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ArticleTitle	Salt Taste and Salt Sensitive Hypertension in HIV	
Article Sub-Title		
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Journal Name	Current Hypertension Reports	
Corresponding Author	FamilyName	**Kirabo**
	Particle	
	Given Name	**Annet**
	Suffix	
	Division	Department of Medicine
	Organization	Vanderbilt University Medical Center
	Address	Room 536 Robinson Research Building, Nashville, TN, 37232-6602, USA
	Phone	
	Fax	
	Email	Annet.Kirabo@vumc.org
	URL	
	ORCID	
Author	FamilyName	**Masenga**
	Particle	
	Given Name	**Sepiso K.**
	Suffix	
	Division	HAND Research Group, School of Medicine and Health Sciences
	Organization	Mulungushi University
	Address	Livingstone Campus, Livingstone, Zambia
	Division	Department of Medicine
	Organization	Vanderbilt University Medical Center
	Address	Room 536 Robinson Research Building, Nashville, TN, 37232-6602, USA
	Phone	
	Fax	
	Email	
	URL	
	ORCID	http://orcid.org/0000-0003-4376-5831
Author	FamilyName	**Pilic**
	Particle	
	Given Name	**Leta**
	Suffix	
	Division	Faculty of Sport
	Organization	Allied Health and Performance Science, St Mary's University
	Address	Twickenham, London, UK
	Phone	
	Fax	
	Email	
	URL	
	ORCID	
Schedule	Received	
	Revised	

Accepted 7 Feb 2023

Abstract

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To provide a summary of current literature and propose potential mechanistic models to help us understand the role of HIV infection/antiretroviral therapy (ART), salt taste sensitivity (STS), and salt sensitivity of blood pressure (SSBP) in hypertension development.
Recent Findings:
The epithelial sodium channel (ENaC) is the main protein/sodium channel for recognizing Na + in the tongue and mediates preference to low-medium salt concentrations in animals and humans. Considering the pressor response to oral salt in individuals with SSBP, poor STS may worsen blood pressure. Specific genetic variants in ENaC are linked to salt taste perception and hypertension. HIV infection, some ART, and specific antihypertensive drugs are associated with reduced STS and an increased liking for salty foods.
Summary:
Persons with HIV (PWH) on ART may have a decreased STS and are at a higher risk of developing salt-sensitive hypertension. Inflammation mediated by dietary salt is one of the drivers of poor STS and salt-sensitive hypertension among PWH.

Keywords (separated by '-') Salt taste sensitivity - Salt sensitivity of blood pressure - HIV - Hypertension - ENaC

Footnote Information This article is part of the Topical Collection on Inflammation and Cardiovascular Diseases

Current Hypertension Reports
https://doi.org/10.1007/s11906-023-01236-6

INFLAMMATION AND CARDIOVASCULAR DISEASES (A KIRABO, SECTION EDITOR)

Salt Taste and Salt Sensitive Hypertension in HIV

Sepiso K. Masenga[1,2] · Leta Pilic[3] · Annet Kirabo[2]

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Keywords Salt taste sensitivity · Salt sensitivity of blood pressure · HIV · Hypertension · ENaC

Introduction

Hypogeusia related to salty taste is associated with increased salt intake and, consequentially, the development or exacerbation of hypertension [1]. In persons with HIV (PWH) where the prevalence of hypertension is high due to antiretroviral therapy (ART) and HIV infection [2–4], evidence of hypogeusia has been reported [5]. However, the underlying mechanisms and cross-talks between HIV status, taste perception or salt taste sensitivity (STS), and salt sensitivity of blood pressure (SSBP) in contributing to hypertension are not well understood. This review presents the current understanding from literature linking HIV infection/ART, poor STS, and SSBP in hypertension development. We have also proposed mechanistic models and hypotheses underlying the role of inflammation in PWH and antihypertensive drugs in mediating decreased salt taste sensitivity and salt-sensitive hypertension.

