Chapter

Hypertension as Three Systematic Dysregulations of Na^+ Homeostasis in Terrestrial Mammal, and Salt in Gut Might Cause Brain Inflammation

Mizuo Mifune and Yoshihiko Kanno

Abstract

Although Na^+ homeostasis in vivo is essential for mammals, it is known that excessive salt (NaCl) intake has played a major role in the development of hypertension. In vivo, there is a hormonal system, the renin-angiotensin-aldosterone system (RAAS), that specializes in regulating Na^+ retention, especially the amount of Na^+ in plasma. Na^+ homeostasis in vivo has been achieved mainly by the RAAS, through regulation of vascular tonus (blood pressure) and Na^+ handling in the kidney (Na^+ diuresis). Recent studies have revealed a third mechanism of Na^+ homeostasis in vivo: regulation of interstitial Na^+ levels in tissues, such as subcutaneous tissues, by tissue macrophage immunity. In the pathogenesis of salt-sensitive hypertension, Recent research have been revealed that three molecular axes (Ang II - Rho/NOX-eNOS system, Aldosterone-rac1 -ENaC system, and tissue Na^+ – TonEBP in macrophage -VEGF-c) are significantly involved in maintaining Na^+ homeostasis in salt induced hypertension. Furthermore, the mechanism by which salt causes hypertension via the immune system (intestinal, local mucosal, and tissue immunity) has also been reported. In this article, we would like to propose that three molecular dysfunctions are involved in the development of salt-sensitive hypertension through three immunological mechanisms in the maintenance of Na^+ homeostasis. Next, I would like to explain the importance of gut-RAAS and abnormality of intestinal microflora (dysbiosis) in salt-sensitive hypertension. It has been known that the metabolites (e.g., short-chain fatty acid neural amino) produced by microflora are deeply involved in central (CNS) and sympathetic nervous system (SNS) activity. In addition, we would like to explain of the importance of brain-RAAS and cerebral inflammation in salt-sensitive hypertension. Moreover, recent research have revealed that the detection-mechanism in the brain for Na^+ concentration ($[Na^+]$) in vivo and in the tongue for $[Na^+]$ in diet. These finding suggests that excessive salt intake may cause brain dysfunction, most delicate organ, before the onset of salt sensitive hypertension, and may also destroy brain structure after the onset of salt sensitive hypertension. Thus, we would like to insist that excessive salt intake might not only induce hypertension, but also be toxic especially for brain. Finally, we would like to explain that The DASH diet (Dietary Approaches to Stop Hypertension) is one of the universal diets for adult human, not only by reducing salt, but also by reducing metabolic stress and improving of dysbiosis.

Keywords: homeostasis, multisystem, immunity, dysbiosis, taste

1. Introduction

For terrestrial mammals, dehydration is fatal. Because, dehydration cause lowering circulating plasma volume (plasma Na^+), lowering blood pressure, and decrease of organ blood flow, leading to death. To prevent dehydration, terrestrial mammals have been developed the mechanisms to maintain BP and Na in the body. This defense mechanism against dehydration is the renin–angiotensin–aldosterone system (RAAS) which is a hormone system that regulates blood pressure, systemic vascular resistance and maintain [Na^+]in the body [1, 2]. To prevent tissue hypo-reflux due to hypotension during dehydration and to maintain the effective circulating plasma volume, Ang-II caused vascular contraction and re-absorption of Na^+ (**Figure 1**).

In the detailed description, when renal blood flow is reduced, juxtaglomerular cells in the kidneys secrete renin into circulation. Plasma renin then carries out the conversion of angiotensinogen, released from the liver to angiotensin I. Angiotensin I is subsequently converted to angiotensin II(Ang-II) by the angiotensin-converting enzyme (ACE) found on the surface of capillary endothelial cells, predominantly those of the lungs. Ang -II is octapeptide described as Ang- [1-8]. There are two receptors for Ang-II, type 1 receptor (AT1R) and type II receptor (AT2) [3]. Ang-II is a biologically active peptide that mediates its effects via the angiotensin-II type 1 receptor (AT1R). On the other side, AT2R exerts mainly anti-AT1R [4]. Ang-II stimulation via AT1R was originally known as a circulating hormone that regulates blood pressure and electrolyte balance by acting on vascular contraction, renal sodium handling, sympathetic activity, and vasopressin release. As detailed description, Moreover, Ang II stimulates the secretion of aldosterone also via AT1R in the adrenal cortex [5].

Aldosterone increases the reabsorption of Na^+ via epithelial sodium channels (ENaC) in the renal tubules (collecting ducts), at the same time causing the excretion of potassium [6]. In this way, systematic RAAS was defined as an endocrine system involved in blood pressure regulation and body electrolyte balance. This pathway (renin – Ang-II-aldosterone axis) is called as "classical and systematic RA(A)S".

