Role of Excess Dietary Salt in the Development of Gastrointestinal Diseases and Microbial Imbalance

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Abstract

Background: Gastrointestinal (GI) diseases are known to be largely influenced by one's lifestyle and dietary uptake. A high-salt diet (HSD) is well recognized as a risk factor for cardiovascular complications, hypertension, and metabolic syndromes. However, the relationship between an HSD and the GI system, which is the compartment that comes in direct contact with exogenous stimulants, has not been fully explored. Aims: We seek to better understand the complexity of the pathogenic effects of an HSD in the context of GI disorders. Methods: By searching the PubMed and Web of science, the review of literature was performed using keywords: high-salt and GI, high-salt and immunity, salt and microbiota, salt and hormone. Results: In this review, we concluded that high-salt intake potentially perturbs the local immune homeostasis, alters the gut microbiota composition and function, and affects the endocrine hormone profiling in the GI system. Conclusion: HSD might get involved in GI diseases through the reshaping of gastroenterological milieu, which could help to better understand the complexity of the pathogenic effects of an HSD in the context of GI disorders.

Introduction

The incidence of GI disease is closely associated with lifestyle and diet. People eating more fiber and vegetables get fewer GI diseases, while diets high in sugar, salt and fat have been clearly considered to be the GI diseases generator [1, 2]. Sodium chloride from dietary salt provides essential electrolytes to the human body and plays a vital role in maintaining the stability of the intracellular and extracellular environments. Despite its indispensable involvement in many physiological activities, excessive salt uptake is regarded as detrimental for many well-recognized diseases such as cardiovascular complications, hypertension, and metabolic syndromes. Epidemiological studies show that daily sodium intakes vary considerably across population groups from a "no-salt" culture in Yanomamo Indians to 462 mmol/day among Akita prefecture, northeast Japan. Correspondingly, there exists a positive correlation between the morbidity of the aforementioned diseases and the daily salt intakes [3]. Akita prefecture suffers higher death rate from stroke than the southern Japan with daily sodium of 239 mmol/day. People in Turkey consume sodium 308 mmol/day have higher risk for coronary heart disease [4]. Importantly, a high-salt diet (HSD) is proved to have adverse effects on the gastrointestinal (GI) functions [5-8], also with a regional variability. Salting and pickling, as traditional popular ways for preparing food in Japan and some parts of Asia, increase the risk of stomach cancer in these areas [9]. Western diet high in salt contributes to a high prevalence of inflammatory bowel disease (IBD) in the United States and Europe [10]. Clinically, a bland diet, which is considered beneficial for illness rehabilitation, is also frequently prescribed to patients with GI disease; however, the underlying rationale is not fully understood.

The GI system interacts directly with exogenous stimulants, and it can respond to high-salt stimulation in a highly sensitive manner before detectable damage is caused to human health. Thus, even if the sodium concentration in the blood is within a normal range, a disturbance may already exist and this could accumulatively accelerate chronic disease in other body systems in conjunction with different risk factors. Recently, HSD has been shown to disrupt immune homeostasis by its effects on various cell types, causing tissue inflammation at local sites and/or systematic perturbation; in addition, many non-immune components, such as hepatic cells and intestinal endocrine cells, are also negatively influenced by high salt intake. Furthermore, HSD is found to affect the composition and function of the gut microbiome. The gut commensal may exert a synergistic effect with high salt on the development of GI diseases by destroying the physical defense barrier or by modulating the gut-immune axis. The role of the GI hormones also has been renewed recently, that they may exert inflammation regulatory functions in HSD-responsive GI diseases [7, 8].

In this literature review, we consider that the occurrence of the GI disease, to a great extent, is associated with high salt intake. And HSD is found to be in close relationship with gut local immune homeostasis, gut microbiota composition, and endocrine hormone profiling, which are vital components of the gut milieu. Thus, we would discuss whether and how HSD affects the GI milieu through these 3 aspects, to reveal the mechanism of HSD as the GI disease accelerator, and to explore potential therapeutic target for salt-sensitive GI disorder.

