.001$ . \*Significantly different from CTL Na or HNa,  $P < 0.05$ .

vessel responses to exogenous norepinephrine, whereas the neurogenic responses were unaffected by pump blockade (41). Specifically, applications of exogenous norepinephrine to low-sodium and very-high-sodium vessels did not cause different vascular responsiveness, but the neurogenic responses attenuated and reinforced vascular contractions in low-sodium and very-high-sodium preparations, respectively.

These results suggest that the quantal transmitter release per nerve impulse may be directly related to sodium intake in chronic studies (32, 43–45). Transmitter release is decreased when dietary sodium intake is low and increased when sodium intake is high. The results of earlier *in vivo* studies indicated that adrenergic effects in both dogs and humans were attenuated when sodium intake was restricted (46–48). This idea is further supported by Ambrosioni et al (48), who reduced the salt intake (by 50%) of borderline hypertensive patients for 6 wk and showed reduced cardiovascular reactivity (blood pressure) to behavioral challenge (mental arithmetic, bicycling, and isometric exercise) although baseline blood pressure was not altered. Although this study suggested the sodium-potassium transport systems may be the mechanisms responsible, it did not eliminate the role of reduced sympathetic neurotransmitter release. Also, evidence from a salt-loading study (10 g NaCl/d for 2 wk) showed that blood pressure responsiveness was higher during mental arithmetic for normotensive adolescents with hypertensive parents and unchanged in the adolescent offspring of normotensive parents, suggesting a genetic, salt-stress interaction (49).

## RISKS OF LOW SODIUM INTAKE

When sodium intake is abruptly lowered by 50–100% in animals and humans, a series of neural and hormonal compensations attempts to maintain homeostasis. However, long-term reduction in sodium intake appears to be associated with re-

duced sympathetic and neurohumoral adjustments. Long-term changes in SNS function are likely to have several important consequences. For example, when sodium intake is low for long periods of time, reduced norepinephrine release could impair the effectiveness of the SNS in maintaining cardiovascular homeostasis. Increased neuronal discharge rates would be required just to maintain resting cardiovascular homeostasis. Indeed, a sodium-depleted diet produced increased SNS compensation and renin-angiotensin activity with enhanced  $\beta$ -adrenergic receptor function in humans (50). Also, elevated blood pressure in subjects consuming low-sodium diets was shown in several studies (30, 51, 52). Inhibition of angiotensin-converting enzyme lowered blood pressure despite activation of the SNS in acute low-sodium states, suggesting that the renin-angiotensin system was also compensating to maintain blood pressure. The neurohormonal compensation against blood loss is greatly reduced in low-sodium rats despite their near-normal blood volume and exchangeable sodium concentrations, supporting the above hypothesis (30, 38). In humans, Shannon et al (53) showed that low sodium intake did not affect young subjects' responses to upright tilting, but that older subjects failed to compensate to tilting, suggesting impaired baroreceptor reflexes. Therefore, the issue arises as to whether individuals with decreased extracellular fluid reserve and reduced sympathetic compensation, such as aged normotensive persons, should be consuming a low-sodium diet.

## ENDOCRINE INTERACTIONS

Endocrine adjustments induced by high- or low-sodium diets include changes in the renin-angiotensin-aldosterone axis (54, 55), the sympathoadrenal medullary system (56), the ouabain-like natriuretic factor (57), atrial natriuretic peptide (ANP) (58–61), adenosine (62), and vasopressin (63–65). Plasma renin and angiotensin concentrations are inversely related to

dietary sodium (66–68). The number of angiotensin II receptors also varies inversely with sodium intake (69).  $\beta$ -Adrenergic receptor stimulation appears to be responsible for the increased plasma renin activity during short- and long-term sodium restriction (70). The augmented release of epinephrine from the adrenal medulla during SNS stimulation in rats fed sodium-restricted diets was blunted by the angiotensin II antagonist saralasin and the converting enzyme inhibitor captopril, showing that angiotensin II enhances the neurally mediated release of adrenal epinephrine (71). Also, angiotensin II infusion has a more potent pressor effect in the presence of a sodium-replete diet (72). The renin-angiotensin-aldosterone axis is increasingly important in long-term blood pressure maintenance during chronic salt deprivation (66, 73), partly because the SNS reserve is attenuated. However, it does not appear to play a role in salt-sensitive hypertension in SHR. Indeed, Wyss et al (74) showed that chronic captopril treatment enhanced the sodium-induced elevation in blood pressure in SHR.

