Got Salt?

Salt, Dopamine and Health

By John J. Gildea, PhD

What is the most abundant electrolyte found in the human body? Sodium. But isn't a low-salt diet the best policy for most people? Let's investigate that premise.

In this article, I will share with you some principles about salt—and sodium consumption in particular—as it relates to health. Hopefully, these will dispel some sodium myths and convey insights that could change your life for the better.

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CHALLENGING SALT DOGMA

It's time to challenge the old models saying "sodium is harmful" and "everyone needs to reduce sodium consumption." In terms of sodium-dependent blood pressure sensitivity, an individual will fall on a rather wide salt spectrum. In other words, some people need more salt than others to be healthy. If you put a population of people on a low-sodium or high-sodium diet, the blood pressure responses of individuals in that population will fall on a continuous spectrum, which can be divided into three broad categories: salt-sensitive, salt-resistant and inverse salt-sensitive.

For a *salt-sensitive* person (approximately 25 percent of the population), blood pressure goes up on the high-salt arm of the diet relative to the low-salt arm. Sadly, there is no currently available medical diagnostic test for salt sensitivity. In a *salt-resistant* individual, blood pressure stays constant on either arm of the diet, meaning salt has little effect on their blood pressure. Inverse salt sensitivity is a newly recognized category that includes 15 percent of the population; the blood pressure of an *inverse salt-sensitive* person *increases* on the low-salt arm of the diet relative to the high-salt arm.

Knowing where on the spectrum of salt sensitivity you land and acting accordingly may decrease your mortality. In a longitudinal study conducted over twenty years ago, individuals who tested as being salt-sensitive showed, on average, a 20 percent increase in cumulative mortality over the twenty-five-year period, with mortality roughly equal to individuals diagnosed with hypertension.[1]

A recently published longitudinal study found that target organ damage and cardiovascular events in both salt-sensitive and inverse salt-sensitive individuals increased compared to salt-resistant individuals.[2] There are also quite a few papers published in the last few years, reporting on longitudinal studies on hundreds of thousands of participants, which show, using spot urine tests, that low urine sodium is associated with increased mortality. Some researchers have criticized these clinical studies for their use of spot urine sampling and the normalization method used, arguing that the gold standard is to use multiple twenty-four-hour urine samples to measure sodium. However, a study that did use multiple twenty-four-hour urines produced similar findings, showing increased cardiovascular and overall mortality in the low-sodium group.[3]

Being aware of sodium needs and intentionally adding salt to the diet would be beneficial for the majority of people. Undereating sodium stimulates a system that seems to be associated with the majority of ill effects. Thus, finding the right amount of sodium to eat for you as an individual is a really important decision. The only people who should restrict sodium in the diet are those who are salt-sensitive. Knowing whether you are salt-sensitive and how much sodium you should eat is critical—your life may depend on it.

ARTICLE SUMMARY

- Every person has a personalized salt index to maintain normal blood pressure and health, with blood pressure responses divided into three broad categories: salt-sensitive, salt-resistant and inverse salt-sensitive.
- Salt has little effect on blood pressure in salt-resistant individuals (the majority), but in salt-sensitive persons, blood pressure will rise with high salt intake, whereas in inverse salt-sensitive persons it increases with low salt intake.
- The salt-resistant have a lower incidence of cardiovascular events, stroke and organ damage, and lower mortality.
- A system in the kidney recovers a large percentage of salt and returns it into circulation instead of eliminating it.
- The renin angiotensin aldosterone system is a salt safety net, entering into play when the body needs to place more sodium back into circulation—but blood pressure medications can interfere with this.
- A second component of sodium regulation is dopamine receptors in the kidney, which get rid of sodium if you have eaten too much salt.
- Increased blood pressure is a third mechanism for getting rid of excess sodium—but at a cost.
- For multiple physiological reasons, taking a little salt before bed may be a good practice.
- The only people who should restrict sodium in the diet are those who are salt-sensitive.

