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Review article

The power of gut-brain interaction as a promising target for healthy longevity

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Abstract

Hippocrates, the sage of medicine, famously said, "All disease begins in the gut," The gut-brain axis plays an extremely important role in a high-quality strategy for anti-aging throughout the roughly 100-year life span of humans. When the gut-brain axis is functioning properly, it is possible to maintain a healthy body, mind, and cognitive function, while dysfunction in the gut-brain axis can lead to increased risks of a variety of diseases and subsequent deterioration. From this point of view, we call the unlimited power of the gut-brain interaction "gut-brain axis power" and have focused our attention on the molecular medicine of diet and exercise to enhance gut-brain axis power. The degree of gut-brain power varies greatly from person to person, and the power of gut-brain axis is greatly affected by one's lifestyle, including diet, exercise habits, sleep quality, and stress management. Based on this notion, gut brain power is highlighted as a possible factor X to explain individual and constitutional differences in the development and worsening of complications as well as differences in response to diet, exercise, and drug therapy, all of which have occasionally been overlooked in preventive and clinical medicine. The ingested dietary contents are sensed by enteroendocrine cells (EECs) as nutrients, bile acids, or fermentation metabolites of gut microbiota, and are involved in the regulation of secretion of gut-derived peptide hormones, *i.e.* CCK, GLP-1, PYY, and ghrelin. These gastrointestinal hormones then act on the central nervous system (brain) to exert a considerable influence on the control of appetite and food preference. In addition to sensing by EEC, the various bioactive substances in the gastrointestinal tracts send information to the brain via blood and lymph flow or directly via spinal afferents, and determine all modes of behaviour, including eating habits and physical activity, whether consciously or unconsciously. The ultimate key to the "behavioural modification" that is being discussed in various aspects of society can be said to be gut brain axis power.

***KEY WORDS*:** the gut-brain axis power, gut microbiota, gut-derived peptide hormone, brain function, food preference, behavioural modification

Introduction

The brain and gut are closely related through the autonomic nervous system and humoral factors, *i.e.* hormones, cytokines, and bioactive substances which is called the gut-brain interaction (gut-brain axis). When the gut-brain axis is functioning properly, it is possible to maintain a healthy body, mind, and cognitive functions, while dysfunction in the gut-brain axis would lead to increased risks of a variety of diseases and subsequent deterioration. From this point of view, we call the unlimited power of the gut-brain interaction "gut-brain axis power" and have focused our attention on the molecular medicine of diet and exercise to enhance this power. In addition to sensing by EEC, a variety of humoral bioactive substances in the gastrointestinal tract send a vast amount of information to the brain via blood and lymphatic flow or directly via spinal afferents, and determine all modes of behaviour, including eating habits and physical activity, whether consciously or unconsciously (***Fig. 1***, quoted and modified from Ref. 1) [1].

In the field of glycative stress research, imbalance of intestinal microflora (microbiota) has attracted attention of scientists as a factor that hampers the success of various treatments for type 2 diabetes mellitus (T2DM). The alteration of gut microbiota has been found to play an important role in the dramatic improvement of glucose metabolism by weight-