In ongoing sodium studies in SHR and WKY, we measured hormonal profiles after rats had consumed high-, normal-, and low-sodium diets for  $\approx 50$  wk as described previously. SHR fed low-sodium diets had a greater increase in aldosterone (202%) than did WKY fed low-sodium diets (131%) and a greater suppression of ANP ( $-38\%$  compared with  $-14\%$ ) than did WKY and SHR fed control diets (30). ANP does not appear to play an important role in sodium homeostasis in WKY but does respond to alterations in sodium intake in SHR (30). Thus, these data suggest that SHR respond to sodium restriction by exaggerated sodium conservation, consistent with the hypothesis that SHR are more salt sensitive than WKY.

Recently, we examined the involvement of testosterone and the androgen receptor in hypertension. We noted that testosterone contributes to blood pressure control during prepubertal development (75, 76). Just as sodium affects norepinephrine metabolism (28, 31, 34), there also appears to be a testosterone-norepinephrine interaction (77). Testosterone increases  $\alpha_1$ -adrenergic receptors in tail arteries, and castration reduces them (78, 79). Also, testosterone modulates norepinephrine storage and release (80–82). Recently, we showed that castration at 4 wk increased plasma norepinephrine by 25–30% in SHR and WKY fed a high-sodium diet (83).

The vasoconstrictor actions of vasopressin do not appear to be primarily involved in sodium-mediated blood pressure increases in studies on deoxycorticosterone acetate–salt hypertensive rats and SHR (65, 84–86). A phasic release of a postulated ouabain-like factor might then have more evident acute pressor effects because its inhibition of  $\text{Na}^+/\text{K}^+$  ATPase may, by “electrogenic” effects, reinforce both nervous and vascular actions (57, 87, 88), although such effects may be offset by ANP dilator actions whenever this hormone is released. However, the role of the ouabain-like factors is controversial.

Trophic hormonal influences can become involved when sodium intake is chronically altered and might then be more important than the sodium ion per se for altering neuron excitability and transmitter release. Low sodium intake considerably attenuates the transient osmotic and volume peaks associated with sodium intake, as was clear from the blunted intake and excretory profiles in our low-sodium rats. The release of an

ouabain-like factor and of ANP may then be suppressed while the renin-angiotensin-aldosterone release is high. Aldosterone increases both the activity and the synthesis of the membrane  $\text{Na}^+/\text{K}^+$  ATPase pump, tending to hyperpolarize cell membranes. Such long-term hormonal effects may contribute to the attenuated transmitter handling in noradrenergic nerves so as to down-regulate the quantal release. This down-regulation may represent a local neuronal down-regulation caused by the increased sympathetic activity seen under conditions of salt restriction; the opposite would be expected during high salt intake. Thus, in SHR, in which average sympathetic activity is higher than in WKY, the vasoconstrictor fiber influence and transmitter release per impulse in renal and mesenteric vessels is greater (29, 30, 86, 89).

## RENAL AXIS

Guyton et al (90), Hall et al (91), and Cowley et al (92) associated impaired water and salt loss by the kidney with an increase in arterial pressure. Renal function is closely linked to the central and peripheral nervous systems. The control of renal function by renal sympathetic nerves is influenced by interactions among environmental stress, sodium, and a genetic predisposition to hypertension (93). Studies in dogs and rats show that psychologic stress reduces renal excretion of sodium and fluid. Short-term mental stress in conscious SHR increases renal sympathetic nerve activity and decreases urinary sodium excretion (94–96). High dietary sodium enhances the increased renal sympathetic nerve activity and antinatriuretic responses to stress in conscious SHR but has no additional effect on these variables in WKY (94). We found no evidence of long-term fluid volume or cardiac output changes in SHR or WKY after long-term high- or low-sodium treatment (97).