UNDERSTANDING SODIUM HOMEOSTASIS

All animals are basically in balance with sodium consumption and sodium excretion and must maintain their inner ocean of sodium. Thus, the total amount of sodium that someone eats in a given day will be very closely matched with the amount that is eliminated through the skin, urine and feces. If you eat a little bit too much salt and you're in very good health, you'll get rid of that excess salt to return quickly to perfect balance. However, having studied sodium and human health for the last twenty years, I believe there are several important points that everyone should know to help them decide the right amount of salt to eat. Specifically, most people don't consider key factors about how the kidney deals with salt, which leads us to our second principle.

The second principle involves understanding the mechanisms of how the body absorbs, stores and excretes sodium. Your blood is very salty, and all of the blood that goes to your kidney is filtered and needs to be reabsorbed, including most of the salt. In fact, a rough estimate of the amount of salt you have to reabsorb back into circulation is 1.7 kilograms per day. Luckily, there is an entire system in the kidney that recovers a very large percentage of salt and returns it back into circulation instead of eliminating it from the body.[4] Otherwise, we would all need to take in massive amounts of salt every day.

Note that this is a very expensive process in terms of total energy expenditure. Some estimates are that as many as 20 percent of all the calories you eat are used to supply the energy to drive this mechanism of filtering and reclaiming the salt of your kidney. Just one pump—known as the sodium-potassium pump—is so energy-intensive that you can measure this activity as kidney oxygen consumption.

Looking at the recommended dietary allowance (RDA) of salt, we can gain a better understanding of the essential role and function of our sodium-potassium pump system as a key player in the mechanism of sodium absorption, storage and excretion. Although the RDA of salt is 5.8 grams (just over one teaspoon), the average daily intake of salt is 8.5 grams (over one and one-half teaspoons).This intake has not changed during a forty-six-year period despite constant messaging to adhere to the RDA and reduce the amount of sodium in the diet.[5] Eating the RDA, you would reabsorb 99.7 percent of the filtered sodium in your kidney and only get rid of 0.3 percent of that sodium in urine. This shows you how slight increases or decreases in sodium excretion can have large effects on health because reabsorbing sodium takes a huge amount of energy, whereas getting rid of extra is easy—just turn off the spigot for a second and let some spill into your urine. Moreover, the RDA does not account for the degree of exercising, sweating and drinking plain water, which means an even higher percentage of sodium would require reabsorption in order to maintain a balanced system. Thus, the RDA of salt can be a vast underestimate of the amount of salt you need as an individual.

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What happens if you do not consume enough salt for the amount you exercise and sweat out? Not surprisingly, your amazing body has prepared for this contingency by maintaining a sodium reserve. This auxiliary sodium is stored non-osmotically, meaning it does not also have water associated with the stored sodium. The largest repository of sodium is the skin, and the binding entity is referred to as the glycocalyx.

THE SALT SAFETY NET

If you consistently consume too little salt for your body's needs, you eventually will deplete your sodium reserves, mostly in the skin. This activates a counterregulatory system called the renin angiotensin aldosterone system (RAAS). This system enters into play when you need to recover more sodium back into your circulatory system and replenish the sodium storage system. RAAS is your salt safety net—but it comes at a cost.

Because salt is so important for homeostasis, RAAS activation is a good thing if you are eating too little salt. An excess of any individual component of the RAAS, though, can cause high blood pressure and is deleterious, so it is logical—though a little-known fact—that the

majority of antihypertensive medications are designed to inhibit or block an overactive RAAS.

To understand the gravity of RAAS inhibition, allow me to dive deeper into RAAS mechanisms. Here is a quick overview of the villains in high blood pressure.