HSD and GI Immune Homeostasis

HSD Influence the Immune System

Gut is an important digestive organ and the largest immune organ of the body. The gut-associated lymphoid tissue plays an important role in the immune surveillance as well as mucosal immunity even at the where no violation happens, and immunity constitutively responds to foreign or self-antigens to maintain the healthy status. If any violation of the body happens, the innate and adaptive immunity will be initiated. Innate immunity appears rapidly but lacks specificity, and the intestinal mucosa is the first immune defense barrier of gut. Recently, studies revealed the HSD affects the GI immune system detrimentally [11, 12]. First, the sodium was found accumulated in the colons of mice on an HSD, suggesting a direct effect of salt within the colon [12]. HSD provoked a histologically detectable inflammation while exacerbating chemically induced models of colitis in mice by a mechanism dependent on interleukin (IL)-17 production most likely by both type 3 Innate lymphoid cell (ILC3) and Th17 cells [11]. Second, by enhancing cytokine expression during first 3 days of infection, HSD was suggested to potentiate an innate immune response [12]. In order to examine whether and how high salt intake alters mucosal cytokine production, normal intestinal lamina propria mononuclear cells were activated and exposed under HSD. Finally, IL-17A, IL-23R, tumor necrosis factor-α (TNF-α), and retinoic acid-related orphan nuclear receptor-γt (Ror-γT) were found significantly increased in human lamina propria mononuclear cell [12]. Studies have shown that an HSD can induce human circulating monocyte proinflammatory activation and is associated with monocyte-platelet aggregation [13]. Moreover, the activation and function of dendritic cells, M1 macrophages are stimulated on an HSD, while M2 macrophages are blunted found in vitro and in vivo [14-16], accompanied by increased activation of pro-

IL-1β, nuclear factor-κB, and p38/mitogen-activated protein kinase (MAPK)-dependent nuclear factor of the activated T-cell 5 (NFAT5) signaling, and elevated NO production [14, 17, 18]. Interestingly, studies found that macrophages in turn might be pivotal regulators of salt homeostasis by a TonEBP-VEGF-C-dependent buffering mechanism, since the NaCl hypertonicity was proved to stimulate macrophages to migrate in the direction of excess salt concentration in vitro [19]. Besides, by secreting mediators and acting as antigen presenting cells, the innate immune cells also participate in the adaptive immunity. Adaptive immunity, though in many scenarios is protective, is also the amplification and progression of the disease, while HSD is found to take part in this process too. In 2013, studies made it clear that an HSD can enhance Th17-cell differentiation in 2 ways: it directly induces the serum glucocorticoid-regulated kinase 1 (SGK1), which stabilizes interleukin-23 receptor (IL-23R), and also activates P38 mitogen-activated protein kinase and NFAT5, which induce the expression of SGK1; consequently, the production of cytokines such as IL-17A and IL-17F, GM-CSF, and TNF is enhanced [20-22]. Although, whether high salt affects the B cell is less understood, a study indicated that HSD may influence the B-cell differentiation in an indirect way [23], as differentiation of follicular helper T (Tfh) cells displayed an increase following HSD in EAE and a lupus mouse model [23]. The Tfh cells, on the other hand, are involved in the selection of high-affinity B cells during the germinal center response [23]. Additionally, an HSD impairs human Treg function and exacerbates human experimental models of autoimmunity [24]. Safa et al. [25] reported that salt accelerated cardiac allograft rejection in transplantation through serum- and SGK1-dependent inhibition of CD4+Foxp3+ regulatory T cells (Tregs) in a transplanted mice model.

