Can Dietary Sodium Intake Be Modified by Public Policy?

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Clin J Am Soc Nephrol 4: 1878–1882, 2009. doi: 10.2215/CJN.04660709

Sodium chloride holds a unique position in the annals of human existence and science (1). For thousands of years, salt's high value has made it the foundation of a society, a currency of trade, and cause for wars. Over the past century, sodium chloride has been the subject of intense scientific research to understand its role in human physiology and its impact on health. The latter has focused primarily on salt's role in BP regulation, an issue fraught with controversy, as documented a decade ago (2) and still evident in the scientific literature (3,4).

Since the first Surgeon General's Report *Healthy People: Promotion and Disease Prevention* published in 1979 (5), public health guidelines have recommended that adults consume less salt. This culminated in 2003 with the Institute of Medicine (IOM) Electrolyte DRI Committee targeting 2300 mg/d as the safe upper level of sodium in the diet (6). The 2005 Dietary Guidelines recommended this same level for healthy adults and 1500 mg/d for individuals at risk of hypertension (7).

As increasingly more restrictive guidelines have been introduced over the past 30 yr, scientific research has continued to provide new insights regarding the effectiveness and safety of lowering sodium intake. Some, but certainly not all, of the newer data have supported the sodium guidelines (8,9), although the feasibility of their implementation remains in question. It has been assumed that if adults better understood how to reduce sodium in their diets and if more low-sodium foods were available, more individuals would be able to achieve these levels. Public health experts throughout the world have devised strategies targeting greater compliance with the lower sodium recommendations.

In the United States (US), a special IOM committee has recently been charged to formulate such strategies (10). Great Britain initiated an intense public education campaign in 2004 that called on the British food industry to reduce significantly the salt content of foods (11). Within the US, major cities have begun to lay the foundation for eliminating foods deemed too high in sodium, similar to the approach to reducing intake of transfats (12). Once again, these initiatives assume that achieving the recommended goal of reducing sodium intake is physiologically feasible.

Several lines of evidence indicate that the expert committees serving the 2010 Dietary Guidelines process and the IOM's project "Strategies to Reduce Sodium Intake" would serve the public health interests to assess, on a physiologic basis, the feasibility of efforts to lower sodium intake in humans. Specifically, these expert panels should address the questions of whether sodium appetite is modifiable by public policy, or whether it is a physiologically set parameter with a relatively narrow range intended to assure optimal function of a myriad of physiologic systems. These questions are independent of any perceived benefits of lowering sodium intake that have justified past dietary sodium guidelines. If a "normal" range of sodium intake exists that is consistent with the optimal function of established peripheral and central nervous system (CNS) mechanisms, that fact should be the sole basis of national nutrition guidelines for dietary sodium intake. To attempt to use public policy to abrogate human physiology would be futile and possibly harmful to human health.

One line of evidence supporting this proposition is derived from decades of research on the CNS and peripheral mechanisms that control vertebrate sodium appetite. That body of research began with the landmark experiments of Richter (13), which provided the first direct evidence that animals expressed an ingestive behavior designed to assure survival when threatened by sodium depletion. Decades of subsequent research worldwide, much of it published within the past 20 yr, has been summarized by one of the current authors (14). This work has revealed a complex neural network distributed among multiple centers in the brain, which integrates coordinated peripheral input from a number of organs via neural and hormonal signals. Using advanced molecular probes, it is possible to document the activation or suppression of specific subgroups of neurons within these CNS circuits, which among a select number of cell types are unique in their response to alterations in sodium intake, as opposed to the common characteristic of many cell types responding to changes in sodium concentration in the extracellular fluid. An example of such activation and de-activation of critical neural pathways by variations in sodium intake in laboratory animals is portrayed in Figure 1, which is drawn from a previous publication from one of our laboratories (15). Findings reported by a number of other laboratories provide extensive, plausible evidence of a primary role for CNS regulation of sodium appetite (14).

