REVIEW ARTICLE

The Chemical Messengers of the Gut: Significant Players in Human Physiology and Metabolism

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Abstract

The gastrointestinal tract (GIT) releases a diverse array of chemical messengers that exert profound effects beyond local digestion and nutrient absorption. This review highlights two primary categories of gut-derived agents: (1) classical hormones secreted by enteroendocrine cells (e.g., gastrin, GLP-1, secretin) and (2) microbial metabolites (e.g., short-chain fatty acids, serotonin, nitric oxide) produced by gut microbiota. These agents circulate in the blood to all systems, influencing organs such as the liver, brain, adipose tissue, immune system, cardiovascular system, muscles, and bones. Emerging evidence underscores their roles in regulating metabolism, immunity, neurobehavioral functions, and skeletal health, with dietary composition critically shaping their production and effects. While this field is rapidly evolving, this review reflects current knowledge to emphasize the integrative role of gut messengers in human physiology, offering insights into therapeutic opportunities for metabolic, inflammatory, and neurological disorders.

Introduction

The daily meals we consume affect our physiology, metabolism and well-being in ways that exceed their nutritional value. Food intake provides the various nutrients — proteins, carbohydrates, lipids, vitamins and minerals — needed for tissue building and energy requirements. The ability of the digestive system to digest and absorb these dietary components determines the nutritional benefits of the diet to us. The presence and passage of food through the gastrointestinal tract (GIT) stimulates the release of hormones and locally acting chemical substances that, in conjunction with the nervous system, are critical in regulating food digestion and absorption by controlling the timely glandular secretions, gut wall motility and blood flow (1,2).

However, it is becoming increasingly apparent that these hormones and chemical substances have effects far beyond the mere regulation of digestion and absorption of food. These chemical messengers are carried by the blood to the various body organs where they influence their physiology and metabolism. This means that the effects of food are not only due to the provision of nutrients but also to the systemic actions of messengers released in response to the presence and passage of food through the GIT.

Several short chain fatty acids are produced by the gut microbiota by metabolizing the complex carbohydrate making up dietary fiber. The beneficial actions of these agents that will be mentioned in this review add another merit to the inclusion of dietary fiber in our diets.

The Classical Gut Hormones

The GIT epithelium contains various types of enteroendocrine cells. These cells are found all the way from the stomach to the rectum.

However, they are much more numerous in the proximal GIT than distally (3). There are tens of known GIT hormones, and the number is increasing. The classical, best-studied GIT hormones are gastrin, CCK, secretin, GIP, GLP-1, ghrelin, motilin, VIP, and somatostatin (1,2).

Microbial Chemical Agents

The gut microbiota — predominantly bacteria — are most numerous in the colon and distal ileum (4). They metabolize the dietary remnants that reach them. The microbiota produce the short chain fatty acids (SCFAs) butyrate, propionate and acetate by metabolizing complex carbohydrates (5). Acting on amino acids, these bacteria produce histamine, dopamine, gamma-aminobutyric acid and other chemicals (6). These chemical agents act locally on the intestinal mucosa and muscle but are also absorbed into the blood to act systemically. Hence, we now talk about "microbial gut hormones" (7). The bacteria also produce the gasotransmitters nitric oxide (NO), hydrogen sulfide (H2S) and carbon monoxide (CO), which are absorbed into the blood and affect body organs (8).

The gut chemical messengers to the body organs can therefore be viewed as two types: the classical hormones of the enteroendocrine cells and the microbial products.

Actions of the Gut Messengers on Body Organs/Systems

The Liver

The liver is the hub of metabolism of carbohydrates, lipids and proteins. It has major synthetic, deactivation, detoxification, storage and excretory functions. Agents acting on the liver will, therefore, have significant systemic effects.

The portal blood contains the highest concentration of the GIT hormones and microbial products because it drains the gut. This means that the liver is the organ most exposed to the gut chemical messengers.

The GIT hormones modulate carbohydrate, lipid and protein metabolism mainly by acting on the β-cells of the endocrine pancreas to stimulate insulin secretion. Insulin then acts on the liver, adipose tissue, muscle and other tissues, leading to storage of glycogen and fats, protein synthesis and inhibition of proteolysis. The GIT hormones that have a strong stimulatory effect on insulin secretion are the incretins GLP-1 and GIP. In addition, gastrin, CCK and secretin also have a weaker stimulatory effect on insulin secretion (9). Drugs that inhibit the enzymatic breakdown of the incretins (incretin effect amplifiers) and drugs that mimic the incretins (incretin mimetics) are now used in the treatment of type 2 diabetes mellitus (10).

Maintenance of the euglycemic state during fasting has traditionally been attributed to the insulin antagonists glucagon, cortisol, adrenaline and growth hormone. It is becoming apparent that gut-derived serotonin, together with glucagon, markedly increases hepatic glucose output by increasing hepatic gluconeogenesis and glycogenolysis (11).

SCFAs have been shown to be protective to the liver. They improve the intestinal mucosal barrier, regulate liver mitochondrial function, inhibit fat accumulation and reverse insulin resistance. SCFAs are, therefore, being used in the management of liver disorders such as non-alcoholic liver disease (12).

The Adipose Tissue

The GIT hormone ghrelin increases deposition of fat in adipose tissues. This orexigenic hormone is not only the main hunger-stimulating hormone but also acts on adipocytes to increase energy storage by increasing fat deposition in white adipose tissue (13). On the contrary, GLP-1 has been found to inhibit appetite and to decrease fat tissue (14). GLP-1 analogs are, therefore, not only being used for treating diabetes as incretin mimetics, but they are currently used for weight reduction (15).

Serotonin is another gut chemical messenger with significant metabolic effects on adipose tissue. Serotonin stimulates lipolysis in white adipocytes to release free fatty acids and glycerol, which is a key substrate for hepatic gluconeogenesis (16).