Using a different animal model, Anderson et al (99) showed a sodium-stress interaction in an avoidance-conditioning paradigm in dogs. Administration of sodium through continuous saline intraarterial infusion (185 mmol/24 h) for 15 d produced progressive hypertension only when coupled to avoidance conditioning. Saline infusion alone and avoidance conditioning alone did not alter blood pressure or heart rate. The results suggested that the long-term effects of psychologic stress and sodium were synergistic, not additive. In a further study this group examined the question of renal handling of the sodium load with and without avoidance conditioning (99). In the absence of stress, arterial pressure and sodium balance remained stable, but with stress, renal excretion of sodium decreased relative to sodium intake and urine volume increased relative to water intake. The sodium retention (15% increase) was accompanied by increased plasma sodium concentrations. The authors concluded that the SNS did not play a significant role in this type of hypertension because neither  $\alpha$ - nor  $\beta$ -adrenergic blockade prevented the pressor responses in normal-sodium dogs before stress. Further, sustained  $\alpha$ -adrenergic blockade or renal denervation did not prevent the development of progressive hypertension in sodium-loaded dogs. This result does not necessarily contradict the SHR studies because 12–15 d of saline loading and stress procedures produced increased arteriolar smooth muscle sodium and water contents, suggesting that a neurogenic component was not involved.

In humans, psychologic stress may induce sodium and fluid retention. Direct evidence of sodium retention was provided by

Light et al (100) in male college students (18–22 y old) during 1 h of competitive tasks. Subjects who retained sodium, fluid, or both during stress had reduced glomerular filtration rates, increased reabsorption of sodium, or both, and the SNS was implicated. Most who showed sodium retention had a hypertensive parent, suggesting a genetic relation.

### SALT SENSITIVITY

A genetic sensitivity of blood pressure to alterations in dietary sodium is apparent from studies in animals and humans (101, 102). Salt sensitivity of hypertension is associated with renal, hemodynamic, and metabolic disturbances that may increase the risk of cardiovascular and renal morbidity (103). Some animal species are more sensitive to sodium than others, and even within a species there are genetic variants that are resistant or sensitive to sodium. Low-salt diets have been shown to lower blood pressure in  $\approx 30$ –60% of subjects with essential hypertension (51, 103–105) and 25–40% of normotensive subjects (51, 106). The search continues to identify physiologic or genetic markers of these salt-sensitive individuals and thus to predict who may best benefit from salt reduction. Some of the markers being evaluated are calcium metabolism (107–109), plasma renin concentrations (51, 110, 111), SNS function (104–106, 112–114), haptoglobin phenotypes (115), abnormal renal and adrenal responses to angiotensin II (116), natriuretic hormone alternations (107, 117), different types of salts (118–121), abnormal renal acid-base regulation (122), and renal retention of sodium (110, 111, 123).

Sodium handling appears to be determined by both genetic and environmental influences (124). For instance, some individuals may be salt sensitive only under stressful conditions when multiple neural or endocrine systems are activated. SHR<sub>s</sub> have a neurogenic hypertension and variable salt sensitivity, but some SHR strains are highly salt sensitive (18). SHR<sub>s</sub> excrete more  $\text{NaHCO}_3$  than do WKY<sub>s</sub> (125) and they retain more sodium (126). Recently, it was shown that Dahl salt-sensitive rats do not modulate renal apical membrane sodium-hydrogen exchange in response to an 8%-NaCl diet, whereas Dahl salt-resistant rats show a more physiologic response (127). This suggests a possible defect in the renal handling of sodium-hydrogen exchange in salt-sensitive rats.

### STRESS AND SALT APPETITE

Although regulation of food intake is basically dependent on energy expenditure, water intake is related to food intake, salt intake, and water loss. Interest in the regulation of salt intake was stimulated by Richter's (128) pioneering studies during the 1930s, which showed increased salt appetite in adrenalectomized rats. Extensive studies performed since then (129, 130) were surveyed in Denton's excellent monograph *The Hunger for Salt* (66). More recently, the central pathways involved in drinking and salt appetite have been studied. For example, stimulation of central angiotensin receptors results in sodium retention and increased sodium intake (131), whereas their blockade reduces sodium appetite (132).

Denton et al (133) showed that mental stress stimulates sodium appetite. Further, SHR<sub>s</sub>, which display a genetically linked central hyperreactivity to environmental stimuli (134),

have a higher sodium appetite than do normotensive WKY<sub>s</sub> (129, 135–137). This increased appetite is evident in the first 3 wk of life (138). These findings are of interest with respect to the relation between survival value and salt intake, stress, and hypertension (5, 9, 66, 89, 130, 139, 140). High levels of psychosocial stress combined with high intakes of salt appear to synergistically potentiate these efferent mechanisms to increase blood pressure. Consequently, repeated daily activation of the central nervous system defense reaction in the presence of high sodium increases SNS activity and renal and trophic neuroendocrine influences (89, 141), with concomitant structural changes in the vascular bed (142) that can lead to or accelerate hypertension. Therefore, individuals at high risk for stress and salt sensitivity should be identified and targeted for intervention.