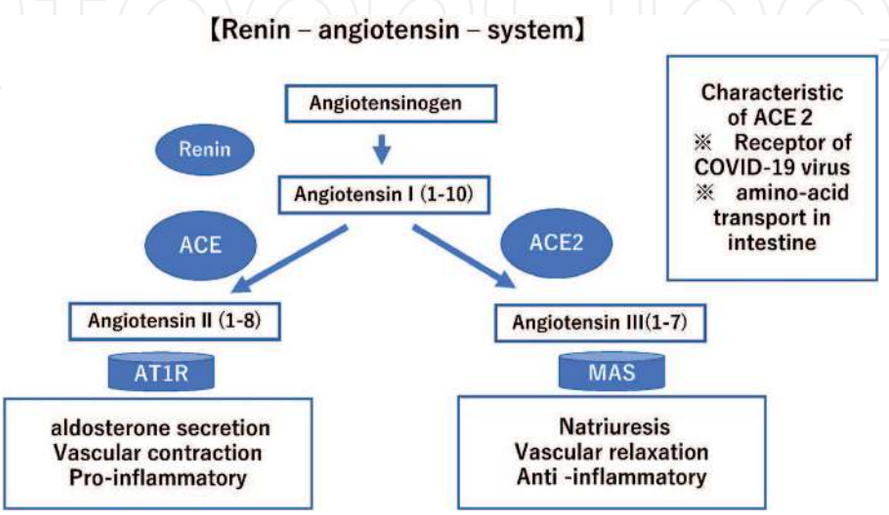

Figure 1.
Bipolarity of pathophysiological effects in renin – angiotensin- system.

Moreover, RAAS is now considered a "ubiquitous" system that expressed locally in various tissue and exerts multiple paracrine/autocrine effects involved in tissue physiology and homeostasis. This concept is considered as "tissue RAAS". Local angiotensin pathway and their physiological importance were elucidated in different tissues including the heart, blood vessels, kidney, brain, adipose tissue, liver, lymphatic tissue, reproductive system, and eye. In these tissues, local RAAS acts independently from systematic RAAS in a paracrine and paracrine manner but may still interact with systematic RAAS to exert endocrine effects [7].

If the RAS is abnormally active, blood pressure will be too high. There are several types of drugs which includes ACE inhibitors, Angiotensin-II type I receptor blocker (ARBs), and renin inhibitors that interrupt different steps in this system to improve blood pressure. These drugs are one of the primary ways to control high blood pressure, heart failure, kidney failure, and harmful effects of diabetes [8].

On the other side, a novel axis of the renin-angiotensin system (RAS) was unveiled by the discovery of angiotensin- (1-7) [Ang- (1-7)]. Angiotensin-converting enzyme 2 (ACE2), not ACE, was shown to be the main mediator of this reaction (Ang-I (1-10) to Ang (1-7), not Ang-II (1-8)), and Mas was found to be the receptor for the heptapeptide. Compared to classical RAS axis (ACE-AngII-AT1R), novel RAS axis (ACE2-Ang(1–7))-MAS act anti-hypertensive and anti-inflammatory effect [9].

In this chapter, we explained that the RAAS system is most pivotal hormonal mechanism for sodium retention in vivo. Apart from the systemic RAAS system, organ-specific effects have been recognized in various organs (kidney, cardiovascular, and brain) involved in sodium retention and blood pressure formation (renal RAAS, cardiovascular RAAS, and brain RAAS). Ang-II and aldosterone have been found to have pro-inflammatory effects via AT1R and MR. Originally, the balance between Na and aldosterone should be a seesaw-relationship, but it has been found that this relationship is broken in the development of salt-sensitive hypertension. Thus, a boost and runway of RAAS, the most important mechanism to maintain of Na homeostasis for terrestrial mammals, has been recognized as the basis for the development of hypertension.

2. Vascular tonus dysfunction by AngII-RhoA/NADPH-eNOS axis

Ang-II has three physiological effects to elevate blood pressure via AT1R, vascular contraction, renal absorption, and aldosterone secretion. As detailed description, Ang II is a potent vasoconstrictive peptide that causes blood vessels to construct via AT1R in vascular smooth muscle cell, resulting in increased blood pressure. Ang II also activate sodium reabsorption through NHE3 via AT1R in the renal tubules (proximal duct). Moreover, Ang II stimulates the secretion of aldosterone also via AT1R in the adrenal cortex.

