A Critical Literature Review on Hypertension, the Taste of Salt, and the Relationship Between the Two

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Abstract

This review aims to study hypertension, the taste of salt and the proposed relationship between hypertension and the taste of salt. High blood pressure, or hypertension, is known to have many deleterious effects on the body that puts people at a higher risk of developing other illnesses and/or diseases, such as obesity and diabetes. The rat model is used as a biological model to better understand how hypertension develops and what affects it may have on intake of sodium, particularly the intake of sodium salts – primarily NaCl. There has been a recent rise in the number of hypertensive people in the world, particularly in America. This rise has been coincident with a noticeable rise in the amount of salt consumed. While much research has been done in an attempt to unravel the mystery behind the relationship between hypertension and the taste of salt and its intake levels, more research is still necessary to completely answer all questions and fully tie this connection together to provide a comprehensive understanding of this complex relationship.

Introduction

Out of the various senses humans have, the gustatory system is one of the least understood. The basic transduction mechanism for taste involves either ion channels depolarizing the membrane via ionotropic transduction or metabotropic receptors creating depolarizations via the second messenger system. The transduction mechanism for the taste of salt entails the passage of a sodium ion through a channel in the apical membrane of receptor cells (Heck et al., 1984 as cited in Mattes, 1997). This ion channel can be blocked by the compound amiloride. Previous research indicates that these amiloride-
sensitive sodium channels make the vast majority of channels involved in the response to sodium chloride in rats; however, while still important in humans, they are likely less involved (Brand et al., 1985 & Formaker et al., 1988 as cited in Mattes, 1997).

There are several peripheral nerves that carry taste information to the brain. These most importantly include the chorda tympani (CT) nerve and the glossopharyngeal nerve (GL). Taste receptors in the posterior part of the tongue are innervated by the lingual branch of the GL, which can be stimulated by the presence of NaCl stimuli (Frank and Pfaffman, 1969 as cited in Flynn et al., 2003). As far as neural signaling is concerned, there are three primary nerves that innervate the tongue in humans: the CT branch of the facial nerve, the GL nerve, and the vagus nerve. Rats also have the greater superficial petrosal (GSP) nerve innervating the oral cavity for the palate. These nerves all converge at the nucleus of the solitary tract (NST) in the brainstem. Salt taste processing is performed primarily by the CT nerve, which branches from the facial nerve, because it innervates the anterior two-thirds portion of the tongue (Curtis and Contreras, 2006).

Human neonates either lack the ability to differentiate between salt and water solutions or perceive each as equally palatable because they do not ingest one solution more than another when provided free access to both solutions (Mattes, 1997). However, these results have not been reaffirmed by other research and a consensus is yet to be reached regarding the human ability to choose preference over salt solutions and water as infants (Zinner et al., 2002). If humans are like rats and sheep, then humans experience a delay in the functionality of amiloride-sensitive channels in taste cells that causes a developmental delay in the sensitivity to sodium chloride (Mattes, 1997).
Previous research has suggested that differences in race and age may affect salt-taste sensitivity and preference, such that adolescents, particularly African-American adolescents, appear to prefer higher concentrations of salt solutions than adults (Desor et al., 1975). Evolutionarily speaking, there may be a distant explanation for the salt appetite in humans. Some scientists have suggested that the diet of ancestral humans was predominantly vegetarian. Because herbivores are known to prefer sodium chloride so much more than nonsodium salts that they actively seek out sodium chloride, it is possible that ancestral humans once shared this same characteristic and thus evolved behavioral, neural and hormonal mechanisms to ensure sufficient sodium ingestion (Denton, 1982 as cited in Mattes, 1997).

As far as the aversiveness and appetitiveness of a salt solution is concerned, upward and downward hedonic shifts are possible dependent upon external circumstances. A downward hedonic shift occurs in which reduced-sodium foods become less aversive in normotensive and hypertensive people after their exposure to salt has been restricted for eight to twelve weeks (Bertino, 1982 & Mattes, 1990 as cited in Mattes, 1997). An upward hedonic shift may occur if sensory exposure to salt increases such that preference shifts towards higher concentrations of salt (Bertino, 1986 as cited in Mattes, 1997).

Overall, there is a lack of consensus in the realm of taste researchers on the association between blood pressure and salt preference. While many studies do indicate a significant association (Mattes, 1987; Bernard et al., 1980; Shepherd et al., 1984; Shepherd et al., 1986; & Chan et al., 1985 as cited in Mattes, 1997), other studies observe no such relationship (Mattes, 1985 as cited in Mattes, 1997). Human studies focused on
the relationship between blood pressure and salt appetite lack uniformity in their experimental procedures thus producing a convoluted mess of differing results (Arguelles et al., 2007). The following paper serves as a review of the research that has been done using human participants as well as rats as a biological model in order to better understand the factors that do affect the taste of salt and how blood pressure may be related to the taste of salt.

**Research With Humans**

Although there is some controversy over the ability of infants to differentiate between salt stimuli and water as neonates, there have been numerous studies indicating that such a capability does exist. Some have demonstrated this in studies that exhibit a difference in the mean number of sucking responses to salt stimuli compared to water (Crook, 1978; as cited in Zinner et al., 2002), and other studies have reported similar findings based on facial responses to salt stimuli compared to water (Nowlis, 1973; as cited in Zinner et al., 2002).