Background

Hypertension is the leading cause of preventable deaths worldwide, as it serves as a primary contributor to myocardial infarction, stroke, heart failure, and kidney disease [6]. Hypertension is more common among persons with HIV (PWH) compared with the HIV-negative population [2] especially in low- and middle-income countries. In sub-Saharan Africa, the prevalence of hypertension among PWH is over 50% [2]. HIV is a risk factor and exacerbator of poor salt taste sensitivity (STS) [5, 7], salt sensitivity of blood pressure (SSBP) [8••], cardiovascular disease, and early death [9, 10]. STS is the minimum concentration at which an individual is able to perceive a salty taste, and it affects dietary habits including the intake of salt [11, 12], and therefore, low STS indirectly increases the risk for the development of hypertension [13]. Decreased STS is associated with high salt intake in normotensive and persons living with hypertension [12] and elevated blood pressure

This article is part of the Topical Collection on *Inflammation and Cardiovascular Diseases*

✉ Annet Kirabo
Annet.Kirabo@vumc.org

[1] HAND Research Group, School of Medicine and Health Sciences, Mulungushi University, Livingstone Campus, Livingstone, Zambia

[2] Department of Medicine, Vanderbilt University Medical Center, Room 536 Robinson Research Building, Nashville, TN 37232-6602, USA

[3] Faculty of Sport, Allied Health and Performance Science, St Mary's University, Twickenham, London, UK

in healthy adults, regardless of other risk factors for hypertension [14••]. Previous studies have also shown that high dietary salt contributes to inflammation and vascular dysfunction and exacerbates SSBP [15] and is especially worse in PWH [8••]. SSBP is when changes in blood pressure (BP) mirror changes in dietary salt intake/depletion [16]. SSBP is more common in people of African descent at a rate of 75% [17] and is a risk factor for hypertension in the normotensive populations [18, 19]. Both STS and SSBP are independent predictors of hypertension, stroke, and cardiovascular death [20, 21]. However, the link between SSBP and STS in both HIV-negative and PWH is not clear.

There is a clear genetic predisposition for the perception of different tastes, determined by genes coding for the taste receptors expressed in the tongue [22]. The two main receptor/channel proteins determining STS are the epithelial sodium channel (ENaC) formed by the gene products of SCNN1A, SCNN1B, SCNN1G, and SCNN1D and the transient receptor potential cation channel subfamily member 1 (TRPV1) encoded by the TRPV1 gene [23••]. Prior studies, mostly from western countries, indicate that variations in genes coding for the above-mentioned taste receptors are associated with STS and also suggest that preference for salty taste may be a driver of salt intake [24, 25]. However, to date, there is scarcity of data exploring the link between these genetic variations, STS and SSBP, as well as the role that HIV infection plays in modulating salt taste and the pressor effects of dietary salt. Our central hypothesis, illustrated in Fig. 1, is that STS contributes to the pathogenesis of SSBP and cardiovascular disease driven by treated HIV and inflammation and that genetic variations in the taste receptor genes including those coding for ENaC play a role. This paper aims to address multiple critical gaps in the literature including the lack of understanding of genetic predispositions to STS in relation to SSBP and the contribution of treated HIV in PWH. We have summarized the evidence and proposed mechanistic models linking salt taste, SSBP, and genetics to hypertension and the role of HIV in modifying the risk for the development or progression of hypertension.