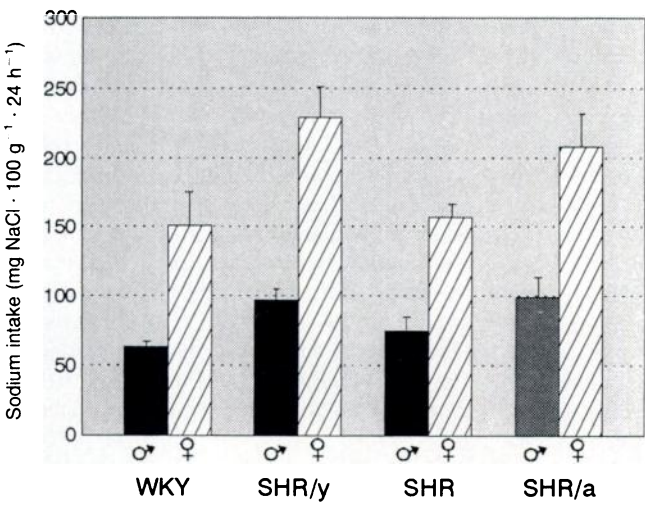
In our studies (for 11–12 wk), sodium appetite and water intake were  $\approx 50\%$  higher in SHR<sub>s</sub> than in WKY<sub>s</sub>, and both psychosocial intruder stress and adrenocorticotrophic hormone injection increased sodium appetite in both strains (143). Why do SHR<sub>s</sub> show a 50% higher sodium appetite than do WKY<sub>s</sub> during baseline resting conditions? Responses in SHR<sub>s</sub> (134), like early neurogenic variants of human primary hypertension (144), display a central hyperreactivity to even trivial environmental stimuli. This central hyperreactivity reinforces the engagement of a defense reaction with neurohumoral changes that result in reduced renal sodium losses, increased gastrointestinal sodium reabsorption, and a stimulated salt appetite that enhances salt intake (89). Enhanced sodium intake would be advantageous in most environmental stress situations by protecting cardiovascular function and maintaining the controlling neuroendocrine responses (86), such as sympathetic activity, and by increasing the amount of transmitter release per impulse (40). Factors that contribute to the increased sodium appetite in SHR<sub>s</sub> likely include increased sodium loss via urine and stools (145). SHR<sub>s</sub> have increased sodium absorption in the small intestine compared with WKY<sub>s</sub> (146), perhaps as a compensation for losses from other sources.

Female WKY, borderline hypertensive (SHR/y, SHR/a), and SHR strains have significantly elevated voluntary sodium intake (**Figure 5**). When these animals were exposed to 2 h of intruder stress, the percentage of sodium intake increased more in males than in females although females had higher absolute intakes (**Figure 6**).

A sexual dimorphism in salt appetite was reported in several species. In female rats water and salt intakes are reduced during estrus (147), although female rats and monkeys typically ingest more salt than do males even when they are not influenced by ovarian hormones (148). Female 2-d-old rats treated with testosterone ingested salt as if they were males tested in adulthood (149). Stricker et al (150), in an elegant study, found that estrogen treatment of gonadectomized, sodium-deprived, 8-d-old Sprague-Dawley rats inhibited the sodium appetite normally seen in both sexes, suggesting that circulating concentrations of estrogen are critical for the maintenance of sodium appetite.