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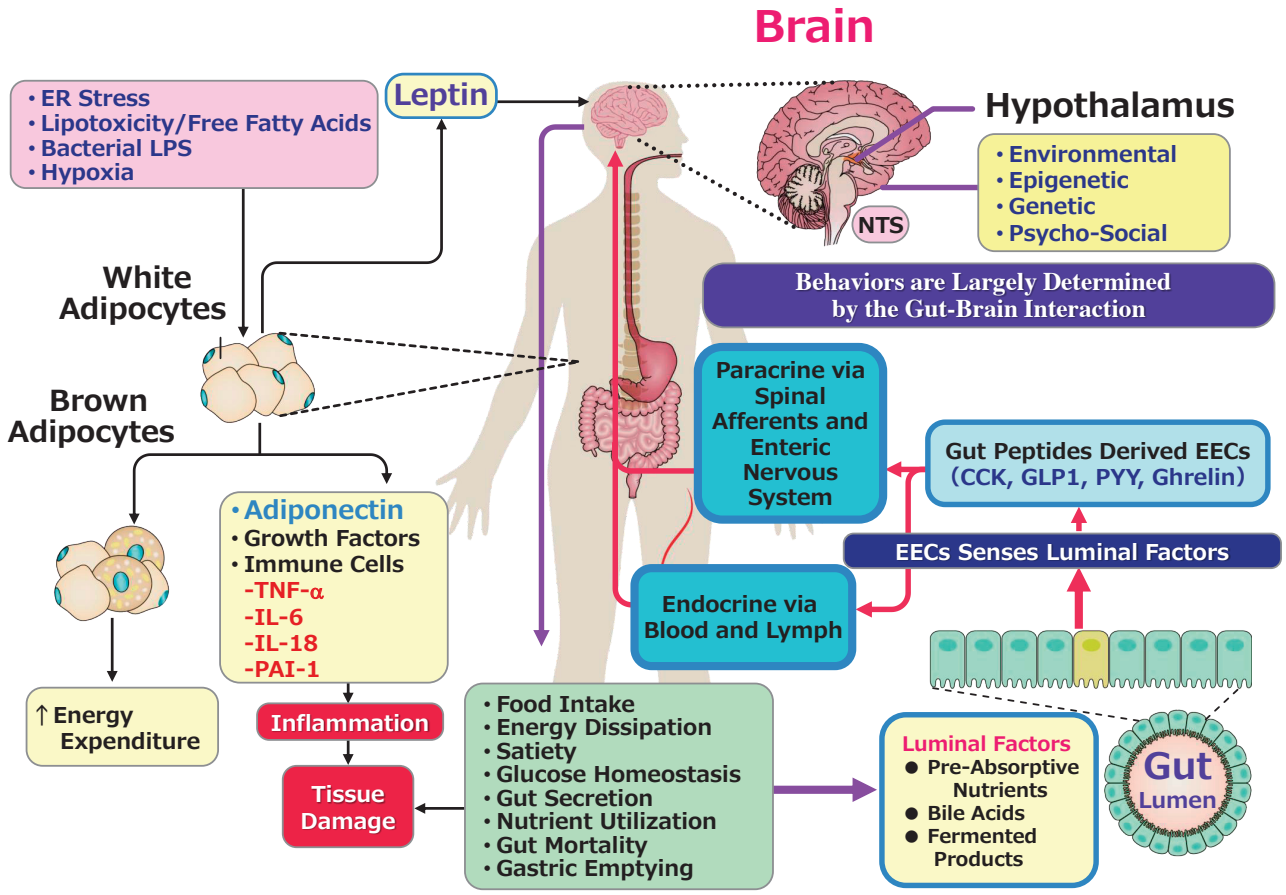

Fig. 1. **A panorama of gut-brain axis.**

EEC, entero-endocrine cell; ENS, enteric nervous system; NTS, nucleus tractus solitarius; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; LPS, lipopolysaccharide; PYY, peptide tyrosine (Y) tyrosine (Y); TNF, tumor necrosis factor; IL, interleukin; PAI, plasminogen activator inhibitor. Quoted and modified from Reference 1.

reduction and metabolic surgery (bariatric surgery, *i.e.* sleeve gastrectomy, bypass surgery) [1] and also in the mechanism of action of metformin, a drug for T2DM [2]. It has been pointed out that in many patients with T2DM and obesity, even if they consume a lot of dietary fiber, their energy consumption efficiency is reduced due to accelerated degradation of flavonoid, and that dysbiosis is associated with impaired gastrointestinal mucosal barriers and resultant production of a variety of pro-inflammatory substances, which subsequently enter the systemic circulation and cause chronic inflammation in organs involved in glucose metabolism including the brain [3].

We have recently reported a novel mechanism by which extra virgin olive oil (EVOO) effectively ameliorates gastrointestinal barrier dysfunction and impaired gastrointestinal immune function observed in obese and diabetic mice fed an animal fat [4]. The polyphenols and oleic acid abundantly contained in EVOO reduce microglial inflammation in the central nervous system (CNS), while enhancing the expression of amyloid-β transport protein and promoting amyloid-β clearance. In the circulation, they lower LDL-cholesterol levels and elevate HDL-cholesterol levels, thus reducing the risk of cardiovascular events. Furthermore, in the gut microbiota, they also increase the ratio of short-chain fatty acid (SCFA)-producing bacteria, thereby increasing the blood concentration of SCFAs, and induce the differentiation and maturation of regulatory T cells, and suppress inflammation of the gastrointestinal tract [5].