Ang-II also exerts three pathological effect, oxidative stress production, induction of inflammation and fibrosis [10]. Ang II stimulation can activate NAD(P)H oxidase to produce ROS, resulting in oxidative stress damage [11]. ROS production in VSMC by Ang II caused also mitochondrial dysfunction and cellular injury [12].

In vascular smooth muscle cells, RhoA/ROCK determine sensitivity to vasoconstrictors by Ang II in salt-sensitive hypertension [13, 14]. The Rho family small GTP binding protein, what is called Rho GTPase (consist of Rho (RhoA, C), Rac (Rac1,2) and Cdc42), is part of the Ras superfamily and has important functions in regulating intracellular signaling and cell morphology. The Rho family has various cellular functions such as cell migration, phagocytosis, endocytosis,

morphogenesis, and cytokinesis. The Rho family is also involved in cell cycle progression and gene expression, cell polarity, hematopoiesis, and Wnt signaling [15].

In endothelial cells, the RhoA/ROCK activation and ROS production via Ang-II stimulation in VSMC pathway negatively regulates NO production through eNOS dysfunction [16]. Endothelial dysfunction is caused by reducing NO bioavailability, leading to peroxynitrite (ONOO-) formation which is reactant superoxide with NO. Endogenous NO is critical for regulating renal hemodynamics and sodium homeostasis, including renal vasodilation and natriuresis [17], and is also control cerebral blood flow and Cerebrospinal fluid Na concentration [18].

The importance of NO in vivo cannot be overestimated. To maintain of homeostasis, the cellular action of nitric oxide, which is second messenger is as important as oxygen [19]. At first, vascular smooth muscle is dilated by NO produced by endothelial Nitric Oxide Synthase (eNOS), which is present in vascular endothelial cells. NO is a molecule with a simple chemical structure that exists in a gaseous state at room temperature. NOS is an enzyme involved in the metabolic reaction that synthesizes L-citrulline from the amino acid L-arginine to form L-citrulline and NO. There are three types of NOS: eNOS, which is found in the vascular endothelium; neural NOS (nNOS), which is found in nerve cells; and inducible NOS (NOS), which is induced by stress. It has been reported that excessive salt overload reduces the vascular dilation response, and arginine administration is known to restore this function. In the development of essential hypertension, oxidative stress (superoxide (O2-), hydrogen peroxide (H2O2)) produced by NADPH oxidase and xanthine oxidase in blood vessels reduces the production of NO by eNOS, which is thought to be one of the mechanisms of essential hypertension [20].

In addition, the activation of eNOS in the export and import arteries increases the renal medullary blood flow. Activation of nNOS in the macula dense decreases the regulatory capacity of TGF. In addition, iNOS decreases the renal Na reabsorption capacity. Thus, impaired endothelial function via dysfunction of eNOS due to increased oxidative stress is the cause of the development of hypertension from resistance vascular dysfunction. Furthermore, dysfunction of other NOS (nNOS and iNOS) is also involved in impaired medullary blood flow and tubular function in the kidney [20]. Thus, NOS in vascular endothelial cells is the most important molecule for the regulation of total peripheral vascular resistance, and other NOS also function in specific roles in the kidney and brain, and under specific conditions such as during inflammation. This suggests that dysfunction of these three NOSs may be the cause of the development of hypertension. In addition, the dysfunction of NOS is thought to be caused by increased oxidative stress, both systemic and local. Therefore, the activation of RhoA and the production of ROS by Ang II in VSMC caused NO production system in eNOS in endothelial cell might be pivotal mechanism of contractile augmentation and reducing renal blood flow, resulting Na retention in salt induced hypertension [21].

We would like to propose that the dysfunction of AngII-RhoA/NADPH-eNOS axis found in salt-sensitive hypertension cause vascular dysfunction by tissue local oxidative stress formation [22].

3. Na^+ retention by aldosterone-rac1-ENaC axis cause in vivo

Ang II is a typical hormone that contracts the vascular smooth muscle of resistance vessels, but Ang II also has two other effects, such as sodium reabsorption in the proximal tubule and aldosterone secretion from the adrenal gland [23]. The action of aldosterone is mediated by serum and glucocorticoid-regulated kinase 1 (SGK1) as a transcription factor, which is involved in the synthesis of ENaC

protein in the luminal membrane, the synthesis of Na^+ pump (Na^+/K + - ATPase) in the lateral basement membrane, and the inhibition of endogenous sodium pump, and activation of endogenous sodium pump inhibitory factor (digitalis-like substance) [24].