Zinner et al. (2002) tested the association between neonatal blood pressure and salt-taste responsiveness in 283 healthy infants between the ages of two and fourteen days old. Rubber nipples connected to cannulas that measured sucking response to the drops of solution it dispensed. The different solutions included water, 0.1 molar NaCl, and 0.3 molar NaCl. Zinner et al. (2002) demonstrated that infants prefer sucrose solution to water and prefer water to the salt solutions based on the number of mean sucks per burst for the various stimuli.
Although some research has suggested differences in salt-taste responsiveness based on race (Desor et al., 1975), Zinner et al. (2002) found no significant difference existed in the salt-taste responsiveness across either gender or race. Interestingly enough, there was a significant difference in the salt-taste response based on birth weight. A more pertinent finding was that there were more infants in the highest percentage for diastolic blood pressure showing a significant preference for salt stimuli over water, while there were more infants in the lowest percentage for diastolic blood pressure showing a significant aversiveness for the salt stimuli compared to the control of water. These results were only significant for the diastolic blood pressure and were not significant for the systolic blood pressure; however, the reason behind this is not well understood. These neonatal blood pressure differences still existed in infants at one month old with preferential versus aversive responses to salt stimuli. Because there are discrepant findings and conclusions about whether there is a link between blood pressure and salt-taste, it may be that such a link does exist early in life before many environmental factors can play a larger role. There is also the possibility that amniotic fluid sodium levels may influence neonatal salt-taste responsiveness. However, such an association is currently speculation and requires further research (Zinner et al., 2002).

A longitudinal study of these neonates would be interesting to compare how many of the neonates with preferential salt-taste responses eventually did develop hypertension later in life to those with aversive salt-taste responses. Such a study would provide further insight into how strongly environmental factors throughout life typically impact the development of hypertension.
Environmental Effects on Hypertension

There are many possible environmental causes of hypertension, many of which are believed to remain unknown. Many essential trace elements such as zinc, iron, and copper influence blood pressure through their participation in enzyme reactions directly related to blood pressure regulation. Such a relationship was first speculated as a possibility because of the observation that the blood pressure medications also acted as strong binding agents for the essential metals. Heavy metal ions such as cadmium, thallium, mercury, and lead affect hormone metabolism, vasoconstriction, and renal tubular function. Thus, their presence may be a contributing factor directly or indirectly to the development of hypertension (Saltman, 1983).

One of the major reasons why so many researchers believe there must be strong environmental effects on the taste of salt and thus its consumption and thus the development of hypertension, is the research that demonstrates that salt taste can be modified by restricting salt intake. When sodium levels are depleted, higher concentrations of salt solutions become less aversive and encourage the ingestion of more salt than usual. Furthermore, many researchers are also convinced that there must be environmental components to the taste of salt because twin studies do not indicate a strong genetic component (Beauchamp et al., 1983). Thus, following the notion that the taste of salt affects the ingestion of salt and that differences in the ingestion of salt may influence the development of hypertension, it is logical for researchers to believe there must be several different environmental causes of hypertension.

Saltman (1983) concluded that there might be an environmental basis for some forms of hypertension and that (while differences in the amounts of trace elements may
not be the primary cause of hypertension) such differences in the amounts of trace elements can play a contributing role. Although irregular levels of trace elements, particularly copper deficiencies, have the potential to produce hypercholesterolemia and may be involved in hyperlipidemia, trace elements have not been conclusively shown to affect taste acuity or directly lead to hypertension. To date, evidence suggesting cadmium’s role in the development in hypertension has been ambiguous. While essential trace elements and toxic heavy metals may be contributing factors in the development of hypertension, there remains no direct evidence that they are associated with or lead to the development of hypertension (Saltman, 1983).

Hypertension and Salt-Taste and Its Relationship With Other Diseases

There is a relationship between increased sodium load and hypertension, which leads to vascular and renal injury. Some research suggests that salt-sensitivity increases exponentially with the progression of kidney disease (Wilcox, 2009 as cited in Wright and Cavanaugh, 2010). A review of dietary sodium recommendations for people with kidney disease offering some suggestions of how to get patients to manage their dietary sodium intake better explained that most people with hypertension are also salt-sensitive and for them, a low sodium diet is the recommended treatment (Wright and Cavanaugh, 2010). However, with kidney disease, the ability to detect or taste salt is impaired. This impairment leads to increased salt intake in order to make food more palatable (Fernstrom et al., 1996). Several factors are known to increase the salt-taste threshold in humans. These include diuretics, the development of diabetes, and habitual high sodium ingestion. A certain amount of controversy still exists over whether high dietary sodium
intake has the negative clinical implications associated with it (Wright and Cavanaugh, 2010). Regardless, the relationship between salt-taste and hypertension is clearly an important to research because of its relationship with other diseases. Further research in this area can also lead to supplemental better understanding of other diseases.

Because it is established that hypertension is more prevalent among diabetics, alterations in salt taste perception are not limited to hypertensive patients and/or patients with kidney disease but also includes some diabetic patients. Hypertension is more prevalent among diabetics (Isezuo et al., 2008). With the purpose of determining the relationship between blood pressure in type 2 diabetics and salt taste perception, Isezuo et al. (2008) measured the salt taste sensitivity/detection threshold (STST) and the maximum tolerable concentration of salt solution in normotensive diabetics, hypertensive diabetics, and control participants. The control participants had neither hypertension nor diabetes and lacked a family history of either disease. People with type 2 diabetes have impaired salt taste perception and a correlation exists between salt taste perception and blood pressure. Each subject group differed significantly in their STST as well as in their mean maximum tolerable concentration of salt solution. There was a positive correlation between age and salt-detection threshold. There was also a positive correlation between the duration of type 2 diabetes and STST and maximum tolerable concentrations of salt solution. The salt-taste insensitive participants (people who were given such a title after salt taste threshold trials) were more prevalent in the two experimental groups than in the control group. The STST is associated with the mean arterial pressure (MAP) of participants, even when age, gender, weight and family history of hypertension and hypertensive medication are all accounted for (Isezuo et al., 2008).
Thus, the impaired salt perception of the type 2 diabetics may help to explain the development of hypertension. Salt taste perception may be genetic because no apparent relationship exists between the environmental factors and the salt-taste thresholds. One existing theory is that insulin-resistance may explain the relationship between type 2 diabetes, hypertension, and salt-taste sensitivity, but more research is required for its validation. Most importantly, impaired salt-taste perception may cause involuntary excessive intake of salt that leads to the development of hypertension (Isezuo et al., 2008).