Genetic Variations in Taste Receptor Genes and Salt Taste Sensitivity

Taste sensitivity is an important factor in dietary habit development [11]. The five defined human tastes are sweet, sour, bitter, salty, and umami [26], with a potential sixth taste, fat taste ("oleogustus") recognized recently [27]. Among these, salt taste which is a specific sensation elicited by sodium ions (Na^+) was studied early and linked to hypertension [28]. ENaC has been proposed to be the main protein/sodium channel for recognizing Na^+ in the tongue and therefore in mediating preference to low-medium salt concentrations in animals and humans [29•, 30•, 31]. ENaC is expressed in the cells of the kidney and other tissues such as endothelium, vascular smooth muscle, tongue, colon, and immune cells [32]. ENaC consists of three homologous subunits: α, β, and γ, and in humans, a fourth subunit, δ, which is functionally similar to the α-subunit, is present such that either αβγ or δβγ are expressed to attain full channel activity [32, 33]. ENaC maintains body salt and water homeostasis and regulates blood pressure in the kidney. The human fungiform taste papillae of the tongue (Fig. 2) expresses α-, β-, and γ-ENaCs (also possibly expresses the δ-subunit missing in rodents [34]) with Na^+ sensing mechanisms for influencing salty taste [35, 36]. In the tongue, ENaC is involved in transepithelial sodium transport [37]. ENaCs are reported to be located at the apical membrane and basolateral ends of fungiform taste cells with the δ-ENaC exclusively restricted to the taste pore region in both fungiform and circumvallate taste buds [29•, 36] (Fig. 2). The basolateral compartment of the taste cells is exposed to an extracellular solution containing about 150 mM Na + suggesting that ENaC here could

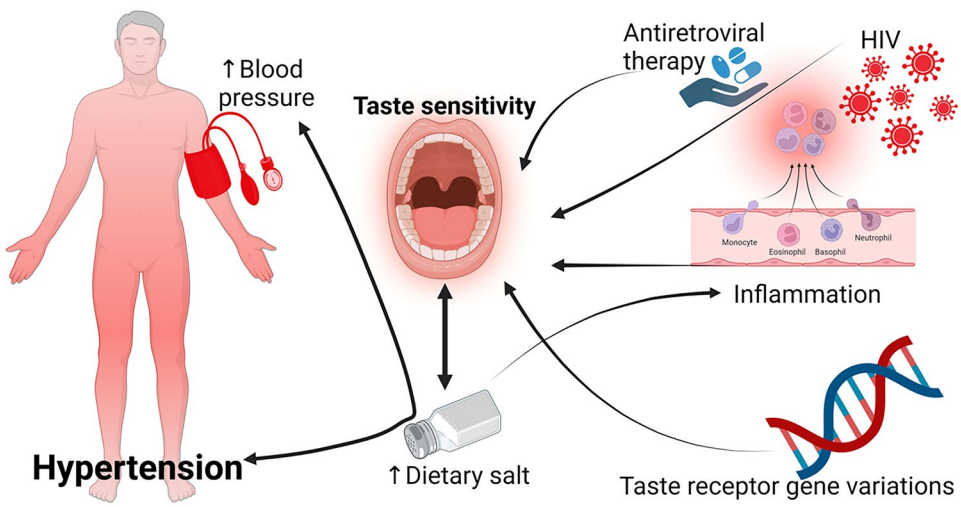

Fig. 1 Proposed model of salt taste sensitivity induced hypertension in HIV

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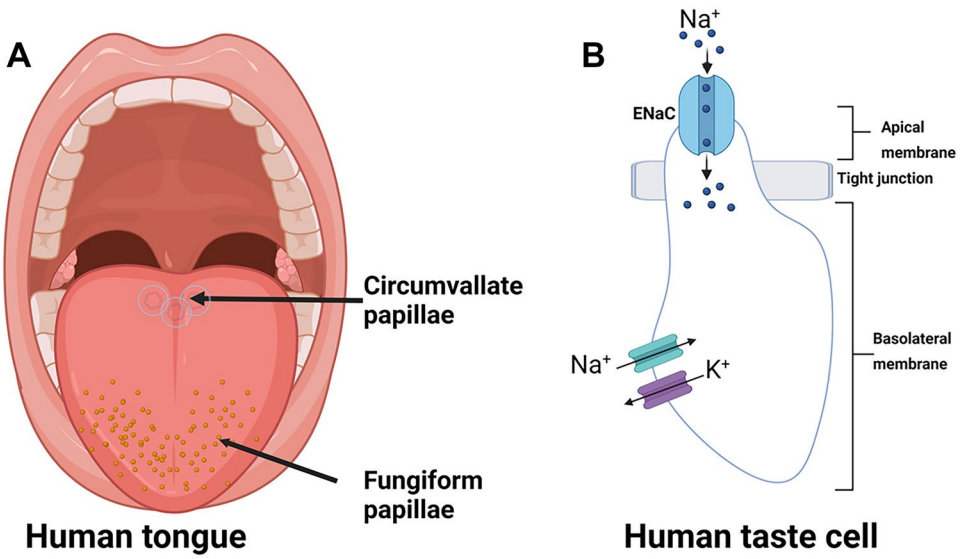