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/411–1878

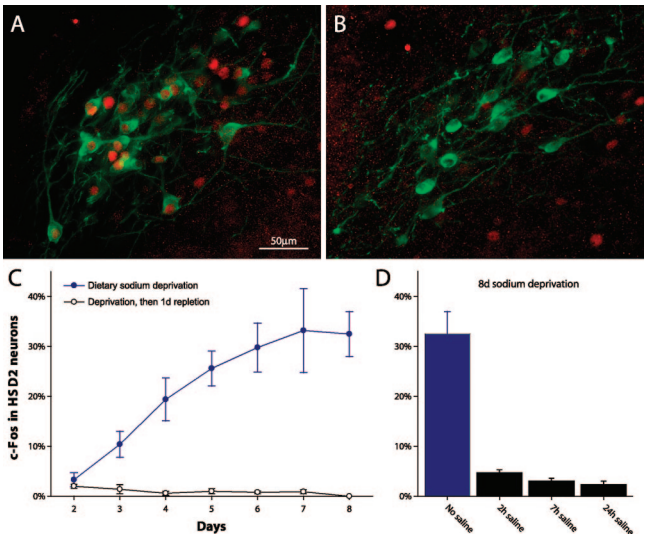

Figure 1. Aldosterone sensitive 11 β-hydroxysteroid dehydrogenase type 2 (HSD2) neurons in the nucleus tractus solitarius (green) are activated by dietary sodium deprivation and inactivated by sodium ingestion. The sensitivity of these cells to ingested sodium or sodium intake, unique to a few select cell types, should be contrasted to sensitivity to changes in the sodium concentration in the extracellular fluid compartment common to most cell lines. (A) In rats fed a sodium-free diet, the HSD2 neurons dramatically increase their expression of a neuronal activity marker, c-Fos (red). (B) If sodium-deprived rats are switched to a high-sodium diet for 1 d, c-Fos immunoreactivity is virtually eliminated in HSD2 neurons. (C) The percentage of HSD2 neurons exhibiting c-Fos activation increases progressively over 8 d of dietary sodium deprivation. (D) In contrast, the activity of HSD2 neurons (percent c-Fos expression) in sodium-deprived animals is rapidly diminished if they voluntarily ingest an NaCl-containing solution (3% NaCl). Reproduced with permission, reference 15.

The complexity and sophistication of the central control of sodium appetite offers compelling support for the proposition that vertebrates evolved a mechanism to assure that their physiologic needs for sodium are defended when dietary access to it is limited or when excessive amounts of sodium are lost under conditions of stress such as hemorrhage, sweating, or diarrheal illness. The importance of angiotensin II, aldosterone, and other peripheral signals to these CNS circuits activating sodium appetite is consistent with an objective of maintaining optimal extracellular volume status (14).

The second line of evidence is based on the more precise measurements of salt intake in humans that have accumulated over the past two to three decades. Those data provide an opportunity to determine whether a "normal range" of sodium intake can be defined in humans, consistent with the neuroscience research suggesting that salt consumption is a homeostatically regulated variable with a relatively narrow range. Within the past two decades, the British Foods Standards Agency (FSA) has carried out six carefully executed surveys of demographically defined populations within the United Kingdom (UK) (16). Those surveys used state-of-the-art collection and measurement of 24 h urinary sodium excretion (UNaV). The FSA surveys of 24 h UNaV provide a longitudinal assessment of sodium intake across a variety of regions in the UK. In addition, within the timeframe of the FSA surveys, several other government-sponsored studies of the UK or closely related demographic groups have included UNaV measures (17,18).

Figure 2 depicts average UNaV (mean ± 2 SD) of those 13 surveys beginning with Intersalt (19) sites Belfast, Birmingham, and South Wales in 1984 to 1985. Each survey had virtually identical representation of female and male participants. Several points are obvious. First, UNaV and, thus, dietary sodium intake has varied minimally in the UK over the 25 yr encompassing these surveys. The mean (± SD) sodium intake over the time period 1984 to 2008 was 150 ± 7 mmol/d. Second, more than 6300 subjects, many providing multiple samples, are the source of these 24 h UNaV measurements from a variety of regions of the UK and Ireland, and they fall within a relatively narrow range.

Not shown, but assessed by us, was the individually determined mean and range of UNaV for women and men where the gender breakdown was available from the survey. Sodium intake for women was 129 ± 6.3 (mean ± SD). Likewise, male sodium intake, which included a 1982 survey of only men living in London (20), was constant over the same period, although, as would be expected on a caloric basis, higher than that of women, 169.4 ± 11 (mean ± SD). The male and female analyses excluded the three Intersalt sites, as the published data provided only the mean for the combined cohort. This statistical analysis of all available 24 h UNaV from the UK does not support recent FSA pronouncements that their national campaign directed at sodium reduction has achieved a significant reduction in the population (16).