Hypertension is not only often associated with diabetes, but is also related to obesity. Díaz et al. (2006) analyzed the prevalence of obesity in children whose parents have hypertension and found some interesting relationships that provide a better understanding of how hypertension and its effect on salt-taste perception has widespread effects on the body. Obesity is a significant independent predictor of hypertension. Previous results have shown an association between arterial hypertension and the ability to detect salt compared to children and adolescents with normotension and their ability to detect salt (Málaga et al., 2003 as cited in Díaz et al., 2006). Even though obese children with hypertensive parents have higher systolic arterial tension levels than children who are not obese, these differences are not attributable to a difference in activity of the renin-angiotensin paradigm nor are these differences attributable to a difference in salt-taste sensitivity.
Genetics of Hypertension

Many factors seem to contribute to essential hypertension and it is probable that salt-sensitive hypertension may be largely genetically determined (Zinner et al., 2002). Some sources claim human hypertension is a complex disease that is both multifactorial and polygenic, with a genetic determination contribution of roughly 30-50% (Ward, 1990). Regression analyses limited to infants with a familial history of high blood pressure demonstrated a much greater difference in blood pressure according to the babies’ salt-taste responses. This implies there may be a significant genetic role in hypertension (Zinner et al., 2002).

Chinese researchers Wu et al. (2010) conducted a study that included 1243 monozygotic and 833 dizygotic Han Chinese twins to determine the role of genetics on hypertension. The heritability of systolic blood pressure was 46% and of diastolic blood pressure was 30%. Furthermore, their results indicate that the correlation between body mass index and blood pressure was roughly 85%. Additionally, Wu et al. (2010) concluded that a higher body mass index might actually reduce the heritability of systolic blood pressure through a greater impact of environmental effects.

Hypertension in humans is hard to study because overall blood pressure involves the individual contribution of several genes, their interactions with one another, and their interaction with the environment, particularly with diet. There are 26 different chromosomal locations in the human genome in which it has been predicted that there are blood pressure-related genes. Ultimately, more animal research is required for the cloning and functional characterization of genes that are particularly important for multifactorial diseases such as hypertension. As genetic maps improve and the genome is
more fully understood, the value of these genetic animal studies will become ever more important to providing a better understanding of human hypertension as well as better therapies for such a disease. (Stoll et al., 2000).

One particular case study sheds some more light on the complicated genetic story behind hypertension. A 24-year-old woman diagnosed with hypertension associated with hypokalaemia displayed abnormal taste perceptions in taste trials. This patient was unable to detect the taste of salt at all concentrations. At very strong NaCl concentrations of 320 mM and 1000 mM, she still failed to identify the saltiness but did describe the taste as bad. Furthermore, this patient identified bitter substances and sour and vice versa. A genetic abnormality of the Epithelial Sodium Channel (ENaC) may explain such unusual perceptions because ENaC is involved in Na+ reabsorption in the distal nephron as well as taste perception on the anterior portion of the tongue (Lefrancq et al., 2007).

**STST and Exercise-induced Hypertension**

Salt taste sensitivity is defined as the ability to detect the flavor of salt. A person’s salt taste sensitivity threshold (STST) may quantifiably influence ingestion of salt. Because sodium ingestion is associated with hypertension, it is therefore possible that people with hypertension have, on average, a significantly different STST than normotensive people. A previous cohort study (Jackson et al., 1985 as cited in Rabin et al., 2009) explains that patients with exercise-induced hypertension (EIH) develop arterial hypertension approximately four years later. This suggests that EIH may predict future arterial hypertension. However, it is important to note that not all researchers agree on the predictive value of EIH. Majahalme et al. performed an experiment testing the
blood pressure responses to both dynamic and isometric exercises. Ultimately, their conclusion was that even with blood pressure readings, the blood pressure changes through dynamic exercise serve as a very weak predictor of future blood pressure and that the blood pressure changes through isometric exercise only slightly improves such predictive power (Majalahme et al., 1997). As the research of Carroll et al. (2003) indicates, however, the predictive power of EIH for future hypertension may vary with socioeconomic position and sex.

To more accurately try to determine whether an association existed between EIH and STST, Rabin et al. (2009) divided 203 normotensive participants into two groups: those with normal STST and those with increased STST. Participants were also divided into two groups based on blood pressure after performing a stress test: those with EIH and those with a physiological normal response (n-EIH). Participants with EIH displayed a higher mean STST than the n-EIH participants. This association between EIH and STST existed independent of gender, body mass index, and age. There was a significant correlation, however, between gender and EIH, in which there were many more men than women with EIH. The higher the STST is, the less sensitive an individual is to NaCl perception. It is likely that a person with a diminished sensitivity to salt would ingest more salt than otherwise would. This increased intake of salt may then lead to EIH and eventually arterial hypertension. Thus, a high STST may serve as a reliable marker predicting current hypertension or the future development of such a disease (Rabin et al., 2009).
The Rodent Model

   Rats provide researchers with an animal model for which they can often better understand the biological mechanisms under which we too operate. Because rats are so genetically and, as far as the brain is concerned, anatomically similar to humans, results from research performed with rats can often be generalized to the human population. Of course, there are differences between rats and humans; thus, assumptions cannot be made and research on humans is often needed as well.