Our recent studies have shown that oral administration of γ-oryzanol, a functional component found only in high concentrations in brown rice (rice bran), to genetically obese mice dose-dependently increased the ratio of Bacteroidetes/Firmicutes (B/F) ratio, which is closely associated with restoration of intestinal bacterial diversity and improvement of glucose metabolism [6]. In addition, our study demonstrated that consumption of a brown rice-fermented beverage containing high levels of γ-oryzanol increased the B/F ratio in humans as well [7], and also significantly increased intestinal bacteria classified as Lactobacillus and Clostridium, which are involved in the production of SCFAs and reduction of inflammation, compared to a control brown rice-fermented beverage that did not contain γ-oryzanol (Akamine Y, Masuzaki H, *et al.*, manuscript in minor revision 2022).

Based on the fact that a variety of fermentation metabolites, *i.e.* SCFAs, considerably impact brain function, it is highly expected that food choice such as EVOO and γ-oryzanol contributes to improve the gut-brain axis power.

Mechanisms of appetite loss with aging from the viewpoint of gut-brain axis

An appetite loss with aging decreases physical strength, and immunity, thereby causing sarcopenia and frailty, and eventually worsens quality of life (QOL) over a long period of time. This is in a sharp contrast to the current situation where obesity and metabolic syndrome associated with overnutrition are being highlighted in middle-aged and mature generations. The term "frail" refers to a decline in spare capacity in daily life, and encompasses not only frailty in the narrow sense of musculoskeletal weakness, but also social frailty and mental frailty including cognitive impairment and depression. In the elderly, frailty, sarcopenia, and T2DM are recognized as a triad that exacerbates each other, and overseas data have shown that the progression of sarcopenia is definitely faster in elderly people with T2DM than in those without T2DM [8].

The mechanism of appetite loss with aging involves two types of functional abnormalities: one in the brain itself, which is the center of appetite regulation, and the other in the gut-brain axis. Although the mechanism of appetite loss with aging of the CNS is still not fully elucidated, functional magnetic resonance imaging (fMRI) analyses suggest that the insula, one of the key regions in enhancing eating behaviour, is sometimes dysfunctional in the elderly [9]. Notably, it has been reported that the dysfunction of the insular cortex is deeply involved in the pathogenesis of a severe form of anorexia nervosa (AN), and it is hoped that fMRI approaches will reveal the entire picture of underlying mechanisms of appetite loss with aging in appetite-regulating brain regions including the insula.

On the other hand, a couple of mechanisms whereby dysfunctions in the gut-brain axis lead to age-related appetite loss have also been clarified (***Fig. 1***). It is known that secretion of cholecystokinin (CCK), a potent appetite-suppressing peptide produced in the duodenum and jejunum, increases with age, and is considered as one of the pathological causes of appetite loss in the elderly [10]. Also, secretion of ghrelin, which is produced by the stomach and exerts a strong orexigenic action, decreases with age, suggesting its role in the pathogenesis of decreased appetite in the elderly (***Fig. 2***) [11]. Impact of aging on the production and secretion of other gut-derived hormones of the appetite suppressive system, *i.e.* amylin, glucagon-like peptide 1 (GLP-1), and bombesin, have not yet been reported.

The frequency of malignancies also increases in the elderly. It is known that lactate, whose production is increased in many cancer cells, reaches the CNS and suppresses methylmalonyl CoA, which potently acts as an appetite stimulant in the hypothalamus [12].
Methylmalonyl CoA is synthesized into fatty acids such as palmitate by fatty acid synthase (FAS) in microsomes. In fact, inhibitors of FAS and carnitine O-palmitoyltransferase 1 (CPT-1) involved in this pathway are known to cause hyperphasia and resultant obesity in mice [13].