Renin (the "R" in RAAS) is necessary for converting a protein called angiotensinogen—made by the liver and, to a lesser extent, the kidney—into a peptide called angiotensin 1. Angiotensin 1 is converted to angiotensin II by an enzyme called Angiotensin Converting Enzyme 1 (ACE1). Angiotensin II is the peptide that causes the majority of sodium reabsorption. Angiotensin II binds to and activates a receptor called the angiotensin II type 1 receptor (AT1R).

The second "A" in RAAS is aldosterone, made by the adrenal cortex. Inhibitors of renin, ACE1, AT1R and aldosterone are important antihypertensive medications. Epinephrine is another hormone that is linked with RAAS and can increase blood pressure. Beta adrenergic receptor blockers—so-called "beta blockers"—are a class of antihypertensive medications meant to block the effects of epinephrine. Some individuals with resistant high blood pressure undergo a medical procedure called renal denervation treatment, which disrupts the nerve going to the kidney that produces epinephrine. However, this modality of reducing hypertension also reduces the production and signaling of angiotensin II. Thus, blood pressure medications and interventions, by interfering with RAAS and epinephrine, interfere with the vital modes of reabsorbing sodium back into circulation. It is curious that the main strategies for lowering blood pressure involve medication that blocks counterregulatory mechanisms used to reabsorb sodium back into circulation, but reducing sodium intake stimulates these mechanisms.[6]

THE ROLE OF DOPAMINE

There is another crucial component of sodium regulation not yet discussed—the dopaminergic system in the kidney. This opposing system to RAAS is often disrupted as people age and has been found to have reduced function in those with hypertension and salt sensitivity.

Dopamine is crucial to kidney function, and proper function of the kidney's dopaminergic system is necessary to prevent salt sensitivity. When activated, multiple dopamine receptors systematically get rid of sodium if you have eaten too much salt. If you eat excess sodium and your blood pressure goes up, it likely means the dopaminergic system in the kidney is broken, and you are not able to get rid of excess sodium. When this system is broken, you have to find another way to rid yourself of excess sodium—again, to balance your sodium intake and sodium excretion. Local production of dopamine from circulating L-dopa by the kidney causes natriuresis, which decreases reabsorption and delivers the excess sodium into your urine.

Fundamental studies carried out in mice involve raising the amount of dopamine produced in one cell type in the kidney (called the proximal tubule) by blocking its degradation. With the increased local dopamine production, a number of mechanisms are activated that can protect against known insults that cause hypertension.[7] Conversely, blocking the production of dopamine locally in the same cell type cuts a mouse's lifespan in half.[8] Understanding low sodium and high sodium—and how the kidney is set up to reabsorb virtually all of the sodium that is filtered—you can see that activating dopamine locally allows you just to get rid of a little bit of that sodium into the urine to maintain sodium balance.

STRIKING A BALANCE

Is there a mechanism for getting rid of excess sodium when your dopaminergic system is broken or your RAAS is overactive? Yes—high blood pressure! A phenomenon called pressure natriuresis is activated when your dopaminergic system is broken; this substitute system steps in when your blood pressure goes up and uses hydrostatic pressure in the kidney to get rid of additional sodium.[9] By this alternative method, your own increased blood pressure is the mechanism for getting rid of excess sodium but at the expense of the pressure damaging organs in the process.

It is important to realize that every person has a balance between the dopaminergic system and the angiotensin system,[10] and each person

SALT-SENSITIVE OR INVERSE SALT-SENSITIVE?

SIGNS THAT YOU ARE SALT-SENSITIVE
- Blood pressure rises on a diet containing salty food
- Tendency to diabetes and metabolic syndrome

SITUATIONS SHOWING YOU NEED MORE SALT
- Dry skin, prone to wrinkles
- Chronic fatigue
- Brain fog
- Low sex drive
- Difficulty dealing with stress
- Tendency to overheat when exercising
- Following a high-protein, low-carb diet

has a personalized salt index to maintain normal blood pressure and health.[11] Some of you are lucky and are salt-resistant, so you don't see huge effects of salt on your system. The balance of sodium is maintained relatively consistently in your system, and your blood pressure stays perfectly normal whether you eat high or low amounts of salt. As you might have guessed from the studies cited earlier, salt-resistant individuals have a much lower incidence of cardiovascular events, stroke and organ damage as well as lower mortality. Conversely, if you are on the salt-sensitive or inverse salt-sensitive ends of the spectrum, you accrue more organ damage, cardiovascular events and mortality.