   Recent research has indicated that there may be a potential transduction mechanism for water in taste receptor cells that may play an integral role in salt transduction. Through a three-step process in which researchers performed immunocytochemistry to label the proteins that make up aquaporin (AQP) channels, a reverse transcription-polymerase chain reaction to determine whether the proteins were present or not, and a patch-clamp recording to test the functionality of the AQP channels through electrophysiology measures, researchers were able to conclude that AQP channels are an integral part of salt transduction. The salt/water balance in taste receptor cells is important to the ability to transduce the presence of salt. Hypoosmotic-induced currents in rat taste cells were reduced by the AQP inhibitor tetraethylammonium. Thus, the signal to detect salt can be dampened by blocking the AQP channels. If this inhibition of AQP channels were to occur, it is reasonable that it may indeed lead to an increased consumption of salt (Watson et al., 2007).
Sex Differences in Gustatory Processing

Most NaCl gustatory-related research on rats has used male rats as the subjects. This is because researchers do not have to worry about the menstrual cycle of female rats imposing any influential changes in taste-responsiveness during the experiment. However, there have been numerous studies that specifically use both male and female rats in order to look at how gender affects the taste of salt. For both rats and humans, males and females differ in their food intake and research suggests that females’ salt intake changes throughout their menstrual cycle. This suggests that there may be sex differences in sensory processing of NaCl taste. To determine whether sex differences in NaCl preference are due to hormonal affects on gustatory processing, researchers recorded electrophysiological activity from the CT nerve in response to various concentrations of NaCl solution in male rats, ovariectomized female rats given estradiol benzoate, and ovariectomized female rats given an oil vehicle (Curtis and Contreras, 2006).

These potential differences in sensory processing may not be unique to NaCl, however. Researchers addressed this question by evaluating the affect of estrogen on female rats in taste responses and ingestion to NaCl as well as sucrose, along with the taste responses and ingestion of NaCl and sucrose in male rats. In this experiment, after performing both sucrose testing and NaCl mixed with sucrose (NaCl-S) testing on male rats, researchers bilaterally ovariectomized the female rats and all female rats underwent both sucrose and NaCl-S testing in both oil vehicle (OIL) injected conditions and estradiol benzoate (EB) injected conditions. An estrogen-replacement schedule was used
that mimics the fluctuation patterns of estrogen during the menstrual cycle (Curtis et al., 2004).

The CT responses to NaCl-S concentration were influenced by sex and more specifically by estrogen levels. Independent of estrogen, female rats prefer isotonic and hypotonic NaCl-S solution more strongly than do male rats. This is likely due to a lower NaCl detection threshold in female rats. Male rats were also found to be more sensitive to high levels of NaCl-S than females under high estrogen conditions (Curtis and Contreras, 2006). Furthermore, because Curtis et al. (2004) found no difference in the results between males and females or between the OIL and EB rats at the high concentrations of sucrose, estrogen does not appear to diminish the palatability of food. Female rats are less sensitive to sucrose solutions compared to males, regardless of EB treatment (Curtis et al., 2004). Thus, although estrogen differences can account for the sex differences in sucrose intake, there are likely other biological contributions and perhaps other hormones making such differences.

Sex differences in behavioral taste responses were more pronounced for the NaCl-S solutions than for the sucrose solutions. Male rats showed less preference for NaCl-S solutions than female rats regardless of treatment. Thus, sex differences do not appear to depend directly on estrogen levels, thus suggesting that either testosterone plays a role or that estrogen plays a more critical role in the developmental stages of life that has long-term effects on taste (Curtis et al., 2004). These experiments demonstrate that hormones do, in fact, regulate gustatory processing to a certain extent. It is possible that sodium loss may lead to more NaCl ingestion as a compensatory mechanism (Curtis and Contreras, 2006).
Increased NaCl ingestion during and after pregnancy has also been documented (Pike and Yao, 1971) and may be a compensatory response to the increased vascular volume of pregnancy or as a compensatory mechanism to replenish fluid and electrolyte loss from lactation after pregnancy (Curtis and Contreras, 2006). Pike and Yao (1971) were interested in determining whether pregnancy in the rat induces increased NaCl appetite compared to controls and if so, whether the increased appetite for NaCl effectively prevents stress on the renin-aldosterone mechanism of Na⁺ conservation. Sodium restriction has deleterious affects during pregnancy of the rat due to extraordinary stress on the renin-aldosterone Na⁺ conservation mechanism. The amount of sodium consumption required increases during pregnancy because of the physiological changes associated with pregnancy, such as the expansion of tissue fluid volume and blood volume. Rats on a sodium-restricted diet during pregnancy do not display the typical expansion of tissue fluid volume and blood volume. Furthermore, such rats will develop hyponatremia, hyperkalemia, and diminished concentrations of sodium in the bones and muscles. The stress on the renin-aldosterone system causes juxtaglomerular degranulation as well as zona glomerulosa exhaustion. The pregnant rats on a sodium-restricted diet displayed an increased appetite for sodium chloride. Free access to salt solutions and water did not lead to any deleterious effects, such as observable cardiovascular-related problems (Pike and Yao, 1971). Thus, the high estrogen levels associated with pregnancy serve to promote greater NaCl ingestion to benefit the mother and her offspring (Curtis and Contreras, 2006).
Adrenal Glands and the Taste of Salt

The function of the adrenal glands has been implicated to have an important influence on the taste of salt. Removal of the adrenal glands eliminates secretion of aldosterone. Because aldosterone is important for sodium retention, the loss of aldosterone secretion yields a loss of sodium. In sodium-deprived rats, suprathereshold NaCl concentrations are not as aversive to the rat as they normally would be because of a decrease in peripheral nerve signals that alter the rat’s perception of the solution such that it perceives high NaCl concentrations less intensively and thus demonstrates appetitive behaviors towards it. Kosten and Contreras (1985) performed an adrenalectomy on rats and analyzed their ingestion behaviors and their neural responses to various salt solutions to determine if adrenalectomy leads to decreased peripheral nerve responses to NaCl solutions.

