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Salt Taste Sensitivity in CKD: Does it Affect Salt Intake?

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See Clinical Research on Page 1254

Hypertension is the leading risk factor for cardiovascular diseases and chronic kidney disease (CKD), and salt intake is a major factor affecting blood pressure. Most individuals consume more salt than recommended, increasing their risk of cardiovascular diseases and CKD progression. Salt intake is a highly regulated process beginning with neural circuits that regulate recognition of salt in food (taste) and a complex array of cardiovascular, renal, and neural systems that change intake by feedback and feedforward control systems.[1] Exciting advances in salt taste physiology using genetically modified mice have clarified the mechanism of signaling at the receptor level (via the amiloride-sensitive sodium [Na] channel [ENaC] and perhaps other receptors) as well as the processing of these signals in the brain. Two anatomically separate systems regulate salt taste; salt appetite is controlled by a circuit located in the hindbrain dependent on aldosterone and local angiotensin production. Aversion to high salt liquids is mediated by a different region located in the forebrain, where prostaglandin seems to be the major signal.[2] Although studying salt taste in humans uses less powerful tools, human psychology allows a more detailed description of the sensation of salt. There are many differences in taste physiology between mice and humans. Among the most salient, is the role of ENaC. Deletion of this transporter eliminates salt sensing in mice. However, in humans it appears that amiloride blocks only a small but variable fraction of salt taste.[3] The cause of this difference is difficult to ascertain, it might be biological or due to assay differences. For example, it is known that the level of expression of each of the 3 subunits of ENaC is quite different in the salt receptors of fungiform or circumvallate papillae, which are in different regions of the tongue. Further, recent findings show that ENaC might function not only as an ion channel but also as a salt receptor and each of these functions might be mediated by different subunits or combination of subunits whose sensitivity to amiloride might be different.[4] The assays used differ between mice and humans; animals are salt-depleted or salt-loaded and their response to drinking solutions of different salinity is then measured. In humans, filter papers soaked in different solutions are applied to the tongue, whereas others use solutions that expose the whole mouth to the tastants. Each of these assays exposes different parts of the mouth to salt and produces somewhat different quantitative results.

Studying the threshold at which humans recognize salt reveals a surprising variability among members of a cohort of normal subjects (see Figure 1, lower left panel blue bars). A very high salt concentration produces an aversive response in animals (mediated by bitter receptors), whereas humans characterize the taste as unpleasant, but interestingly not bitter.[5] Even here, the Na concentration at which that sensation is reached is again quite variable and absent in some normal subjects (Figure 1, right panels blue). Presumably, such individuals never find salt unpleasant, regardless of concentration.

Several possible causes for these variations might include genetic, physiological, or disease states. Polymorphisms in the beta subunit of ENaC seem to increase the threshold for salt taste.[6] Volume depletion by diuretics is enough to increase the aldosterone level and reduce the threshold.[7] The oral microbiome has also been studied, and it appears that the microbiome of the more sensitive tasters has an abundance of 5 classes of microorganisms that are not present in those with a higher threshold for

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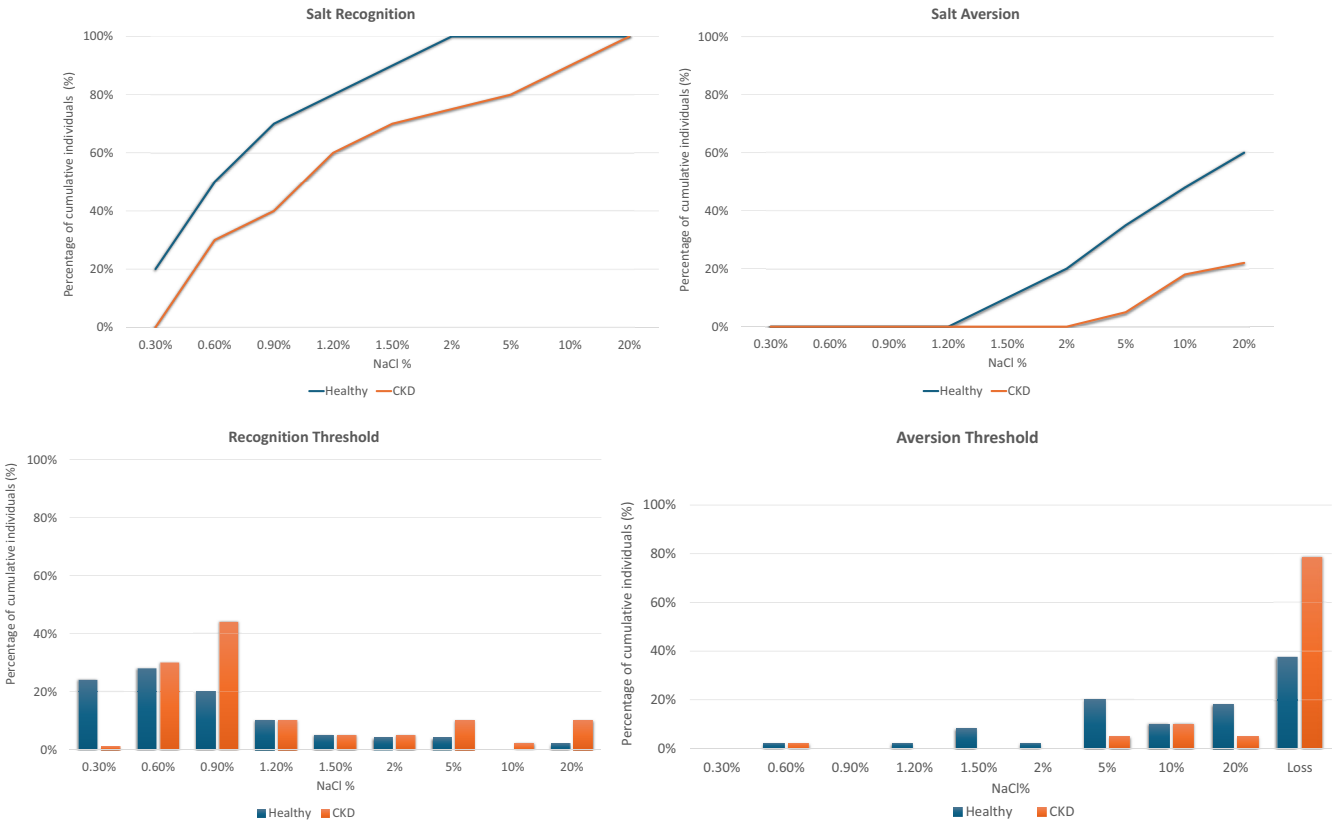