Maintaining a balance of sodium in your system is integral no matter where you land on the spectrum but is especially important to those sensitive at either end.

So, who are the people who really have to constrain the amount of sodium they eat? Those designated as salt-sensitive will have salt-sensitive hypertension and the associated substantial decrease in lifespan if they do not reduce sodium consumption. In those individuals, the systems we have discussed—RAAS and the dopaminergic system—will also help excrete the excess sodium that can lead to high blood pressure.

SALT AND CIVILIZATION

At this point, I'd like to try to connect sodium and the Weston A. Price Foundation. One of the first things I remember about reading Dr. Price's book *Nutrition and Physical Degeneration* is that landlocked civilizations often would make sure they had trade routes to the sea. There were undoubtedly a number of reasons for this, but the one relevant here is that there was a necessary nutrient—salt—that had to be collected and transported in order to have a civilization that thrived. Every civilization had salt.

The Weston A. Price Foundation has held true to the major principles on necessary nutrients elaborated by Dr. Price in the 1930s. Notably, mainstream science is now more in line with the foundation's once-contentious stances on saturated fat, cholesterol, sugar consumption and the "X factor" (vitamin K2). The solid evidence base of the Weston A. Price Foundation never changed, but science has simply caught up. The topic of salt may be the next scientific dogma that gives way to traditional wisdom.

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How does this relate to the way native cultures ate and the amount of salt they consumed? As was well-documented by Dr. Price, native cultures ate very little sugar and at the same time consumed higher amounts of fat and the associated fat-soluble vitamins contained within. The connection to salt is pretty striking. Studies show that if you restrict sugar *and* you restrict salt, you induce insulin resistance, the beginning stage of diabetes.[12] Similarly, the literature indicates that approximately 60 percent of individuals who are overweight and have hypertension and type 2 diabetes—also called metabolic syndrome—are salt-sensitive. They can't eat too much salt or their blood pressure will increase. Just from these two examples, you can see that getting the correct amount of

CHLORIDE: THE OTHER HALF OF SALT

The other half of salt, chloride, is the second most abundant electrolyte and the most abundant anion (atoms with a negative charge). Like sodium, chloride is an essential mineral, meaning that without it, you will perish.

Does the universal tenet that one should reduce salt intake make sense in light of the role of chloride in human physiology? Most physiologists recognize chloride as essential for osmotic pressure in extracellular fluid and acid-base balance—by being the inverse of bicarbonate in the blood's buffering system—and as necessary for nerve cell conduction. Chloride is rarely a focus because of the kidney's ability to get rid of excess chloride in urine readily. However, measurably low chloride—called hypochloremia—has dire consequences. Deficiency of chloride is a controversial topic, but low chloride levels on hospital admission have been reported as an independent risk factor for mortality in heart failure, one that is even stronger than low sodium.[21]

Chloride is a necessary component for adequate production of stomach acid and is essential for digestion and absorption of nutrients, including other minerals and vitamin B_{12}. A lesser-known function of chloride—but a highly relevant one—is its role in innate immunity. It is necessary for the myeloperoxidase system, an important component of the immune system.[22] Additionally, chloride is a necessary cofactor for enzymes, including ACE2; a decrease in function of ACE2 is associated with severity of Covid-19 infection.

salt is crucial.