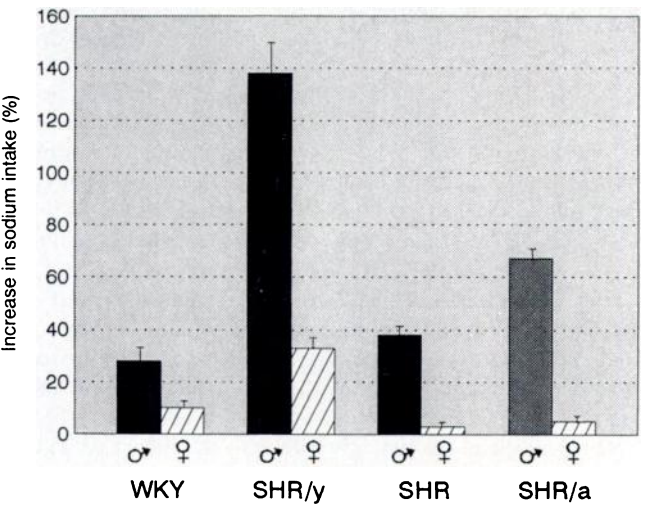
Other mechanisms may contribute to the increased salt appetite in SHR<sub>s</sub>. DiNicolantonio (151) studied blood pressure and salt appetite in cross-suckled SHR<sub>s</sub> to determine whether changes were associated with plasma renin or angiotensin-converting enzyme activity. A maternal factor transferred during nursing apparently was involved in the development of





**FIGURE 5.** Baseline sodium intake in male ( $n = 6$ ) and female ( $n = 6$ ) rats of four strains: normotensive Wistar Kyoto rat (WKY), hypertensive spontaneously hypertensive rat (SHR), SHR/y borderline hypertensive (rat with Y chromosome from SHR in males) and SHR/a borderline hypertensive (rat with Y chromosome from WKY in males).  $\bar{x} \pm SE$ . Sodium intake was significantly higher in females than in males in all strains,  $P < 0.01$ .

high blood pressure in the SHRs. The blood pressure of SHRs cross-suckled on normotensive Sprague-Dawley mothers was 20 mm Hg lower at 8–20 wk of age than that of SHRs suckled on SHR mothers. However, the exaggerated salt appetite of the SHRs was not altered by cross-suckling, suggesting that this characteristic was inherited independently of maternal factors. A central neuropeptide may be involved because intracerebro-ventricular administration of captopril (152) or atrial natriuretic peptide (153) attenuated the salt appetite of SHRs. Other evidence for involvement of central neuropeptides in salt appetite includes the observation that salt appetite induced by restraint stress and food deprivation in male Swiss-Webster mice was reduced by either naloxone or captopril treatment (154). Additionally, neuropeptide Y has also been implicated in salt appetite. High sodium intake or chronic stress alone did not

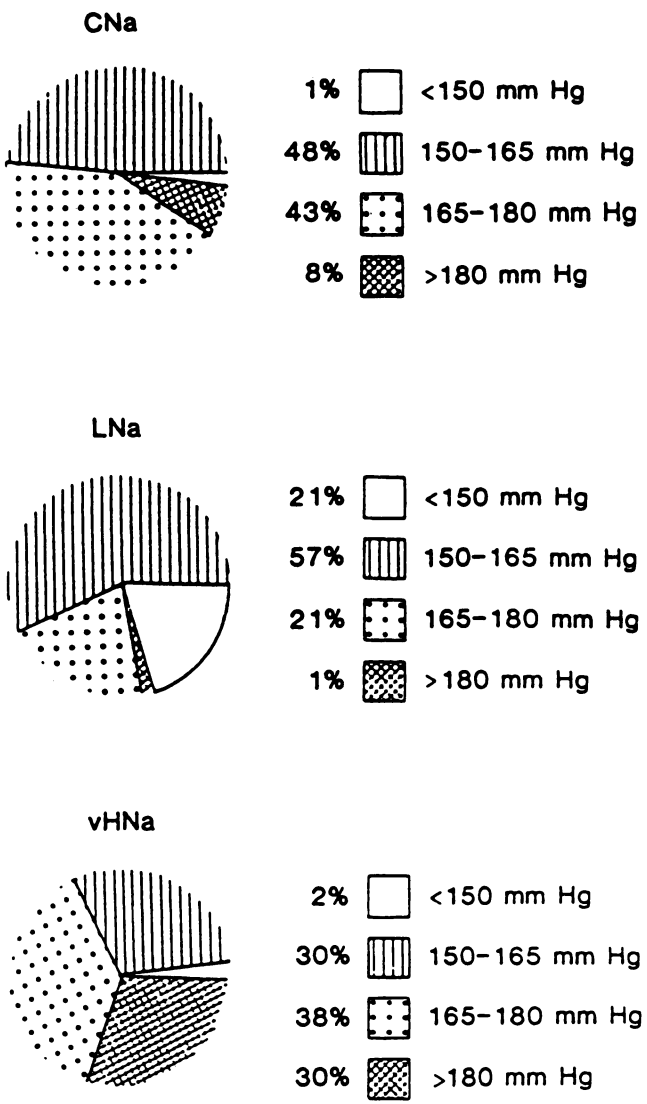


**FIGURE 6.** Percentage increase in sodium intake after 2 h of intruder stress in the same four strains as in Figure 5.  $\bar{x} \pm SE$ . Males showed a greater percentage increase in all strains,  $P < 0.01$ .