Figure 1. Healthy adults (blue) patients with chronic kidney disease (red). Recognition threshold to salt (left panels) and aversion to salt (right panels). Each panel shows the cumulative percentage of individuals responding to the specified salt concentrations. Data redrawn from Okuno-Ozeki *et al.*[5]

Na tasting.[8] Moreover, dividing a cohort of normal subjects into those with low threshold and those with high threshold shows that the more "sensitive tasters" seem to have more serine proteases in their saliva than the less sensitive ones,[9] leading these authors to speculate that the serine proteases which are well-known enhancers of ENaC conductance[4] might be the explanation. Those whose threshold was higher had more protease inhibitors in their saliva. Incidentally, we can also propose that there might be a protease in the saliva (or produced by bacteria) that can digest the amiloride-binding site from ENaC, leading to the variable amiloride sensitivity of salt taste in humans, although none has so far been found. With perhaps the possible exception of volume depletion, the above possible causes await more definitive studies.

Kusaba *et al.*[S1] found that patients with CKD have a higher threshold for salt taste than healthy subjects, but when the patients were placed on a salt-restricted diet, their threshold for tasting salt decreased. The same investigators have now turned their attention to salt aversion in a paper published in this journal[5] (Figure 1). They examined a cohort of healthy subjects and found that almost 70% of them had a salt threshold of 0.9% NaCl or less. However, in patients with CKD, the recognition threshold of 0.9% was attained in only 40% (Figure 1, left panels, red). Among these patients, 10% did not recognize even 20% NaCl as salty. To study aversion, the salt concentrations in the filters applied to the tongue were increased until an unpleasant taste was recognized. Remarkably, 38% of healthy subjects did not find salt concentrations as high as 20% as unpleasant, that is, they had no salt aversion. Among the patients with CKD, 79% showed complete loss of aversion to salt (Figure 1, right panels, red). Sweet taste was not disturbed, whereas sour and bitter taste thresholds were attenuated but to a lesser extent than that of salt. Most patients with CKD have volume expansion, which might explain the changes in the salt threshold; however, the changes in aversion are puzzling. The authors suggest several other plausible possibilities that might have altered their sense of taste,

including oral hygiene, which, given the new studies on the oral microbiome, are well worth investigating.

One important question raised by these studies is whether changes in salt threshold or aversion have any effect on salt intake. One study on healthy Nigerian subjects showed that subjects with a low threshold of recognition for tasting salt had a lower intake (as measured by 24-hour Na excretion) and the reverse was true for those with a higher threshold.[S2] However, the study was performed on only 37 people. Another equally small study in Brazil using dietary recall to estimate salt intake showed similar results.[S3] Still, a larger investigation (again with dietary recall estimating salt intake) studied 2 Japanese populations, one of which habitually had a larger salt intake. They did not show a very strong association between threshold and intake except in men aged 30 to 59 years in the high salt intake group.[S4] That there is a physiological feedback system between salt taste and salt intake is unequivocal. However, whether this loop determines salt intake in "free range" humans living in conditions of food abundance in high resource countries is much harder to study and even harder to prove. Dietary salt is determined by habit as well as the social, cultural, regional as well as the ever-constant imperatives of commerce and advertising in our environment, much more than by feedback loops of physiology and neuroscience. Otherwise, how could we explain the long-term success achieved by a few governments in reducing the salt intake of their population.[S5] In general, food purchased already prepared in restaurants and other venues has a much higher salt content than food prepared at home. In the United States, it has been estimated that 71% of the salt in food is obtained from food prepared outside the home.[S6] Why you dribble soy sauce (14% NaCl or 2500 mEq Na/l) on your sushi whereas your tablemate prefers to eat it plain is more a matter of "taste" rather than gustatory physiology.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

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