The guiding principle here is that if you eat lots of sugar, eating a relatively lower amount of salt somewhat makes sense—even though it is not ideal—because the normal homeostatic systems are able to reabsorb more salt back into the circulatory system. If you are eating low sugar, however, you will tend to spill sodium into your urine, and your salt needs will increase.

SALT BEFORE BED

I met Sally Fallon Morell, founder and president of the Weston A. Price Foundation, at a meeting recently, and in her talk she suggested taking a pinch of salt at bedtime to aid falling asleep. I was intrigued when I put this suggestion in the context of what I know about sodium and the body.

There are a few physiological phenomena that really make sense to me relating to the timing and sensing of sodium in the body. The first physiological phenomenon is called the gastrorenal reflex, a term coined by our research group.[13] When you ingest salt, it goes into your stomach. In the base of your stomach, called the antrum, there are cells called G-cells that show sodium-induced increased dopamine locally and lead to the production of gastrin. Gastrin then leaves the stomach and goes to the kidney, where gastrin along with locally produced dopamine leads to natriuresis—or the elimination of sodium into the urine.[14]

I am struck by the timing of taking salt in the evening. A little-known fact is that a very popular and successful antihypertensive drug, generically called an angiotensin type 1 receptor blocker (ARB), only works when you take it in the evening before bed. Taking salt in the evening offers a similar mechanism: gastrin increases the local dopamine production and activates the dopamine D5 receptor in the kidney. This leads to the proteolytic degradation of the same angiotensin receptor, inactivating the same target as the medication.[15] This may be considered a natural way to reduce AT1R function and its deleterious effects such as high blood pressure, stroke, cardiovascular disease, inflammation, fibrosis, reactive

TESTOSTERONE AND SALT

Testosterone is made by the Leydig cells of the gonads in males and in the ovaries in females, as well as a smaller amount in the adrenal glands. Both testosterone and estrogen are produced from the precursor cholesterol. Therefore, the first thing to know if you are taking a statin or trying to reduce your cholesterol is that you are reducing your sex hormones. In addition, both of these hormones slowly decline with age. Being happy, satisfied and stress-free—and eating a diet with low sugar, adequate salt and rich in micronutrients that include the fat-soluble vitamins—are the conditions we strive for; reaching this goal signals that it is the right time to reproduce. This state of being is inextricably linked with what we universally consider healthy.

Low sodium leads to increased renin angiotensinogen, ACE1, angiotensin II, aldosterone and epinephrine, all geared to increase sodium absorption. Angiotensin II in the testes reduces testosterone.[23] In genetic models of hypertension with rodents (such as the "spontaneously hypertensive rat" [SHR] or Dhal salt-sensitive rats), testosterone can raise blood pressure if the animals are eating a high-salt diet. The classic "high-fat" diet in normal rodents also leads to sodium retention with blood volume expansion and high blood pressure; however, while these diets—high in vegetable oils, sugar and calories—are called "high-fat," they should more accurately be called the "standard American diet." Testosterone in these states can cause sodium retention.

There are also close associations of salt to stress and the stress hormone cortisol. High cortisol can cause sodium retention, and likewise insufficient cortisol can lead to hyponatremia and low testosterone. One of the effects here is via glucose—cortisol is a glucocorticoid, which raises blood glucose, which in turn stimulates sodium retention.

According to a 2022 meta-analysis published in *Nutrition and Health*,[24] low-carb, high-protein diets can reduce testosterone. "High-protein diets cause a large decrease in resting total testosterone" was the surprising conclusion. Many people follow this type of diet to lose belly fat or to increase muscle mass. Under these conditions, sodium would spill into the urine, and likely the drop in sodium would activate angiotensin II and reduce testosterone—although the paper does not propose low sodium as a mechanism. I believe the driving force here is low blood sugar, which reduces glucose-dependent sodium reabsorption and leads to the spilling of sodium into the urine. For any ketogenic diet, you really do need to eat excess salt. Low sodium explains the keto fog so often associated with these diets.