HSD and the GI Disorders

Increasing studies concentrate on characterizing the effects of HSD on GI disorders from an immune-based perspective [5, 6]. Recent studies showed that HSD exacerbated colitis in mice by affecting the gut microbiota and intestinal immune homeostasis [5, 11, 26]. Actually, an HSD has long been demonstrated to disrupt intestinal immunity and increase the risk of IBD [12], exacerbating experimental colitis in both the ceca and colon while increasing immune infiltration, epithelial hyperplasia, and extensive goblet cell loss [12]. The HSD stimulates the Th17 response in both the small and large intestines, increasing the production of IL-17A but suppressing the function of Treg cells, inhibiting the secretion of IL-10 [5] and altering epithelial signaling cascades to promote inflammation. Given that ILC3 is abundant in the gut mucosa, the latest research revealed that the increased IL-17 dependent inflammatory effects of HSD may partially stem from ILC3 [11]. Alternatively, HSD affects the colonic and small intestine mucosal immunity in mouse models by enhancing the expression of pro-inflammatory genes such as Rac1, Map2k1, Map2k6, Atf2, while suppressing cytokine and chemokine genes like Ccl3, Ccl4, Cxcl2, Cxcr4, Ccr7 [26]. In addition, studies also identified HSD as a risk factor for gastritis in models of mouse and human [7, 8], also human functional dyspepsia [27], and gastric cancer of human [28-31]. High salt intake contributes to gastric toxicity because it decreases the viability of gastric epithelial cells, strips the lining of the stomach, alters the viscosity of the protective mucous barrier, thus permitting the entry of carcinogens into the stomach [29, 32, 33]. HSD can also lead to local inflammation and upregulate proinflammatory enzymes and cytokines secreted by gastric epithelial cells, such as inducible nitric oxide synthase, cyclooxygenase-2 [8, 33], IL-1β [30, 34], TNF-α [34], and IL-8 [35]. Studies suggested that high salt intake increases inflammation and fibrosis in liver steatosis mainly by increasing the expression of F4/80 and TNF-α, and the ballooning of hepatocytes [36]. Due to ROS overproduction, excessive salt

intake worsens hepatic lipid peroxidation and accelerates high-fat induced nonalcoholic fatty liver disease and nonalcoholic steatohepatitis [36-38]. Additionally, a chronic exposure of HSD is indicated to cause pancreatic fibrosis in Wistar rats [39]. Studies also revealed that an HSD might get involved in gastroesophageal reflux [40], pancreatic cancer, and esophageal cancer [41-43]; however, more mechanism-revealing studies are needed (Table 1).

Table 1.

The correlation between HSD and GI disorders

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HSD and Gut Microbiota

HSD Alters the Gut Microbiota Profiling

The gut microbiota performs a pivotal role in the host metabolism and is tightly associated with immune cell function and epithelial homeostasis [6, 44]. The GI microflora structure changes according to host metabolism, environment. and diet. Thus, the diet may lead to GI disorders through reshaping of the gut microbiome. High salt intake has been implicated in GI bacterial profile, particularly in the depletion of some bacterial species. A study using Jensen –Shannon divergence indicated that although bacterial load was similar between normal salt diet – and HSD-fed mice, the OTUs of Lactobacillus, Oscillibacter, Pseudoflavonifractor, Clostridium XIVa, Johnsonella, and Rothia were significantly decreased after an HSD on day 14, whereas Parasutterella spp. increased after an HSD [45]. And the study by sequencing the V4 region of 16S ribosomal RNA gene found that HSD increased the Firmicutes/Bacteroidetes ratio, that is, increased the abundances of genera Lachnospiraceae and Ruminococcus ($p < 0.05$) but decreased the abundance of Lactobacillus ($p < 0.05$) [26]. As the onset of Lactobacillus depletion is quick and remarkable, the Lactobacillus murinus is the most strongly associated with HSD [46]. This study also found that reducing intestinal survival of Lactobacillus spp. after high salt challenge would increase pathogenic Th17 cells [46], increase blood pressure [46], and increase colitis in mice [26].

HSD Alters the Gut Microbiota Function

Besides manipulating the gut microbial composition, HSD also influences the microbiota function. A recent study showed that HSD had a certain impact on proteins and polysaccharides degrading enzymes secreted by gut microbiota [47]. Five proteins, cytidylate kinase, trigger factor, 6-phosphogluconate dehydrogenase, transporter, and undecaprenyl-diphosphatase, which were secreted by different gut bacteria, including Atopobium parvulum, Anaerococcus prevotii, Lactobacillus brevis, Anaerostipes hadrus, and Streptococcus agalactiae, had a higher abundance in the HSD-fed mice than those in the LSD group [47]. These proteins are important in the pyrimidine metabolism, ATP binding, materials transferring, cell cycle, and cell division. On the other hand, the HSD was found to exert a synergistic effect with Helicobacter pylori on the development of gastritis [7, 8] and H. pylori-associated carcinogenesis [15, 20, 23, 48]. Studies demonstrated that HSD can alter H. pylori gene expression while