Kosten and Contreras (1985) used eighteen male Sprague-Dawley rats, half of which were adrenalectomized, and recorded the CT neural responses to various NaCl solutions. As expected, adrenalectomized rats ingested more NaCl than controls. The adrenalectomy resulted in decreased neural activity from the CT nerve in response to the taste of NaCl solutions. As a result of adrenalectomy, rats may have lowered their sensory thresholds for NaCl. One hypothetical model explaining the decreased peripheral neural responses to NaCl after adrenalectomy suggests there is a diminished number of functional Na$^+$ receptors in the taste cells. Another model suggests that the altered neural response is due to a change in the receptor itself. The decreased neural response patterns could also be due to hormonal changes and if so, it would likely be due to angiotensin. An additional possible contributing factor to this diminished neural response
phenomenon may be through a decrease in the plasma Na\(^+\) levels in the adrenalectomized rats (Kosten and Contreras, 1985).

**Genetics of Hypertension**

Genetic hypertension is known to be a complex multigenic disorder. To further complicate matters, spontaneous hypertension in the rat model is both multigenic and multifactorial. Systemic arterial pressure is quite difficult as a phenotype to experimentally measure because it is environmentally sensitive, is controlled by numerous complex integrated biological systems, is sensitive to other physical characteristics of the animal such as body mass, and displays diurnal variations (Printz et al., 2003). Nevertheless, researchers have devised numerous experiments to better understand the role of genetics in hypertension and ultimately, how genes affect salt-taste responses and related behaviors.

The use of inbred strains provides much more control in an experimental setting so that researchers can identify the exact contribution of the genes while also controlling for any environmental factors. Many different types of hypertensive strains of rats have been created for experimental purposes, including but not limited to the spontaneously hypertensive rat, the stroke-prone spontaneously hypertensive rat, and strains where high dietary salt intake is necessary to cause hypertension, such as the Dahl salt-sensitive and Sabra rats. Genome wide scanning techniques allow researchers to identify the quantitative trait loci (QTL) responsible for blood pressure regulation. Many researchers utilize microsatellite markers that provide high-resolution genetic linkage maps of the rat
genome (McBride et al., 2003). These methods have identified genes for hypertension on chromosome 1, chromosome 2, and chromosome 10 (Printz et al., 2003).

**Hypertension and the Taste of Salt**

Although there is not a consensus on the relationship between hypertension and an altered taste of salt, it seems the majority of research indicates a difference in the levels of salt-intake by normotensive and spontaneously hypertensive rats. SHR rats can be bred such that they ingest more salt than normotensive rats; however, the exact mechanism contributing to the elevated salt intake remains unknown. It may be due to alterations in the angiotensin system, atrial natriuretic peptide and vasopressin, among other brain neurochemical systems. Enhanced salt intake may also occur because of a change in arterial chemoreceptor activity that appears in spontaneously hypertensive rats (Brown and Czarnecki, 1991 as cited in Flynn et al., 2003). The SHR genotype appears to directly affect the sensory level of salt intake. The oral sensory properties of taste along with visceral feedback signals typically influence the amount of salt intake in normal rats. However, behavioral differences in salt intake may be due to differences in the peripheral taste nerve sensitivity and a difference in the responsiveness of gustatory neurons to salt stimuli (Contreras et al., 1984 as cited in Flynn et al., 2003).

Mierson et al. (1988) demonstrated differences in the Na\(^+\) ion transport processes across lingual epithelia between normotensive WKY rats and SHR rats, such that the SHR rats exhibit a decreased neural response to NaCl that may explain the increased intake of NaCl. There is not uniform agreement on whether an abnormality of sodium transport may somehow be involved in the development of essential hypertension. It is
possible that, genetically speaking, hypertension may primarily be the result of a genetically transmitted membrane defect that alters the mechanisms that determine sodium load. The SHR rats showed increased preferences and decreased CT responses to NaCl and KCl compared to the Wistar-Kyoto (WKY) rats. However, while the decreased neural response to NaCl may be due to a modification of lingual epithelial ion transport, this correlation was not observed with KCl – likely because NaCl and KCl involve different transport pathways. It is possible that the decrease in gustatory neural activity may be due to a receptor change that changes the suprathreshold NaCl intensity and thus encourages the animal to consume more sodium (Mierson et al., 1988).

Blood pressure often affects the intake of water and electrolytes (Bachmanov et al., 1998). Although peripheral neuronal gustatory function likely plays a major role in the explanation behind differences in NaCl ingestion between normotensive and hypertensive rats, it is not sufficient to create such marked differences in NaCl intake patterns between the two strains of rats. Thus, it is likely that the visceral feedback mechanisms as well as possibly other mechanisms all work together to contribute to these NaCl intake differences between normotensive and hypertensive rats. Through these mechanisms, it is possible that the SHR genotype causes the rat to be less sensitive to NaCl-contingent feedback and as a result ingest more NaCl (Flynn et al., 2003).