Essentially, the kidneys promote sodium diuresis by increasing blood pressure, increasing renal medullary blood flow, leading to increasing intraglomerular pressure. This is called baroreflex diuresis, which was firstly pointed out by Guyton. In other words, the kidneys regulate the amount of sodium in the body through the excretion of Na^+, which is called the sodium handling action of the kidneys [25]. This is called renal sodium handling. Renal handling consists of the production of primary urine by maintaining renal medullary blood flow with Ang II and NO, and the reabsorption of sodium in the tubules. To maintain renal medullary blood flow, there is tonus regulation of the two resistance vessels, glomerular export and import arteries, and a tubular feedback mechanism (TGF). Na^+ reabsorption by the tubules is mediated by NHE (Na^+/K^+ exchanger in the proximal tubules [26], NKCC (Na^+/K^+/2Cl- co-transporter) in the ascending Henle loop, NCC (Na^+/Cl- co-transporter) in the distal tubules, and mineralocorticoid receptors in the collecting ducts. The epithelial sodium channel (ENaC) by the mineral corticoid receptor (MR) in the collecting duct, and four main Na^+ reabsorption transporters [27]. At the onset of hypertension, functional changes in renal sodium handling are observed due to changes in renal medullary blood flow and renal tubular Na^+ reabsorption. First, in the proximal tubule NHE, stimulation of tubular AT1 receptors by systemic circulating Ang II enhances Na reabsorption by NHE. Secondly, NCCs in the distal tubule promote Na reabsorption from NCCs with increased metabolic stress (hyperinsulinemia, hypokalemia, glucocorticoids, acidosis) (WNK-NCC system) [28] and activation of the sympathetic nervous system (β3-adrenalegic NCC system) [29]. The final effector of Na^+ reabsorption is the activation of MR by aldosterone stimulation, which results in Na^+ reabsorption from ENaC. Notably, homeostatic activation of rac1 was observed in the abnormal increase in Na^+ reabsorption by MR-ENaC, and it has been reported that MR-ENaC is activated and Na^+ reabsorption is enhanced independently of aldosterone stimulation [30]. In addition, aldosterone is known to promote pathological cardiovascular remodeling by inducing inflammation [31]. Therefore, eplerenone, an anti-aldosterone drug, has been reported to have a predominant inhibitory effect on cardiovascular events in large clinical studies. In addition, eplerenone, an anti-MR drug, has been reported to have a significant inhibitory effect on cardiovascular events in large clinical studies [32].

Aldosterone-activated ENaC is most pivotal in the mechanism of Na^+ retention in kidney was observed. Interestingly, the activation of ENaC was not dependent on the elevation of aldosterone concentration itself, but on the constitutive activation of rac1, a small G protein family with RhoA. We would like to propose that this increased renal sodium reabsorption observed in salt-sensitive hypertension is an abnormality of the aldosterone-rac1-ENaC axis.

4. Three immune mechanisms are involved in the development of salt-sensitive hypertension

Recent studies have revealed that three immune mechanisms are involved in the development of salt-sensitive hypertension [33]. First, excess salt from the diet is involved in blood pressure dysregulation through cytokine production by intestinal immunity [34]. Na^+ in the intestine activates T lymphocytes (TH17 cells) that produce interleukin-17 (IL-17), a strong pro-inflammatory cytokine, in the intestine,

where 70% of the systemic immune cells are located. The increased oxidative stress produced by NADPH oxidase in neutrophils activated by circulating IL-17 was found to be a mechanism that greatly reduced the function of eNOS in the vascular endothelium [35]. It has also been reported that the activation of TH17 cells simultaneously causes a decrease in the function of regulatory T cells (Treg), which control the allergic reaction, a runaway immune response [36]. In other words, excessive salt induces systemic vascular endothelial dysfunction and immunodeficiency through systemic activation of IL-17 by dysbiosis. Therefore, excessive salt is also involved in cognitive dysfunction by decreasing blood flow to the brain [37], and in the development of multiple sclerosis, an autoimmune disease of the brain [38]. We hypothesize that dietary salt impairs the function of the Ang II-RhoA/NADPH-eNOS axis, a blood pressure regulating system, by impairing eNOS function (vascular endothelial dilatation) associated with hyper-cytokine induced oxidative stress via intestinal immunity abnormality.

Second, it has been reported that the acquired immune system, mainly T lymphocytes, may be involved in the function of renal tubules in the regulation of renal Na^+ handling [39, 40]. T-lymphocytes may be involved in the regulation of renal tubular function via stimulation from sympathetic nerve activation (via β3-adrenal receptors) and glucocorticoids (via SGK1 (serum glucocorticoid - regulated kinase 1)) in the renal medulla through activation of mTOR (mammalian target of receptor) [41, 42]. We would like to propose that abnormal activation of T lymphocytes of the acquired immune system reduces the regulatory function of renal Na^+ handling mechanisms manipulated by the aldosterone-rac1-ENaC axis.