Fig. 2 Human tongue and taste bud cell. The human tongue (**A**) and taste cell (**B**) found in the tongue showing entry of sodium ions through the epithelial sodium channel (ENaC). Na^+, sodium ions; K^+, potassium ions

be involved in sodium detection when salt concentration in the food or solution exceeds plasma tonicity [29•]. In mice studies, ENaC has been reported to be sensitive to amiloride blockade resulting in the inhibition of taste responses to salt [31]. Whether this sensitivity of ENaC to amiloride is similar in humans remains controversial [31, 38].

Regarding the amiloride-insensitive part of salt taste receptor, one of the candidates is TRPV1 (transient receptor potential cation channel, subfamily V, member 1; formerly named vanilloid receptor subtype 1, or capsaicin receptor). This receptor transduces painful thermal stimuli and is also activated by capsaicin; therefore, it is considered to be mainly involved in nociception. However, a TRPV1 variant was proposed to function as an amiloride-insensitive salt taste receptor in rodents. It has been reported that TRPV1 knockout mice lack sodium chloride chorda tympani nerve responses in the presence of amiloride, whereas control mice displayed normal levels of nerve innervations [39]. This indicates that by disrupting the function of ENaC and TRPV1 channels concurrently, one may eliminate chorda tympani-mediated salt taste [40]. However, TRPV1 knockout mice do not have deficiencies in behavioral taste responses to salt [41, 42].

Genetic variants in the ENaC and TRPV1 contribute to STS through different pathways that are still unclear [43, 44]. The determination of single nucleotide polymorphisms (SNPs) in the ENaC and TRPV1 genes revealed that SNPs found in SCNN1B and TRPV1 genes were associated with STS and a tendency for liking saltier food products [23••, 40, 45••]. Moreover, rs4790522 polymorphism in the TRPV1 was associated with a lower STS in people with hypertension while the risk for hypertension was increased in individuals with TRPV1 rs8065080 and SCNN1B rs239345 genetic variants [23••].

Pressor Response to Salt, Taste Sensitivity, and Hypertension

The disproportionate change in blood pressure (BP) following changes in salt intake is termed SSBP [16]. In individuals living with hypertension, SSBP is termed salt-sensitive hypertension. The diagnosis of SSBP, which is laborious and not feasible in the clinic, is made by arbitrary cut-offs in the magnitude of the BP response to salt loading or salt depletion, which are achieved by days to weeks of dietary intervention [46, 47]. SSBP diagnosis in persons with hypertension poses a risk for possible hypertensive crisis. Dietary salt intake can unmask a salt sensitivity blood pressure phenotype. While it is well established from clinical observations [48–50], and in some animal studies [51, 52] that high dietary salt (above 5 g/day) contributes to BP elevations and salt-sensitive hypertension, the effect of high dietary salt on BP is heterogeneous. While not directly elevating BP in some individuals, it raises BP in others. A major problem with excess salt consumption is that 50% of the hypertensive population and 25% of normotensive individuals exhibit SSBP [19]. SSBP is an independent risk factor for cardiovascular disease and mortality. It is assumed that individuals with SSBP exhibit an immediate pressor response to oral salt (IPROS). Whether such response relates to conventionally defined SSBP is not known. However, there is evidence that consuming foods high in salt (≈1495 mg of sodium) suppresses brachial artery flow-mediated dilatation within 30 min [53]. Hence, high salt intake may impair vasodilation for an unknown duration during the postprandial periods of the day, increasing the 24-h BP load in susceptible individuals [54••]. IPROS or BP perturbations in general are a risk factor for future development of hypertension and correlate significantly with arterial stiffness indices including