modulating H. pylori-induced virulence factors such as cytotoxin-associated gene A (CagA) [45] and vacuolating cytotoxin (VacA) [21, 23, 49]. A combined effect of NaCl and VacA in vitro and in vivo has been confirmed. Excessive NaCl enhanced the VacA-induced expression of IL-1β and TNF-α mRNAs in gerbils, while increasing IL-1β expression and decreasing TNF-α expression in VacA-treated human gastric epithelial (AGS) cells [22]. By inducing damage to the gastric mucosa with H. pylori, an HSD might also influence GI symptoms in functional dyspepsia [14].

HSD and GI Hormones

Local Functions of GI Hormones

GI plays an important role in endocrine production, and the gut microbiota in the GI tract also resembles an endocrine organ [50]. HSD, as the substance that comes in direct contact with GI, has been studied for effects on the secretion and function of GI hormones. Research have proven that an 8-week HSD caused both exocrine and endocrine pancreatic insufficiency in rats, which significantly decreased plasma levels of α-amylase and lipase, insulin while significantly increasing TGF-β1 and IL6, resulting in pancreatic fibrosis [26]. An insulin decrease has also been observed with HSD-fed Wistar rats [26, 51]. HSD-induced insulin resistance (IR) was found to be driven by impaired microvascular responsiveness to insulin [52] and linked with decreased insulin sensitivity, phosphatidylinositol (PI) 3-kinase or Akt activation [53], and AT hypoxia [54]. Further study indicated that HSD and IR, alone or combined, might have a strong relationship with obesity-related metabolic disorders [55]. Studies showed that high salt intake increased serum gastrin levels relative to an LSD in the Chinese subjects [56], and gastrin is a critical hormonal regulator that is known to induce gastric secretion, stimulate pancreatic secretion, and increase blood circulation and water secretion in the stomach and intestine. As a reaction to salt overload, mammals display decreased serum aldosterone [26], and in the colon display downregulated colonic mineralocorticoid receptors, epithelial sodium channels, and 11b-hydroxysteroid dehydrogenase type 2 [57], promoting the excretion of sodium and resulting in difficulty reaching a sodium balance. Of note, the gut microbiota produces numerous chemicals and hormones, exerting a vital role in regulating complex endocrine networks of the host. A study has observed that administration of L. paracasei F19 and Lactobacillus acidophilus NCFB1748 to GF mice resulted in the upregulation of insulin-sensitizing hormones, adipsin and adiponectin [50]. In another study, HSD was demonstrated to reduce the intestinal survival of Lactobacillus spp. [45]; it could be speculated that HSD may modulate the gut hormones by manipulating the gut microbial composition.

Systemic Functions of GI Hormones

Except the local functions, the gut endocrine always has the cross-talk with other systems. HSD-induced hormone alternations exert an effect on the entire body metabolic homeostasis. HSD, via the gastro-renal axis and cholecystokinin B receptor, elevates the renal sodium excretion, decreases Na+-K+-ATPase activity, and increases the serum gastrin levels, and this might be the underlying mechanism of salt-induced hypertension [56]. Serum endocrine glucagon-like peptide-1 level was found decreased with the change from the LSD to HSD in normotensive salt-sensitive individuals [58]. The glucagon-like peptide-1 is an incretin exhibiting notable benefits on lipid metabolism, atherosclerosis formation,

plasma glucose levels, and maintenance of gastric mucosa integrity, also conferring benefits for blood pressure by natriuresis and diuresis [59]. High salt intake significantly increases fasting ghrelin produced in the stomach in healthy human subjects, stimulating the release of growth hormone, appetite, and fat accumulation; this might be a brain-gut axis related underlying mechanism of obesity [60]. Another study reported that substance P significantly decreased ($p < 0.001$) with high sodium intake (350 mmol/day) in relation to dietary sodium restriction (35 mmol/day) [61]. Substance P is a neuropeptide released from the terminals of specific sensory nerves and is associated with inflammatory processes and pain, and also a trigger for nausea and emesis.