Flynn et al. (2003) evaluated the mechanisms possibly responsible for the elevated intake of NaCl observed in SHR rats compared to normotensive rats through the use of two-bottle and lick-rate analyses to compare salt intake between normotensive and SHR rats. Seven SHR rats and eight normotensive WKY rats were used as the subjects. The researchers also analyzed urine output and the sodium-water balance of the rats. The
initial lick rate was not significantly different between the SHR and normotensive rats. This implies that the SHR rats do not respond differently to the oral sensory properties of NaCl, thus bringing the researchers to the conclusion that other factors must be responsible. The SHR rats did not demonstrate the same concentration-dependent decline in lick rate as the normotensive rats. Also, the SHR rats had a smaller slope in their decay of lick rate than the normotensive rats for the 0.1 and 0.3 M NaCl solutions. Together, these results imply that the SHR genotype makes rats less responsive to the inhibitory properties of the NaCl ingestion-contingent negative feedback mechanism (Flynn et al., 2003).

Electrolyte solutions KCl and CaCl$_2$ tend to taste bitter and are thus aversive to humans and other animals. With this in mind, Bachmanov et al. (1998) decided to test the intake levels of different concentrations of NaCl solutions in addition to different concentrations of quinine hydrochloride in order to determine whether the mice would demonstrate different sensitivities to bitter taste (thus affecting their reactions to KCl and CaCl$_2$) based on blood pressure differences among the mice. Essentially, Bachmanov et al. (1998) analyzed the consumption of electrolytes and quinine by mouse strains with different blood pressures wanting to determine if blood pressure significantly affects consumption of water and electrolytes in three different strains of mice phenotypically expressing high, normal, and low blood pressures. Bachmanov et al. (1998) used female mice between the ages of 5-13 weeks old. Although the researchers were confident that their results could be generalized to all mice and perhaps humans, it is unusual that their study used female mice when, as mentioned earlier, most studies of this sort use male mice because of ovulation cycles and the possible effects such drastic hormonal changes
might have on the results. Until the influence of hormones on the ingestion of NaCl is better understood, it is important to point out such unusual protocols.

Bachmanov et al. (1998) used two-bottle tests to measure fluid intake. One bottle contained water and the other bottle contained the electrolyte solution. The solutions used included six different concentrations of NaCl, six different concentrations of KCl, four concentrations of CaCl2, and six concentrations of quinine hydrochloride. NaCl solutions were presented in increasing concentrations for half of the mice and in decreasing concentrations for the others. After each test series of any given solution, the mice were given water for two days prior the start of the next series of tests.

The results of this specific experiment are important to describe because they demonstrate a wide variation in responses to the different taste solutions. The mice differed significantly in body weight based on blood pressure, such that the normotensive mice were the heaviest and the hypotensive mice were the lightest. The hypertensive mice were in the middle. Intake once corrected for body weight demonstrated that both hypertensive and hypotensive mice consumed a similar amount of water and both consumed more water than normotensive mice. Overall NaCl consumption in the ascending/descending and single concentration series was highest in the normotensive strain and lowest in the hypertensive strain. The hypotensive strain was intermediate and not significantly different from either the hypertensive or normotensive strains. Overall KCl consumption for concentrations between 10-50 mM KCl was highest in the hypotensive strain and lowest in the normotensive strain. The hypertensive strain was intermediate and not significantly different from either the hypotensive or normotensive strains. Overall KCl consumption for the 200 mM KCl concentration was highest in the
normotensive strain and lowest in the hypertensive strain while the hypotensive strain was intermediate and significantly different from the normotensive strain. Overall quinine hydrochloride consumption was significantly highest in the normotensive strain; no significant difference existed between the other two strains (Bachmanov et al., 1998).

It is readily apparent that these results are extremely varied for the different taste solutions amongst the three mice strains. This suggests that the strain differences do not represent generalized responses to the tastants; rather, these results suggest that there are specific taste and/or postingestive properties of the various solutions used in this experiment that determine taste responsiveness in each of the three mice strains. It is unlikely that blood pressure differences contribute directly to a difference in fluid consumption in these three strains and vice versa. Thus, fluid intake is not simply a function of blood pressure and there are evidently more components and factors that must be accounted for that ultimately together all determine fluid intake of electrolyte solutions (Bachmanov et al., 1998).

Environmental Influences On Hypertension and the Taste of Salt

While there is a strong genetic basis to hypertension and researchers are capable of genetically breeding rats with hypertension with each other to examine an increased genetic influence, environmental influences on hypertension cannot be dismissed and often play a large role in the development and course of hypertension. The critical period during which these environmental influences can have their greatest effects occurs during neural development. Neural development is particularly vulnerable to any environmental influences during stages of neurogenesis and rapid maturation and can lead to drastic
morphological changes. The gustatory system, in particular, is especially vulnerable to environmental influences, such as sodium-deprivation, more so than the other sensory systems (Mangold and Hill, 2007).

Previous research has demonstrated that a low-sodium diet given to pregnant rats can affect the size of the neuronal terminal fields of certain neurons in the actual embryos more than a sodium-restricted diet would after birth. More specifically, a low sodium-diet lasting only between embryonic day 3 (E3) and E12 has a greater affect on the size of the neuronal terminal fields in the CT nerve, the GSP nerve and the GL nerves than a lifelong sodium-restricted diet (Mangold and Hill, 2007). This is a paradoxical phenomenon that requires further explanation. A closer look at the GL nerve demonstrates that its projections to all other areas in the brainstem other than the NST are actually unaffected by dietary sodium restriction from E3 to E12 (Mangold and Hill, 2008). It is quite peculiar that only the GL nerve projections to the NST are directly affected by dietary sodium restriction from E3 to E12. However, Pittman and Contreras (2002) demonstrated that it was not only the GL nerve projections to the NST that are directly affected by dietary sodium restriction, but that such manipulations also affected the CT branches to the NST.