Third, tissue immunity, which is controlled by macrophages [43] has been found to regulate the amount of interstitial Na^+ in skin by regulating tissue lymphatic reflux, and it has been reported that dysfunction of this mechanism contributes to the development of hypertension [44]. Excess interstitial Na^+ was found to accumulate in skin and muscle before increasing the amount of circulating plasma Na^+, which might cause salt-sensitive hypertension, by imaging the concentration of 23 Na^+ in tissues using sodium-magnetic resonance imaging (23Na-MRI) [45]. Although the amount of plasma Na^+ is regulated by the RAAS system, high concentrations of Na^+ in the interstitial fluid in subcutaneous tissues activate the mononuclear phagocytic cell lineage (macrophages and monocytes) and induce the transcription of their own osmotic-responsive enhancer binding protein (TonEBP). The increased expression of this transcription factor, TonEBP (tonicity-responsive enhancer binding protein), activate mononuclear phagocytic action. The TonEBP activation increases the expression and secretion of vascular endothelial growth factor (VEGF)-C, induces hyperplasia of lymphatic vessels in the subcutaneous tissue, and removes excess Na^+ via lymphatic vessels [46]. However, the drainage of interstitial Na^+ by increased lymphatic vessels, which is activated by TonEBP-VEGF-C in tissue-macrophage, may not be effective in condition of the loss of intercellular matrix, such as proteoglycans, for some reason, and the buffering and retention effect of Na^+ as interstitial Na^+ is lost, resulting in increased plasma Na^+. In this way, it is assumed that an increase in the amount of Na^+ in the plasma leads to the development of salt-sensitive hypertension. In practice, it has been reported that the amount of Na^+ in the skin and muscles of patients with hypertension is higher than that of normal subjects [47], and that the accumulation of Na^+ in the skin of patients with chronic kidney disease is associated with left ventricular hypertrophy [48]. Therefore, it has been proposed that dysfunction of lymphatic vessels regulated by tissue macrophage in the skin may cause excessive interstitial Na^+ accumulation and associated salt-sensitive hypertension. This mechanism may also be involved in local immunity against bacterial infections, as activation of TonEBP in the skin leads to bactericidal NO production by activating iNOS [49].

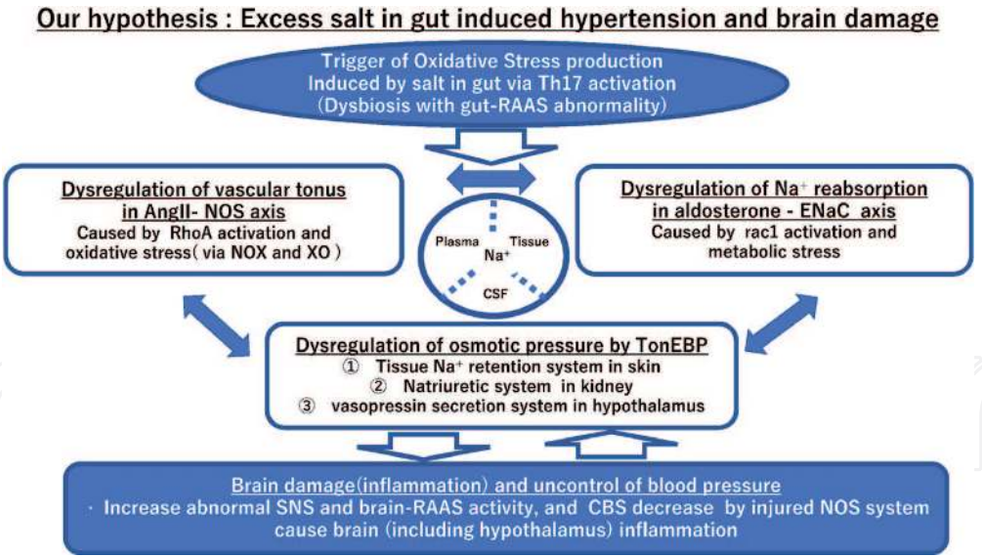

Figure 2.
Na^+ homeostasis in terrestrial mammal body is architected by three axes, Na^+ circulation in side, Na^+ absorption from outside, and Na^+ concentration maintenance in tissue and body fluid.

Surprisingly, TonEBP is also reported to be expressed in the renal medulla and hypothalamus and is involved in the urine concentration mechanism in the renal medulla [50] and the secretion of arginine vasopressin in the hypothalamus [51].