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cardio-ankle vascular index, carotid-femoral pulse wave velocity, brachial-ankle pulse wave velocity, arterial compliance, elastic modulus, arterial distensibility, β-stiffness index, and Young's modulus [55]. Studies on IPROS are scarce. However, we have demonstrated from a prior study the presence of an IPROS in a high proportion (62%) of otherwise normotensive participants [54••]. More studies are required to determine the relationship between IPROS and STS in relation to SSBP and hypertension risk.

Furthermore, we recently examined the link between variants within the genes encoding the 4 ENaC subunits, BP, and kidney function (eGFR). We noted a significant association between variants within the δ subunit and both blood pressure and eGFR, which was surprising as the δ subunit is not expressed in the human kidney [56••]. The δ subunit is expressed in human antigen-presenting cells, and we have shown that dendritic cells (DCs) respond to increases in extracellular [Na^+] in an ENaC-dependent manner, activating a signaling pathway leading to the activation of the NLRP3 inflammasome and release of inflammatory cytokines that sensitize mice to angiotensin II (angII) dependent increases in BP [57]. Volume and sodium handling between salt-resistant and salt-sensitive individuals are the same; therefore, investigating the role of extrarenal ENaC as a key player contributing to hypertension in persons with SSBP remains critical for future therapy and management [15].

Taste Sensitivity May Be Affected by Antihypertensive Drugs and ART

Decreased STS is independently associated with a high intake of salt, corresponding increase in BP, and increased risk for the development of hypertension [1, 14••, 58]. This is compounded by the use of antihypertensive medication which can reduce food taste perception resulting in mild to severe hypogeusia and dysgeusia [1]. Persons with hypertension taking antihypertensive drugs may have lower taste sensitivity and hence a liking for more salty foods compared to healthy individuals [59]. Antihypertensive drugs have been identified to have potential effects on lowering taste sensitivity through mechanisms that are yet to be known [60, 61]. Antihypertensive drugs reported to have this effect include the calcium channel blocker amlodipine, angiotensin-converting enzyme (ACE) inhibitor captopril and angiotensin-II receptor blockers (ARBs) candesartan, losartan, and valsartan [62–65]. The possible mechanism of amlodipine-induced dysgeusia is the inhibition of calcium-sensing receptors that enhance the taste sensation to salt, sour and sweet sensations [62]. Moreover, several other drugs used in the treatment of lifestyle-related diseases and cardiovascular diseases are linked to drug-induced taste disorders by forming zinc chelates [66]. Examples of common drugs with the ability to induce taste disorders include antianemic, antibacterial (ampicillin, ciprofloxacin, metronidazole), antidepressants, cardiac medications, anti-inflammatory (dexamethasone), and central nervous system stimulants (amphetamine) [67].

STS is likely affected by HIV infection and ART usage [68] potentially resulting in increased intake of salt, BP, and hypertension. PWH may have impaired STS due to chronic inflammation or ART [5, 7, 68, 69]. This in turn may affect their dietary intake, which can raise the risk of hypertension and related complications [5, 7]. An example of HIV drugs that have been reported to have a deteriorating effect on taste sensitivity is protease inhibitors [70].

However, there is a dearth of literature on specific ART regimens associated with taste sensitivity, and the mechanisms underlying the development of hyposmia and hypogeusia in PWH are unknown [7, 71]. There is a need for more studies in this area especially that PWH are at higher risk for developing hypertension compared to HIV-negative individuals [72].