Although environmental factors may have their greatest impact during neural development and the embryonic stages of development, the environment is still capable of having strong impacts on hypertension and its association with the taste of salt long after birth. Dietary Na restriction induces a behavioral response to increase sodium ingestion as well as a hormonal response that enhances physiological retention of Na. It is interesting to note that while the hormonal response is much more immediate, occurring
as early as 24 hours after Na deprivation has begun, the behavioral response usually takes longer to occur (Garcia et al., 2008). This behavioral response is referring to an increase in the ingestion of NaCl. Depletion of sodium stores also tends to increase sodium appetite, quite logically, in many species in order to maintain proper homeostasis (Denton, 1982 as cited in Tamura and Norgren, 1997). Therefore, it is possible that hypertension, as a disease in which the blood pressure is elevated, may trick the body into thinking that it is in a greater state of sodium deprivation than it actually is, thereby leading to a greater ingestion of NaCl.

In an attempt to better understand the environmental effects of sodium deprivation during embryonic development, researchers Mangold and Hill (2007) analyzed the extensive reorganization of primary afferent projections into the gustatory brainstem induced by feeding a sodium-reduced diet during development. They found that the E3 to E12 period of sodium-restriction in embryonic development had a considerable impact on the morphology of the peripheral and gustatory systems. What is perhaps most incredible about such findings is that the E3 to E12 period of sodium-restriction occurred before the peripheral and gustatory systems had even developed. This includes the formation of the tongue as well as significant brainstem development, and yet the diet impacted the future development of these systems. Restructuring of the gustatory brainstem appears to be due to an altered embryonic experience, particularly during neurogenesis of the NST. These morphological changes likely affect the control of homeostatic and sensory processes (Mangold and Hill, 2007). The implications of this study and its findings are that a lack of sodium in the diet during embryological development changes the morphology of the gustatory and peripheral systems in such a way that it could indirectly explain an
increased ingestion of sodium or NaCl throughout life leading to the development of hypertension.

In a follow-up study, forty-six Sprague-Dawley rats at postnatal ages of 15 days, 25 days, 35 days, and 40 days were used for afferent nerve labeling. During embryonic development, half of these rats had been fed a sodium-replete diet and were thus used as controls. The other half of the rats had been fed a sodium-restricted diet lasting between E3 and E12 were used as the experimental group. Using a triple anterograde nerve label procedure at postnatal days 15, 25, 35 and 40, Mangold and Hill (2008) were able to analyze the changes of the various taste-related nerves. More specifically, the morphological changes induced by employing a sodium-restricted diet early in embryonic development in rats involved certain taste-related neurons, such as the CT nerve, developing dramatically larger terminal fields (Mangold and Hill, 2008).

In normal rats, the terminal field volumes of the CT nerve, the GSP nerve, and the GL nerve (all in the NST) decrease with age. However, rats that had been on a restricted sodium diet between ages E3 and E12 demonstrated the exact opposite results. Rather, their terminal field volumes of the three aforementioned nerves actually increased with age, with the exception of the GSP nerve, which actually remained unchanged. It seems likely that the reason control rats demonstrate a decrease in the terminal field volumes with age is because of activity-dependent pruning of afferent terminals. On the other hand, the age-related increase in terminal field sizes in the E3-E12 sodium-restricted rats may be due to cellular/molecular differences in the NST that were the result of activity-independent mechanisms. The development of neural coding and sensory-guided behaviors is largely dependent on sodium intake during the embryonic stages of
development. It is possible that the repletion of sodium in sodium-restricted rats after E12 may cause a surge in fetal IGF levels, which are important to brain development. This may cause abnormalities in the development of the NST (Mangold and Hill, 2008). Thus, it may not be the direct nature of the sodium deprivation diet itself that has such drastic consequences, but rather the reintroduction of sodium into the diet that may explain such strong effects. Further research is needed for confirmation.

In adulthood, drastic differences in terminal field volume of gustatory neurons due to gestational dietary manipulations can start from abnormal postnatal development that is determined prenatally (Mangold and Hill, 2008). However, as mentioned earlier, there can also be behavioral and electrophysiological changes in the taste responses to sodium or salt stimuli due to postnatal environmental effects somewhat early in life. Postnatal sodium deprivation results in a specific decrease in the firing rate of CT neuronal fibers in response to sodium salts. However, providing a NaCl-replete diet to sodium-deprived rats for at least 15 days will actually reverse these results. This plasticity of the gustatory system seems to involve changes in amiloride-sensitive components of the taste receptor membrane. Amiloride effectively suppresses neuronal taste responses to NaCl in control rats fed a NaCl-replete diet. In rats given a NaCl-deficient diet, however, amiloride fails to suppress the neuronal taste responses to NaCl (Hill, 1987).

Garcia et al. (2008) sought out to examine the CT neuronal responses to NaCl after brief dietary Na restriction and to determine the CT neuronal responses to NaCl upon lingual application of amiloride after both brief and prolonged dietary Na⁺ deprivation. As expected, the rats displayed a rather immediate hormonal response to the sodium deprivation in which the physiological retention of Na⁺ was enhanced. The much
more interesting result was that Na-deficient rats displayed a behavioral response to sodium deprivation only two days after sodium deprivation had begun. The rats ingested significantly more of the NaCl solution than did the controls. This was surprising because it had formerly been thought to take as long as eight days for any behavioral response to occur (Garcia et al., 2008).