In other words, salt-sensitive hypertension, which is a dis-regulation of Na^+ homeostasis in the body, is caused not only by abnormalities in the regulation of plasma Na^+ by RAAS, but also by the dysregulation of interstitial Na^+ through the tissue immune system (tissue macrophage-TonEBP (macrophage)-VEGF-C/NO). VEGF-C/NO axis) (**Figure 2**).

5. Salt in gut, mediating through microbiome and gut-RAAS, cause hypertension

As mentioned earlier in this chapter, excessive salt in the intestine is assumed to be trigger of onset of hypertension via dysbiosis of the gut microbiome (GM) [52]. In an animal study, it was reported that a decrease in lactobacillus murinus caused by salt intake altered the intestinal microbiome and contributed to the development of hypertension [53]. The effects of dietary content on the intestinal microflora are not limited to salt, but also include due to excessive sugar and carbohydrate, causing abnormalities in glucose metabolism, and to dietary fiber deficiency in the development of hypertension, causing constipation. Single-chain fatty acids such as acetic acid and butyric acid produced by the intestinal microflora have been reported to play a favorable role in the regulation of blood pressure [54]. On the other hand, trimethylamine N-oxide (TMAO), a gut-microbiota of choline and L-carnitine, has been reported to exert vascular injury effects. Thus, the gut and hypertension are closely related, based on the metabolic and immune effects of the intestinal microbiota [55].

Furthermore, the GM is also thought to be involved in sympathetic nerve dysregulation by abnormal metabolism of tyrosine, which is a neurogenic amino acid, synthetized to sympathetic neurotransmitters (dopamine, norepinephrine, and epinephrine) [56]. Among these, tryptophan is the most important neurogenic amino acid [57]. Tryptophan is converted to serotonin, which has various effects on the nervous system, including the central nervous system, peripheral nervous system, and enteric nervous system [57]. Tryptophan is also involved in the function of T-lymphocytes and has been found to have effects on the immune system [58].

Thus, monoamine metabolism in the intestine is very important, and the intestinal microbiota is greatly involved in the control of blood pressure through regulation of the sympathetic nervous system and immunity.

In addition, the intestine has a local RAAS to regulate water uptake of sodium in colon. This is called gut RASS. In this mechanism, Ang-II - AT1R - aldosterone axis is responsible for bowel movement and sodium absorption via ENaC. On the other hand, this Ang-II - AT1 - aldosterone axis influences intestinal inflammation. On the other hand, the Ang-(1–7)- ACE2- MASR axis has been reported to have anti-hypertensive and anti-inflammatory effects [59]. Recent studies have shown that ACE2 is involved in the regulation of amino acid transport in the intestine [60]. In addition, ACE2 is a receptor for the COVID-19 virus, and cytokine storm caused by this viral infection has been found to be due to attenuation of the anti-inflammatory and anticoagulant effects of ACE2. Therefore, this property of ACE2 has led to the development of therapeutic agents for coronaviruses [61].

6. Na^+ sensor in brain cause Na appetite

The brain controls systemic blood pressure and maintains homeostasis of Na^+ in the body through the HPA (hypothalamus - pituitary – adrenal grand) system and the sympathetic nervous system (SNS). In addition, it has been reported that oxidative stress is involved in the pathogenesis of salt-sensitive hypertension by abnormal enhancement of the brain RAAS and SNS [62].

Recent studies have shown that Na^+ homeostasis in the body is maintained by Na^+ sensors (Nax) in the brain that detect cerebrospinal fluid Na^+ (CSF Na^+) [63], and that the brain detects Na^+ in the diet by ENaC in the taste cells on the tongue [64]. Recent studies have shown that the Na^+ concentration in the cerebrospinal fluid (CSF) of salt-sensitive hypertensive rodents is significantly higher than that of the control group, even though the blood Na^+ concentration is the same. Nax exist at the subfornical organ (SFO) and the vasculosum of the lamia terminalis (OVLT) in circumventricular organ (CVO) belonging to the of the third ventricle, which is exceptionally lacking a blood–brain barrier (BBB) [65]. Nax senses changes in cerebrospinal sodium (CSF Na^+) in the SFO and OVLT, and its signals regulate fluid and salt intake behavior in response to dehydrate condition [66]. The signal of increased CSF Na^+ concentration activates the peripheral sympathetic nervous system through activation of the paraventricular nucleus (PVN) and the rostral ventrolateral medulla (RVLM), which are both sympathetic control centers. In addition, this signal is transmitted to the hypothalamus to regulate the vasopressin (antidiuretic hormone) secretion [51]. Thus, the homeostasis of Na^+ in the body is controlled by the activation of SNS and RAAS functions in the brain via CSF [Na^+] signals.