The Role of HIV Infection/ART and Inflammation in Mediating Salt Sensitive Hypertension

HIV infection and the use of antiretroviral therapy (ART) are risk factors for the development of hypertension mediated by inflammatory mechanisms that exacerbate SSBP and STS. The inflammation seen in PWH results from HIV viremia and immune cell activation following infection with HIV [73–75]. Inflammation and adaptive immune activation persist despite viral suppression with antiretroviral therapy (ART) [72]. Immune activation and inflammation are drivers of vascular injury that contributes to the development or progression of salt-sensitive hypertension in PWH [72]. We have recently reported that PWH had a higher prevalence (95%) of SSBP than what has been reported (75%) in the general African population [8••]. There is now strong evidence indicating significant extrarenal involvement in the pathogenesis of SSBP and salt-sensitive hypertension [76]. More specifically, inflammation and vascular remodeling resulting from dietary salt effects, infection, and other hypertensive stimuli are emerging key factors contributing to the genesis and propagation of hypertension with an increased risk for developing hypertension-related complications [76, 77]. Based on studies from our laboratory and others [2, 8••, 76, 77, 78•] as summarized in Fig. 3, we propose that HIV infection and ART and/or dietary salt activate vascular endothelial cells resulting in increased expression of vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1). Thus, increasing the propensity of

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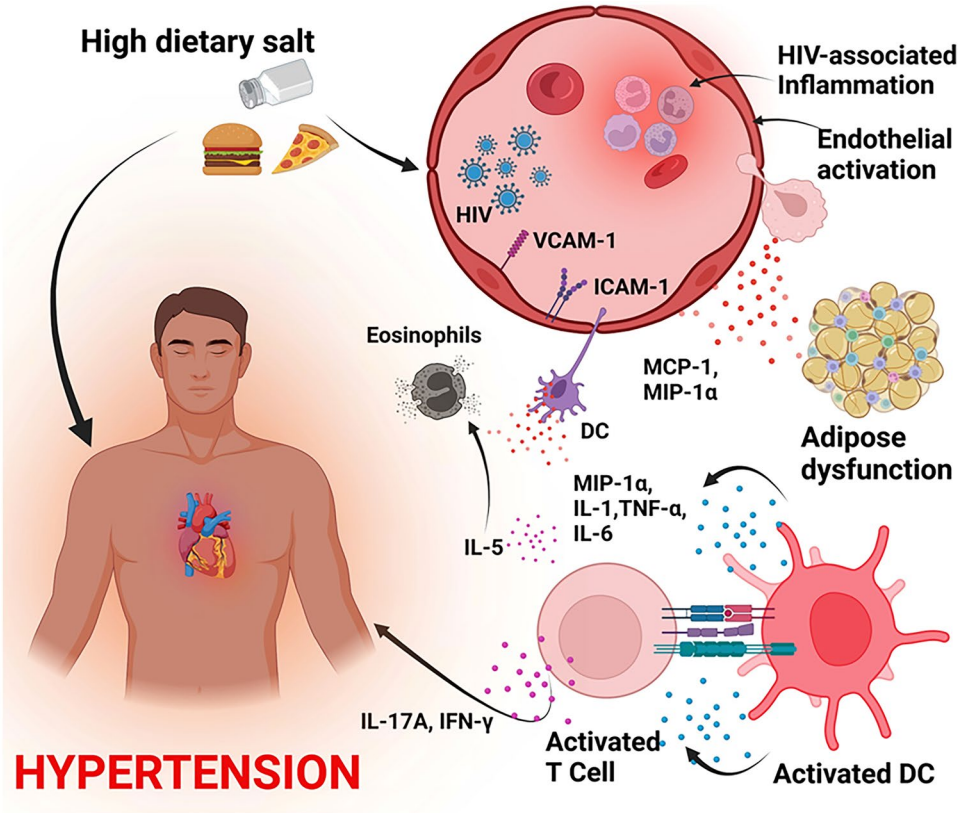