Several of the UK surveys in this analysis were included in the landmark Intersalt study (19). That assessment was carried out in 10,079 adults at 52 sites in 32 countries. The Intersalt authors identified data from four of the collection sites as

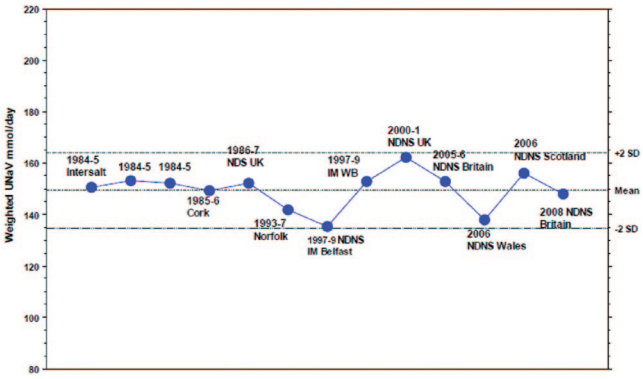

Figure 2. Mean and ± SD 24-h UNaV from 13 published surveys in the UK between 1984 and 2008 with essentially equal representation of women and men (n = 6343). Trend line equation y = −0.097x + 150.4; R2 = 0.0026; UNaV, urinary sodium excretion; UK, United Kingdom; NDS, National Diet Survey; NDNS, National Diet and Nutrition Survey.

outliers, and our analysis of the 48 remaining sites revealed that two additional sites exhibited 24 h UNaV values that were more than 2 SD greater than the collective mean. A recent review (21) identified six additional data sets of 24 h UNaV collected in a manner similar to the FSA and Intersalt methods (22–27). Figure 3 depicts the mean 24 h UNaV for each of the remaining 46 sites from Intersalt, including the three UK sites, the additional six datasets noted above, and the mean values of the primarily FSA-generated UK surveys depicted in Figure 2. That composite assessment of 62 regionally distinct samples of 24 h UNaV (n = 19,151) describes a range of adult human sodium intake between a lower limit of 117 mmol/d and an upper limit of 212 mmol/d, with a mean of 162 mmol/d.

Like the longitudinal 24 h UNaV survey data gathered in the UK, the findings of this analysis are consistent with the concept that sodium consumption is controlled within a defined range. This interpretation is reinforced by the fact that more than 19,000 individuals provided these samples, representing very diverse food environments reflective of a multitude of cultures.

Several studies from the US provide supportive evidence that adult humans naturally seek this range of sodium intake. The Trials of Hypertension Prevention II (TOHP II) randomized 594 subjects into the sodium-restriction limb of that multi-limb study (28). The mean 24 h UNaV of the cohort at entry was 186 mmol/d – well within the range defined by the analysis of the UK, Intersalt, and additional studies noted above. The TOHP II protocol set 80 mmol/d as the target sodium reduction. The authors noted, however, after the initial 6 mo of the 3-yr intervention, participants were unable to lower their sodium intake below 120 mmol/d. That value is remarkably similar to the lower limit our analysis indicated would be achievable in free living adults. Over the next 30 mo, TOHP II participants' 24 h UNaV values regressed toward the mean, finishing at 138 mmol/d, despite continued participation in the protocol designed to achieve the sodium reduction goal.

A second study involving clinical research centers at six US academic medical centers offers additional evidence that the 24 h UNaV data summarized in Figures 2 and 3 define the range of adult human sodium daily intake. This study of sodium restriction in mild hypertension was a randomized, double-blind, crossover trial (29). The cohort's baseline 24 h UNaV was 140 mmol/d, once again within the range defined by the UK-Intersalt data. During the 4-wk run-in period, participants were provided with an extensive manual and weekly dietetic counseling to reach the sodium restriction goal of 60 to 80 mmol/d. With this intense and structured intervention, 99 participants successfully achieved the protocol-set sodium restriction goals. The cohort's mean 24 h UNaV at the end of the run-in period was 76.9 mmol/d. Participants then entered the 8-wk treatment phase and continued receiving instructions on adhering to the low-sodium diet. They were randomized to receive either supplementary sodium chloride, 100 mmol/d in tablet form, or a placebo. After 4 wk, they were crossed over to the alternative treatment for the remaining 4 wk.