significantly alter basal neuropeptide Y or stimulate neuropeptide Y response, but the combination of stress and high sodium significantly increased plasma neuropeptide Y concentrations (155). Some of the confusion in the elucidation of salt-appetite mechanisms may be due to pronounced species differences in the models used (156).

**MONITORING BLOOD PRESSURE OVER 24 h**

Measuring blood pressure once a week does not determine the amount of time the individual spends at various pressure ranges. To determine how sodium altered 24-h blood pressure, direct arterial blood pressure in SHRs fed high- (1.2 mmol Na/g food, or 120 mmol/100 g), control- (0.12 mmol Na/g food, or 12 mmol/100 g), and low-sodium (5  $\mu$ mol Na/g food, or 0.05 mmol/100 g) diets was measured (143) (**Figure 7**). Mean arterial pressure in the control-sodium group was in the

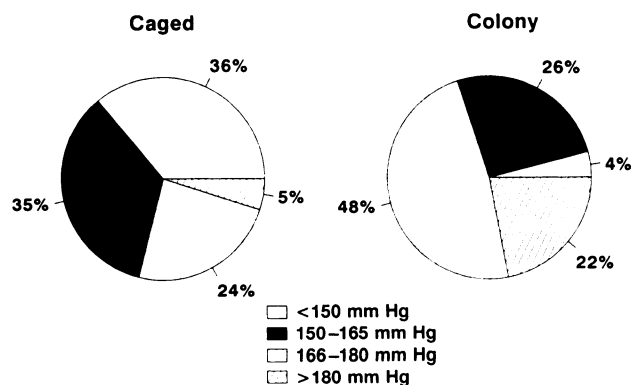


**FIGURE 7.** Percentage of time spent during 24 h at various mean arterial pressure ranges in male spontaneously hypertensive rats ( $n = 5$  in each group) after 10 wk of control-sodium (CNa, 0.12 mmol Na/g food), low-sodium (LNa, 5  $\mu$ mol Na/g food), or very-high-sodium (vHNa, 1.2 mmol Na/g food) diets. Reproduced with permission (143).

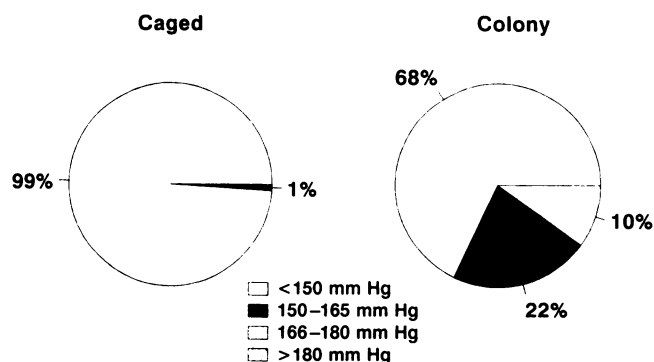
range of from 150 to 165 mm Hg about one-half of the time (48%), whereas the low-sodium group spent most of the time in this range (57%). However, the high-sodium group spent only 30% of the time in this range and 30% in the highest (> 180 mm Hg) range, whereas the controls spent only 8% and the low-sodium group spent < 1% of the time in the highest range (143).

Diurnal mean arterial pressure patterns change markedly in response to alterations in sodium and water intake in SHR. These important differences would not have been detected during routine daytime pressure recordings because the mean arterial pressure increased in association with increased drinking, which, in turn, was dependent on eating, which occurred mainly during the active night periods. These findings reinforce the need for 24-h ambulatory blood pressure monitoring in studies of salt-sensitive hypertension.