Fig. 3 Proposed model of salt and HIV contribution to hypertension. Antiretroviral therapy, ART; vascular cell adhesion molecule-1, VCAM-1; intracellular adhesion molecule 1, ICAM-1; monocyte chemoattractant protein 1, MCP1; macrophage inflammatory protein-1α, MIP-1α; tumor necrosis factor, TNF-α

activated monocytes, with increased production of soluble cluster of differentiation (sCD) 163, to diapedese into tissues where they encounter dysfunctional adipose tissue and convert into activated macrophages and dendritic cells [78•]. The activated antigen-presenting cells, including macrophages and dendritic cells, produce MCP1 (monocyte chemoattractant protein 1), which further increases migration and infiltration of monocyte/macrophages into tissues. They also produce chemotactic cytokine MIP-1α (macrophage inflammatory protein-1α), which activates eosinophils and induces release of interleukin (IL)-6 and tumor necrosis factor (TNF)-α from macrophages and dendritic cells. These antigen-presenting cells activate T cells to produce IL-17A, which contributes to salt-sensitive hypertension. They also produce IL-5, which induces the differentiation of eosinophils [78•].

It is clear from current evidence that HIV drugs, HIV infection, and drugs used to control BP in persons with hypertension have a significant impact on STS. It is also clear that there are specific genetic variations in the ENaC and TRPV1 genes associated with STS. However, the underlying mechanisms associated with these factors are still elusive.

Directions for Future Research

We propose that future experimental and clinical research should focus on the following gaps:

- Explore the expression and function of ENaC found on the tongue and the role of the αβγ or δβγ subunits in salt sensing mechanisms.
- Genetic variants in the genes encoding ENaC in the tongue found in populations of different ethnicity and their relationship with SSBP, taste sensitivity, and hypertension.
- The significance of IPROS in relation with SSBP is a promising area especially since SSBP diagnosis is laborious and unfeasible in the clinic. IPROS may emerge as a potential surrogate for the diagnosis of SSBP. IPROS is feasible in the clinical setup. Reports on IPROS are very scarce. Clinical trials and diagnostic studies are therefore warrantable.
- The role and mechanisms for taste disturbance associated with hypertensive and ART should be studied in detail to help in mitigating some of the complications associated with poor salt taste sensitivity.

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- Studies on the relationship between SSBP and salt taste sensitivity are warrantable as this is yet to be established.

Conclusion

There is strong evidence tying salt taste sensitivity to genetic variants. It is also clear that HIV infection and the use of ART and antihypertensive drugs interact with mechanisms involved in taste sensitivity. Whether this disturbance in taste sensitivity increases salt intake in PWH and hence increases the risk for hypertension is still unclear.

What is Known

- HIV infection and ART are associated with hypogeusia.
- Taste sensitivity has a genetic predisposition.

What is New

- ENaC drives salt taste sensitivity in humans.
- The δ subunit of ENaC may be expressed in the tongue and likely controls salt perception.
- TRPV1 genetic variants may be associated with salt taste sensitivity, salt intake, and SSBP.
- Specific ART and antihypertensive drugs may play a role in disturbing salt taste sensitivity and potentially potentiate a liking for salty food.

Acknowledgements Graphics were produced using www.Biorender.com.

Author Contribution SKM conceptualized the study and wrote the draft manuscript. SKM, LP, and AK wrote and edited different sections of the manuscript. SKM created all the figures. LP and AK edited and reviewed the manuscript. AK conceptualized the framework and finalized the manuscript as well as obtained funding for the manuscript. All authors contributed to article reviews, edited, and approved the final version of this manuscript.

Funding This work was supported by the Fogarty International Center of the National Institutes of Health grants R03HL155041, R01HL147818, and R01HL144941 (AK) and 2D43TW009744, D43 TW009744, and D43 TW009337 (SKM). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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