Being overweight can reduce testosterone because fat cells have aromatase that convert testosterone to estrogen. A consideration when you go on a very calorie-restricted diet and you quickly metabolize fat is that you are releasing toxins stored in your fat.[25]

Since a low-salt diet is also likely to be low in chloride, a reduction in ACE2 would occur since chloride acts as a cofactor for enzymatic activity, and this would reduce the protective arm of RAAS. This would lead to the increased production of angiotensin II by the fact that low ACE2 would redirect the conversion of angiotensin I away from the production of angiotensin 1-9 and angiotensin 1-7 and down the path to angiotensin II. By contrast, stimulation of the ACE2 arm of the RAAS increases testosterone.[26]

oxygen species and vasoconstriction.

Another effect of taking a pinch of salt at night, is that when you eat salt and produce gastrin, this gastrin goes to the sphincter at the top of your stomach and closes it.[16] This would be protective against acid entering the esophagus. Because this part of your digestive system does not have a protective layer of mucus, this sphincter not closing could cause epigastric distress and conditions like gastroesophageal reflux disease (GERD). Salt effectively closes the sphincter.

Continuing with the idea of salt before bed, increasing sodium is known to reduce epinephrine production. Low sodium activates the production of epinephrine, a stimulating hormone, while salt turns off the production of epinephrine, allowing you to relax and go to sleep. The timing of this before bed seems appropriate. When you are sleeping, your heart rate and blood pressure decrease and allow repair, especially of the small capillaries throughout the body.

This maneuver before bed might be something to try for yourself, especially if you are following the dietary guidelines set forth by WAPF.

THE TEST OF TIME

Many tenets of health and nutrition that Weston Price discovered have brilliantly stood the test of time in spite of the suggestions coming from mainstream science that encourage high sugar and carbohydrate consumption while promoting lower cholesterol and saturated fat. Salt may be another area of the diet where Dr. Price had it right—generations before science figured it out.

In fact, I wrote a paper where I showed that if you remove cholesterol from the kidney, you get salt-sensitive hypertension.[17] Recently, researchers found that cholesterol actually binds to the dopamine D1 receptor and allows it to function more efficiently.[18] The implication is that lowering cholesterol by diet or drugs might make you more salt-sensitive.

Other habits to consider regarding salt and health are common practices that tend to push you toward the RAAS-stimulated side of the balanced system. One is drinking large amounts of water when you are not thirsty. An extreme version of this is known as water intoxication. Yet, any movement toward hyponatremia—low sodium in the blood—may be harmful. It would be better to increase salt and drink a normal amount of water—or add a pinch of salt to the water you drink!

Other behaviors that may put you at risk of hyponatremia are to exercise extensively for long periods of time or spend long periods of time in a sauna or be outside in excessive heat. The amount of salt loss during these activities can be detrimental, especially if you are actively trying to restrict sodium intake as dietary guidelines universally suggest. The videos of marathon runners at the end of a race stumbling and passing out are hard to forget. This is the consequence of drinking too much water without replacing salt at the same time. Interestingly, consuming both glucose-containing and electrolyte-containing drinks specifically during these extreme endurance events can combat this effect.

Hyponatremia has other deleterious effects and increases your chance of fatality from any accident, dramatically so if the accident leads to substantial blood loss. One paper studying the elderly shows that if you are hospitalized and have hyponatremia (versus just hospitalized), your chance of death increases by 273 percent within one year.[19] It has also been shown recently that athletes practicing or competing for extended periods of time have a high incidence of hyponatremia.[20] If you take salt before exercise, performance is vastly improved, and it appears that at least a portion of this effect is due to core body temperature cooling. But that is a discussion for another day.

In conclusion, I hope you have a better understanding of the importance of sodium in human health and the natural mechanisms that help the body find an internal balance. There is indeed a great deal of wisdom in the especially pertinent Wise Tradition of reducing sugar and having adequate sodium consumption.

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