Another important variable in both animal and human studies of salt-sensitive hypertension is the social environment. The social conditions of high sodium exposure are difficult to measure in human studies, but data support the hypothesis that stressful conditions potentiate the effect of high sodium on blood pressure. In our animal studies with SHRs and WKYs in which we use aortic telemetry (Data Sciences, Minneapolis), there is a pronounced difference in blood pressure patterns between animals housed singly in a standard cage and the same animals housed in a social interacting colony, competing for partners, food, and water. SHR males fed high-sodium diets and housed singly in a standard cage spend 24% of their 24-h cycle at moderately high pressures (166–180 mm Hg) and 5% of their time at > 180 mm Hg, whereas the same animals fed high-sodium diets and housed in a colony spend 48% of their time at 166–180 mm Hg and 22% at > 180 mm Hg (Figure 8). Normotensive WKYs also show a small blood pressure effect under these conditions (Figure 9); measuring tail blood pressure once per week did not reflect this effect. Recently, Calhoun et al (157) also showed that 8% NaCl for 2 wk produced a significant rise in mean arterial pressure taken by aortic telemetry. Circadian rhythm analysis showed that SHRs had elevated night (active time) and day mean arterial pressure, whereas WKYs only had elevated night mean arterial pressure.



**FIGURE 8.** Percentage of time spent in four blood pressure ranges in a 24-h period averaged over 48 h for male spontaneously hypertensive rats ( $n = 6$ ) fed high-sodium diets (1.2 mmol/g food) and housed singly in a cage and the same animals housed in a territorial colony. Blood pressure was measured by aortic telemetry.



**FIGURE 9.** Percentage of time spent in four blood pressure ranges in a 24-h period averaged over 48 h for male Wistar Kyoto rats ( $n = 6$ ) fed high-sodium diets (1.2 mmol/g food) and housed singly in a cage and the same animals housed in a territorial colony. Blood pressure was measured by aortic telemetry.

## STRESS AND SALT SENSITIVITY IN HUMAN POPULATIONS

Both animal and human salt studies show that psychosocial stress increases salt appetite. As Henry (7) pointed out, these observations prompt a careful reconsideration of the human studies showing that blood pressure is proportional to salt intake. Our studies and others (34, 158–160) suggest that increased blood pressure in population studies may result from increased psychosocial stress (161). If stress promotes increased salt intake, and salt intake modifies pressor responses to stress, then a feedback loop is operating, making it difficult to determine cause and effect without properly designed studies. It should be feasible, on the basis of this premise, to demonstrate relatively low blood pressures during high salt intake in populations with low psychosocial stress (as in our rat studies) and rising blood pressures with age in populations consuming low salt but under high psychosocial stress.

Such studies have not been carried out, but observational studies in human subjects support Henry's premise (7). For instance, data from a Central African city in Malawi show that with a low (2 g/d) salt intake, blood pressure rose with age in a social system where traditional ways were changing and psychosocial stress was high (162). Furthermore, Timio et al (17) measured blood pressure in a group of nuns who consumed > 12 g salt/d; their average blood pressure of 127 mm Hg at 58 y was the same as that recorded at age 38 y. In the control women living in the city, blood pressure increased from 127 to 167 mm Hg during the same period. Genetic differences were unlikely, and although there was no real measure of psychosocial stress, the authors attributed these results to higher stress in the city women.

## CONCLUSION

Salt is necessary for life processes and, depending on the body's need (eg, in a hot environment while exercising), the range of sodium intake varies. Our bodies can adjust to a wide range of sodium intake with hemodynamic, neural, and endocrine responses. Because of a wide range of individual responses to low- and high-sodium diets, it may not be prudent to make the same dietary recommendations for everyone. Would



we recommend an angiotensin-converting enzyme inhibitor or a diuretic for all hypertensive individuals? As stress testing is used to push the heart and unmask potential problems with oxygen delivery, so perhaps should we develop standardized stress tests to identify people at high risk from a reduced or elevated sodium diet.

Population and clinical studies are needed to examine the stress-sodium interaction in which stress is quantified with and without high sodium intake. The chronic effects of everyday social stressors potentiated by high sodium intake and the influence of sex, personality, age, and salt sensitivity must be examined. Furthermore, integrative studies are needed to assess the chronic effects of low and high salt intakes on individuals and populations of normotensive, hypertensive, salt-sensitive, and salt-resistant individuals. Future research on salt and cardiovascular disease should examine individual phenotypic differences in response to salt at both the molecular (cellular) and integrative levels (163).

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