Humans perceive five basic tastes: sweet, sour, bitter, umami, and salty. ENaC, which is present in taste cells in the taste buds of the tongue, detects salty taste. This ENaC, as mentioned earlier section, is in the renal collecting ducts and is also the final regulator of natriuresis. In vertebrates, ENaC is found in the colon, lungs, and sweat glands, in addition to the kidney and tongue, and regulates sodium reabsorption. In addition, ENaC and MR have been found to coexist in the brain choroid plexus, where SFO and OVLT, those which sense CSF Na^+, are located. In other words, humans sense Na^+ in the ENaC of the tongue and regulate the excretion of Na^+ out of the body through urine (kidneys), sweat (sweat glands), and stool (colon). This Na^+ balance for Na^+ homeostasis is controlled by the brain, which senses Na^+ in the CSF and controls the Na^+ input via the tongue and Na^+ output via kidneys [67, 68].

In addition, it is known that excessive salt intake and emotional stress can cause a significant increase in blood pressure. Emotional stress increases blood pressure by activating SNS and RAAS, and the blood pressure elevation caused by this stress is greater in salt-sensitive patients than in salt-resistant patients [69]. As a reason why salt preference, in concert with emotional stress, exacerbates salt-sensitive hypertension, it has been shown that Ang-II activation of AT1R occurs in various brain regions (amygdala, anterior hypothalamic area, PVN) related to stress response [70]. In salt-sensitive hypertension, abnormalities of the RAAS and SNS are observed also in the brain, and this is mediated by increased oxidative stress and inflammation in the brain, which in turn leads to dysfunction of salt-tasting taste cells in the tongue and increased Na^+ concentration in the CSF [71]. Furthermore, as mentioned above, it has been found that excessive salt causes inflammation in the brain by decreasing cerebral blood flow due to dysfunction of NOS in systemic blood vessels caused by salt-induced dysbiosis.

Thus, in salt-sensitive hypertension, excessive salt causes brain RAAS and SNS abnormal activity through increased intracerebral inflammation and oxidative stress, when the mechanism of the regulation of Na^+ homeostasis in the bran is disrupted, leading to systemic circulatory failure, neurological dysfunction, and chronic inflammation.

7. Epigenetics in salt-sensitive hypertension

In addition to genetic predisposition, environmental factors experienced during fetal life and childhood have been found to influence brain and nervous system functions through epigenetic changes. For example, the DOHaD theory (developmental origins of health and disease) has been proposed that inadequate nutrition during fetal life may lead to the risk of chronic diseases such as hypertension in adulthood [72]. It has also been pointed out that excess salt also may induce epigenetic salt-sensitive hypertension [73]. For example, it has been reported that salt-sensitive hypertension is caused by abnormalities of the glucocorticoid system in uterine environment. In addition, transcriptional changes in genetic activity due to DNA methylation and histone modifications in ENaC and NCC, which regulate sodium reabsorption in the kidney, have also been reported [74]. These finding suggests that excessive salt intake may lead to the development of salt-sensitive hypertension through acquired genetic changes, and the importance of salt reduction education from an early age [75].

8. Preventive diet for hypertension

The INTERSALT study, which is an international study that compared blood pressure in populations in the world with different amount of salt intakes, has revealed the relationship between salt intake and blood pressure. There was a strong positive correlation between daily urinary sodium excretion and the degree of increase in blood pressure with age [76]. This suggests the importance of reducing Na^+ intake. The antagonistic effect of K^+ on Na^+ has been recognized [77], and it has an antihypertensive effect on the kidneys by promoting the excretion of Na^+. According to Eaton et al.'s estimate, K^+ intake in the Paleolithic period was 6070 mg/day, but in modern society, it has dropped to 2500 mg/day, about 1/3 [78]. In fact, in a meta-analysis on the antihypertensive effect of K^+ loading, it has been pointed out

that the higher the NaCl intake, the more marked the antihypertensive effect of K^+ in salt sensitive hypertension [79].

In the United States, the DASH diet (Dietary Approaches to Stop Hypertension) has been proposed as a hypertensive diet. This diet was recommended by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in the United States to improve hypertension. The DASH diet recommends fruits, vegetables, whole grains, and low-fat dairy products, and has been established as evidence in large-scale studies [80, 81]. The DASH-diet is based on Na^+ restriction and K^+ supplementation, suppression of intestinal inflammation by limiting fat, and intake of prebiotics such as dietary fiber. Among these, the production of short-chain fatty acids such as butyric acid, lactic acid, and acetic acid from dietary fiber by microbiota is said to contribute significantly to anti-inflammatory effects and improvement of energy metabolism. From this point of view, it is no exaggeration to say that the DASH diet is an all-round health food formula because of its low Na^+ content, proper intake of K^+ that excretes sodium, low fat content that suppresses inflammation in the intestines, and high fiber content. However, a risk of salt restriction in daily diet is attended in the special but often patients in Japan. They are elderly patient with hypertension, and patients receiving hemodialysis. As both have a risk of malnutrition by carrying out the salt restriction, the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019) allowed them to take salt over 6 gram per day [82]. We also emphasize that decreasing salt intake from 20 gram to 15 gram per day has enough meaning as salt restriction [83].