During the 4-wk placebo phase, their 24 h UNaV regressed toward the mean, stabilizing at 120 mmol/d UNaV. During the 4 wk of active treatment with 100 mmol/d of sodium chloride, UNaV increased to 176 mmol/d, closely approximating the 100 mmol increase the treatment should have produced. This finding indicates that when participants were blinded to their treatment, they naturally increased their sodium intake by approximately 45 mmol/d. When crossed over to active treatment with 100 mmol/d of sodium, those whose intake had been 120 mmol/d on placebo did not increase to 220 mmol/d, but stabilized at about 176, indicating an innate tendency to limit sodium intake by reducing it from the diet. The lower limit of 120 mmol/d defined in this trial and the observed upper limit of 176 are consistent with those established by the analysis of 62 available 24 h UNaV data sets, as well as the intake boundaries observed in TOHP II.

Further evidence that the lower limit of sodium intake these data define represents a physiologic set-point is reflected in the relationship of UNaV to circulating levels of renin, angiotensin II, and aldosterone. Clinical studies over the past three decades have established that for each of these humoral factors, limiting sodium intake below approximately 120 mmol/d evokes a rapid and exponential-like increase in their plasma levels (30–32). Specific, commonly used pharmaceutical agents target a reduction in levels of these hormones for the purpose of lowering both cardiovascular and all-cause mortality.

These established relationships among dietary sodium, hormones, therapeutic agents, and health outcomes are all consistent with the principle that human physiology has established a minimum dietary sodium intake that approximates the level identified above. That conclusion does not deny the existence of unique populations or clinical circumstances associated with UNaV values substantially lower, but these scenarios are not the norm, as the evidence we have cited indicates. Also, other dietary nutrients may influence the set point for salt ingestion and, consequently, certain physiologic relationships. Finally, 24 h UNaV does not represent an absolute measure of dietary sodium intake, as incomplete collections and/or nonrenal losses of sodium such as perspiration might underestimate actual intake. Nevertheless, it is considered the research standard and

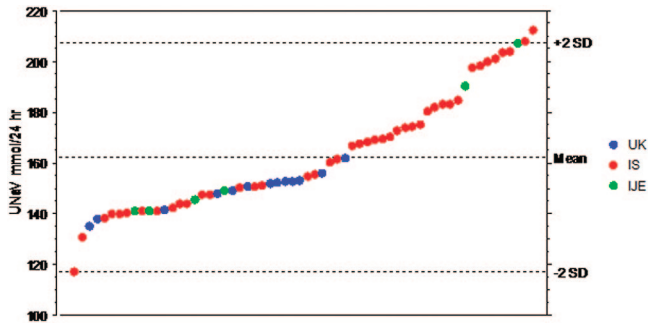

Figure 3. Mean (± 2 SD) 24-h urinary sodium excretion worldwide. Data from 62 survey sites in 33 countries; n = 19,151 subjects. Mean 24-h UNaV = 162.4 ± 22.4 mmol/person per day. Blue dots represent 13 UK sites including three Intersalt sites from the UK; red dots represent the remaining 43 Intersalt sites from outside the UK; and green dots represent six survey sites from ref. 21.

when applied to a sample size as large as the one we have identified, the impact of such limitations is greatly reduced.

The likelihood that these diverse sources of data, encompassing multiple population surveys from over 30 distinct cultural settings, in randomized as well as double-blind crossover trials, have defined the same range of sodium intake in adult humans purely by chance is exceedingly small. Instead, they provide compelling evidence, especially when viewed in the context of the recent advances in the neurosciences identifying CNS circuits that respond to peripheral inputs and control sodium appetite, that human salt intake is set within a physiologic range. As such, it is unlikely to be malleable by public policy initiatives, no matter how well intended.

The current IOM committee convened to consider strategies for lowering sodium intake should first consider whether such strategies can ever alter, or should attempt to alter, what appears to be a physiologically set normal range in adult humans. The current Dietary Guidelines Committee should thoughtfully consider the same question. That question is particularly appropriate as the current Dietary Guideline, set in 2005, of 2300 mg or 100 mmol/d is substantially below the lower limit of 117 mmol/d that this extensive body of data indicates is normal. The importance of addressing this question is fundamental to assuring the feasibility of national nutrition recommendations. If sodium intake or that of any other nutrient is physiologically determined, then our national nutrition policy must reflect that reality in its guidance. To do otherwise will expend valuable national and personal resources against unachievable goals.

Disclosures

Drs. Stern and McCarron have consulted with the food industry and the Salt Institute in the past; none of those relationships were involved in this analysis. All authors have been recipients of grants from the US government, some of which have impacted US nutrition policy.

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See related editorial, "More Mixed Messages in Terms of Salt," on pages 1699–1700.