While the CT neurophysiological taste responses to sodium salts decrease in rats given a sodium-deficient diet, compared to control rats, this neuronal taste-response deficit does not occur in response to non-sodium salts. Sodium deprivation may in fact reduce the number of functional amiloride-sensitive sodium components on taste receptor membranes. Because the decrease in neuronal taste responses is not permanent and returns to normal levels once the rats are given a NaCl-replete diet, the implication is that the functionality of the amiloride-sensitive sodium components must be somehow recovered and restored (Hill, 1987).

As demonstrated by Tamura and Norgren (1997), the methods by which sodium depletion occurs differ in the effects they have on gustatory neural response to sodium, but still nevertheless do increase sodium appetite. Eight male Sprague-Dawley rats were used to determine how sodium-replete and sodium-deplete diets affect the gustatory neural responses in the NST, much like many other experiments. However, these rats were given injections of furosemide to produce acute sodium depletions and the rats were subjected to sodium-replete and sodium-deplete conditions for a total of four alternating conditions for each rat. This technique makes this experiment so unique. Alternating between sodium-replete and sodium-deplete diets is known to increase sodium-intake in each condition, as it did in this particular experiment (Sakai et al., 1989).
Dietary restriction to sodium induces a sodium appetite more slowly than furosemide injections do. When given furosemide injections, rats in the sodium-deplete conditions have significantly higher neuronal responses to NaCl compared to rats in the sodium-replete conditions. Although the neuronal responses are higher during sodium-deplete conditions than they are during sodium-replete conditions, the rats still have a higher preference for salt in the sodium-deplete conditions than in the sodium-replete conditions. Because the results in regards to the neuronal responses to NaCl between the two groups are essentially the opposite of those observed in the NST neurons of rats whose sodium appetite is induced by dietary sodium restriction, the gustatory system’s coding of intensity for sodium seems to be dependent not only on the deprivation condition of the rat, but also dependent on the method by which the rat is deprived (Tamura and Norgren, 1997). Because such a slight difference in the methodology used to deprive rats of sodium can alter the results regarding the neuronal responses to NaCl, this experiment serves to highlight how hard it is to generalize any results because of the many components involved and their influences on the taste of salt, on hypertension and thus the relationship between hypertension and the effect it has on the taste of salt.

Regardless of what methods are used to raise the sodium appetite in rats, whether it is through dietary sodium restriction or through furosemide injections, rats inevitably ingest greater amounts of highly concentrated salt solutions that they otherwise would avoid. The different methods used to produce such strong sodium appetites, although each sharing the same end result, appear to differ in the way they alter the gustatory code for NaCl (Tamura and Norgren, 1997).
Conclusion

This review aimed to study hypertension, the taste of salt and the proposed relationship between hypertension and the taste of salt. Hypertension has many negative effects on the body that puts people at a higher risk of developing other illnesses and/or diseases, such as obesity and diabetes. The rat and mice models are very beneficial to understanding hypertension, the taste of salt, and the relationship between the two because of the high degree of similarity between these rodent models and humans. With the alarming rate of increased reported incidences of hypertension, particularly in America, the importance of such research becomes greater.

Research on humans has made great headway in our understanding of hypertension and the taste of salt and their relationship with one another. Most researchers will agree that neonates do have the ability to detect salt and that race and gender differences may exist – particularly during childhood. There is a relationship between birth weight and salt-taste response. This relationship is similar to the relationship between a higher body mass index and the existence of hypertension in adults, suggesting that genetics plays a significant role in the development of hypertension as well as a strong relationship between obesity and hypertension. It is possible that the relationship between the taste of salt and hypertension is strongest in infancy before any environmental effects can interfere. Environmental factors must play a role in the development of hypertension; it is simply a matter of identifying these factors. Trace elements, for example, are believed to play a contributing role, although they are clearly not a primary cause of hypertension. Certain disease states are known to affect one’s ability to taste salt, such as kidney disease and diabetes. It is important to
understand these diseases in order to better understand the mechanisms behind the ability to taste salt and how it relates to hypertension and the possible development of any other diseases. Genetic factors account for roughly 30-50% behind the development of hypertension. The genetics behind hypertension are difficult to study, however, because of the interactions of genes with one another as well as the interaction between the environment and the genes. Exercise-induced hypertension may be used as a predictor for future arterial hypertension, although all researchers are not in agreement with the validity of such a test.

Research on rats has also been equally if not more important than the research that has been performed with humans. Research on rats has shown that there are sex differences in NaCl detection thresholds, such that females have a lower threshold than males (likely due to higher estrogen levels). Genetic testing has identified genes for hypertension in rats on chromosomes 1, 2, and 10. WKY rats differ from SHR rats in that SHR rats exhibit a decreased neural response to NaCl that may explain their increased intake of NaCl. There is a critical period of the environmental influences during the stages of neurogenesis and especially from E3 to E12. Neural responses to sodium deprivation seem to involve both the GL branches to the NST as well as the CT branches to the NST.

As agreed upon by most researchers, although not all, there are some critical links between blood pressure and the taste of salt (and thus its ingestion). However, this relationship has not been comprehensively studied using homogenous methods; rather, the protocol used in these experiments has been more of a hodgepodge of various methodologies that are all trying to answer the same question. As such, the results have
not always indicated the same thing, thus more research is clearly required in this field to clear up the several discrepancies and disagreements that exist.
Works Cited


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