The Immune System

The GIT is the site where most interactions between the immune cells and the environment occur. Most of our lymphocytes reside in the gut. The gut also contains most of the commensal microorganisms (17).

The intestinal microbial SCFAs have important local metabolic and regulatory actions. They act on the intestinal epithelial cells and the mucosa-associated lymph tissues. Their effects on these tissues influence the differentiation of the intestinal epithelial cells, phagocytes, B cells and plasma cells, in addition to the regulatory and effector T lymphocytes (18,19). These SCFAs have also been implicated in modulating the immune response at extra-intestinal sites, such as the liver, the lungs, the reproductive tract and the brain (18,20).

Changes in the composition of the intestinal microbiota are expected to change the amounts and ratios of the SCFAs and other metabolites produced by these organisms (21). These changes in gut microbiota (dysbiosis) are now linked to autoimmune disease, insulin resistance, type 2 diabetes mellitus and obesity (22,23).

The Brain

The brain is a main target for the gut chemical messengers. These messengers are known to modulate appetite, mood, emotions, memory and sleep.

Cholecystokinin, glucagon-like peptide-1, pancreatic polypeptide, oxyntomodulin and peptide YY act through distinct mechanisms to suppress appetite. On the other hand, ghrelin acts on the brain to induce hunger and stimulate food intake (24).

Although the cross-talk between the gut and the brain is known to be through the neural networks, it is becoming increasingly apparent that the gut chemical messengers — hormones and microbial products — are important mediators of the gut's influence on brain function (25). It has been documented that patients with a range of psychiatric disorders shared similar patterns of dysbiosis of the gut microbiome. This dysbiosis included depletion of some anti-inflammatory bacteria and increased numbers of pro-inflammatory bacteria (26).

Ghrelin has been shown to have a powerful influence on the hippocampus, an area of the brain critical for learning and memory. As ghrelin is the “hunger hormone,” it has been advocated that hunger is good for learning and memory (27).

Some of the metabolites produced by the gut microbiota are known to be associated with induction of wakefulness. These metabolites include the neurotransmitters serotonin, γ-aminobutyric acid (GABA), and dopamine (28).

The Cardiovascular System

SCFAs, particularly butyrate and propionate, reduce blood pressure, improve ischemic/reperfusion injury and decrease the risk of coronary artery disease and atherosclerosis. These positive effects of SCFAs are mediated by their anti-inflammatory actions and by modulating the workings of G-coupled receptors, which are used by many neurohumoral transmitters acting on the cardiovascular system (29).

It has also been reported that gut chemical messengers could be involved in the pathogenesis of essential hypertension, either through decreased production of vasodilator agents or increased activity of vasopressor agents. Changes in the types and numbers of enteroendocrine cells have been noticed in patients with hypertension (30).

Muscles

Skeletal muscle wasting (sarcopenia) is a feature of several chronic gut disorders, such as inflammatory bowel disease. Although chronic inflammation and malnutrition are important factors in the development of sarcopenia, it now appears that loss of the actions of some GIT hormones might be involved. It has been shown that the GIT hormones GLP-1, GLP-2 and ghrelin have anti-sarcopenia actions. They ameliorate muscle wasting by suppressing myostatin and muscle atrophic factors (31).

Bones

It has been observed that bone resorption increases during the night compared to daytime. Investigations of this circadian phenomenon revealed that three GIT hormones inhibit bone resorption during the day because they are secreted in response to food in the gut. The three hormones are GIP, GLP-1 and GLP-2. GIP not only inhibits bone resorption but also enhances bone formation. The implication is that these hormones guard against osteoporosis (32).

Recommendations and Future Research

Further research is needed to explore how diet and gut microbiota influence the production of chemical messengers and their impact on overall health. Understanding how different dietary components regulate these messengers could lead to personalized nutrition strategies aimed at preventing and managing metabolic diseases. More studies should focus on the role of gut-derived neurotransmitters in mental health disorders and cognitive function.

Investigating the therapeutic potential of probiotics and prebiotics in modulating gut messengers could open new avenues for treating obesity, diabetes, and inflammatory conditions. Advancing technology in microbiome analysis will help identify new gut-derived molecules and their systemic effects, offering insights into novel drug targets. A deeper exploration of the gut-brain axis and its implications for neurodegenerative diseases could lead to groundbreaking treatments. Expanding clinical trials to assess the long-term effects of gut messengers on human health will be crucial for integrating this knowledge into medical practice.

Conclusions

The gut is not merely a site for digestion and nutrient absorption but also a crucial endocrine organ that significantly influences human physiology and metabolism. The classical gastrointestinal hormones and microbial-derived chemical messengers play key roles in regulating metabolic processes, immune responses, neurological functions, and cardiovascular health. The emerging understanding of gut-derived messengers highlights their systemic impact, reinforcing the concept of the gut as an integrated signaling hub.

Diet composition profoundly affects the secretion of these messengers, with different macronutrients stimulating the release of specific gut hormones, while gut microbiota contributes additional bioactive compounds. The interplay between diet, gut messengers, and overall health and well-being underscores the importance of balanced nutrition in maintaining physiological homeostasis and preventing metabolic disorders.

Future research should focus on further elucidating the intricate connections between gut-derived messengers and systemic diseases, with particular attention to their roles in metabolic syndrome, neurodegenerative diseases, and immune dysfunctions. Advancing our understanding in this area will pave the way for innovative therapeutic strategies, including dietary interventions, microbiome-targeted therapies, and pharmacological modulation of gut-derived signals. By recognizing the gut as a central regulatory system, we move closer to personalized medicine approaches that leverage the gut's influence to optimize health and prevent disease.

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