9. Finally, low-salt diet may protect our brain

As vertebrates evolved from the sea to the land, they developed the RAAS system and came to have a Na^+ retention system that could withstand desiccation and dehydration.

Furthermore, humans began to develop a taste for salt, finding it delicious in their meals. With the increase in industrial production of cheap NaCl, excessive

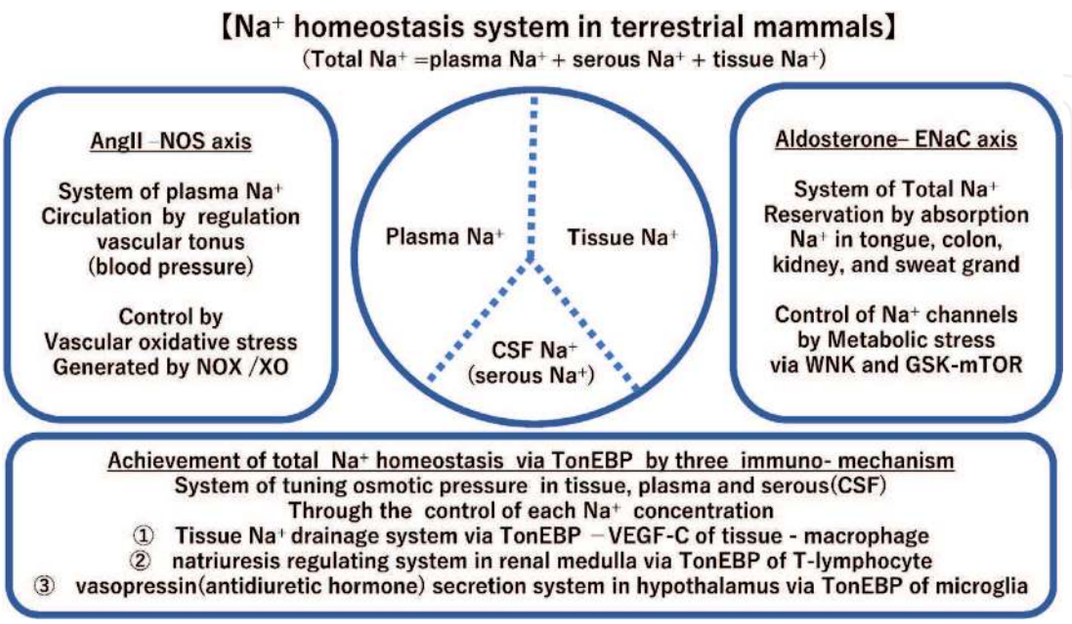

Figure 3.
Our hypothesis: Excess salt in gut induced hypertension and brain damage in a deterioration spiral manner among three systematic dysregulation of Na^+ homeostasis.

salt intake first became possible, causing hypertension and hypertensive diseases such as stroke. Furthermore, it has very recently been pointed out that excess salt can trigger dysbiosis of the intestinal microflora, which can lead to autoimmune brain diseases. In this study, we clarified that three mechanisms that maintain Na^+ homeostasis (the circulating plasma Na^+ system (AngII-eNOS axis), the total Na^+ retention system in body (Aldosterone-ENaC axis), and the tissue Na^+ sensing system (TonEBP (in macrophage)-VEGF-C axis) are impaired in salt-sensitive hypertension (**Figure 3**).

In the brain, which is the command center of Na^+ homeostasis in vivo, excessive salt causes cerebral blood flow (CBF) decrease because of NOS dysfunction. Secondly, ENaC dysfunction in taste cells causes taste disorder, which leads to a preference for strong salt tastes. In addition, the increase in CSF Na^+ leads to the activation of tissue macrophages in the brain (microglia) via TonEBP activation, which causes inflammation in the brain. Thus, we pointed out that the same molecular biological mechanism that leads to the development of salt-sensitive hypertension may also lead to brain toxicity in the form of exacerbation of salt preference (toxicity), emotional instability (CBF decrease), and pathological brain remodeling (structural damage in the brain such as atrophy). Excess salt may also lead to further development of acquired salt-sensitive organ damage through epigenetics. Therefore, we would like to emphasize that it is extremely important to be aware of salt reduction in our daily diet.

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