Discussion

Salt is ingested every day, at every meal, and saltiness is a preferred flavor. But HSD has been proved to be a risk factor for various disorders including GI diseases [11, 16]. And GI disorders are known to be closely related to disturbance of GI milieu including gut immunity, gut microbiota and GI hormones. Thus, it is important to clarify the relationships among HSD, gut immunity, gut microbiota, and GI hormones. The present literature review concludes that HSD not only plays an important role in some autoimmune diseases, but also, by initiating innate and adaptive immunity, breaks the gut immune homeostasis, participating in the progress of common GI diseases. IBD has long been recognized as a multi-factor-induced inflammatory disease. HSD is demonstrated to add to the risk by altering the secretion of inflammatory cytokines mediated by innate immune cells, and by stimulating the Th17 and ILC3 response in intestines, but by suppressing the function of Treg cells [5, 6, 11]. This could be an underlying mechanism for a bland diet to be considered beneficial for illness rehabilitation and is frequently prescribed to patients with GI disease. HSD also affects the gut microbiota composition and function. HSD-induced depletion of L. murinus led to aggravation of experimental autoimmune encephalomyelitis and salt-sensitive hypertension by modulating TH17 cells. This alternation was offset by the treatment of L. murinus in mice [47]. On the other hand, HSD could enhance the H. pylori gene expression and modulate the H. pylori-induced virulence factors CagA and VacA, aggravating a local inflammation and facilitating the H. pylori-associated carcinogenesis [45, 48, 49]. Accordingly, HSD may get involved in the gut-immune axis through altering the gut microbiota, and the gut organism could be a potential therapeutic target for HSD-related disorders. GI hormones have a powerful and a wide-range function in the human body. HSD influences the endocrine of the local organ such as decreasing plasma levels of α-amylase and lipase, insulin which are secreted from pancreas [27], and also play a systemic role via gastro-renal axis or brain-gut axis [56, 59]. The regulation of GI hormones is crucial for gut homeostasis in the treatment of HSD-related GI disorders. However, the 3 major aspects of the GI milieu also interact with one another to maintain gut homeostasis. Increasing research testified the gut microbiota-immune system crosstalk. Numerous studies have demonstrated that GI bacteria participate in B cell differentiation, maturation, and activation. And B cell maturation in Swedish infants was shaped mainly by Escherichia coli and Bifidobacteria colonization [62]. L. murinus in host intestinal could modulate the Th17 cells and is vital in the formation of some autoimmune diseases [46]. Moreover, gut commensals protect the intestinal against pathogenic microbes by maintaining gut integrity and regulating intestinal barrier permeability [63]. Reciprocally, the host immune state plays a key role in the composition of gut microbiota, such as the intestinal IgA, which was found to influence the gut microbiota composition [41]. Gut hormones modulate the immune system and exert important roles in process of autoimmune disorders. Not only bacteria in the gut produce hormone-like chemicals and

regulate hormonal secretion, but they can also potentially respond to the hormones secreted by the host [50]. Most importantly, HSD could alter the gut immune homeostasis by exerting synergistic effect with gut microbiota or affecting the release of GI hormones. The gut commensals are critical in the integrity of intestinal mucosa, and co-effect with an HSD could initiate the innate immunity in GI disorders [14]. As the gut microbiota resembles an endocrine organ and secrets hormones, HSD influence them both resulting immune alternations [50]. Generally, the gut immunity, gut microbiota, and GI hormones are vital components of gut milieu, and they have a cross-talk with one another, which is important in the formation and development of GI diseases. And HSD has an important effect on their networks, breaking the gut homeostasis (Fig. 1). Unfortunately, at present, there is a lack of specific research discussing the cross-talk in one GI disorder. And the disorders of pancreas and liver have been barely studied from an immunological perspective. And in the future, more attention should be paid to the ILC3, which is a newly found cell type taking part in the GI tract mucosal inflammation.

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