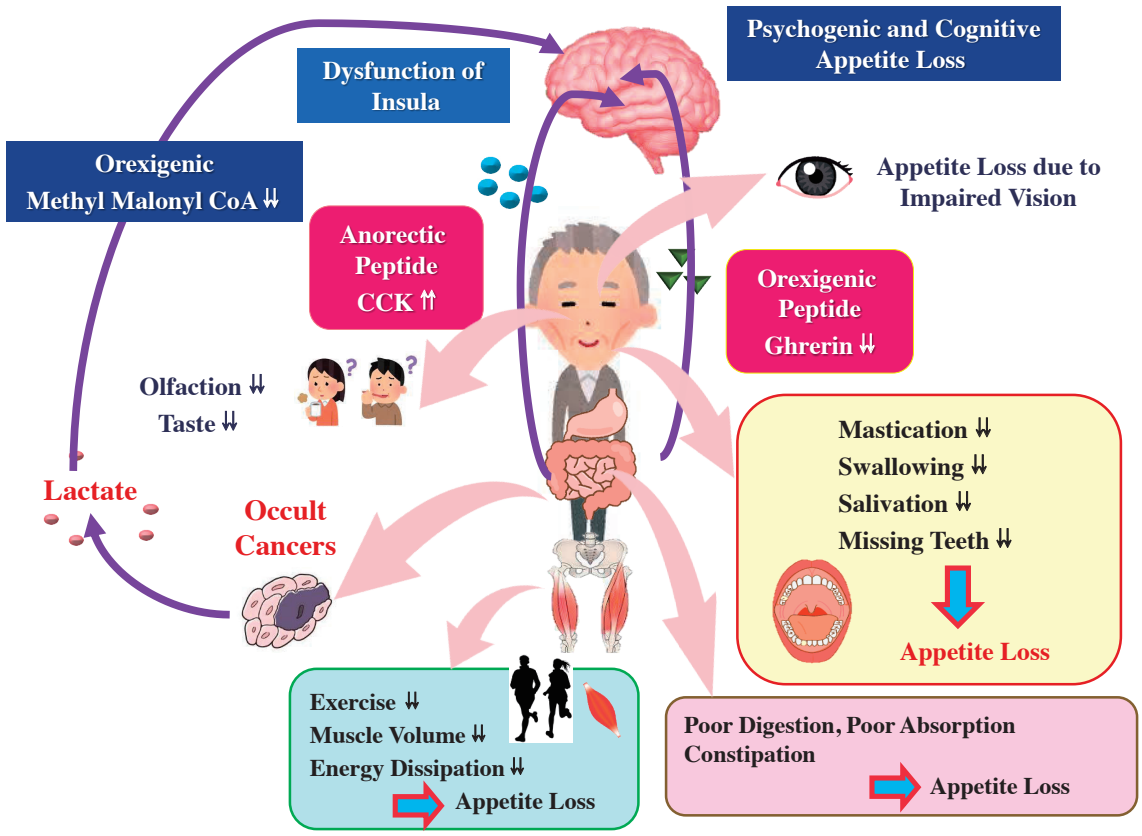

Fig. 2. **Plausible mechanisms on aging-related appetite loss in relation to the dysfunction of gut-brain axis.**
CCK, cholesystokinin.

The mechanism of age-related appetite loss also includes factors related to brain function in a broad sense, such as psychogenic appetite loss, loss of appetite due to cognitive decline, dysfunctions in the appetite center itself as well as in the gut-brain axis. In addition, as shown in ***Fig. 2***, there is a complex involvement of factors including impaired sense in vision, smell, and taste, as well as masticatory and swallowing functions, oral functions, digestive functions, and also impaired appetite due to decreased physical activity.

The key to gut-brain axis: Functions and pathological significance of fermentation metabolites

Some intestinal bacteria have enzymes that break down plant-derived fibrous polysaccharides, which were originally unable to be used as nutrition. Humans have a long history of forming a symbiosis that promotes energy reserves for starvation with the help of intestinal bacteria. In fact, germ-free mice in which intestinal bacteria were removed by administering high doses of antibiotics are remarkably thin and do not become obese. Moreover, they are characterized by a marked deterioration in kidney function. This notion shows that the inability to produce sufficient amounts of a series of SCFAs due to insufficient fermentation of intestinal bacteria causes enormous adverse effects on the physiological accumulation of body fat and the maintenance of renal function[1)]. Conversely, when the intestinal bacteria of healthy mice were transplanted into the digestive tract of germ-free mice, the thin germ-free mice began to gain weight. The ecosystem formed between the intestinal bacteria and the host worked favorably in times of starvation, but it also poses a risk of inducing obesity under conditions of insatiable diet and imbalanced gut microbiota (dysbiosis)[3)].

For example, the acetic acid produced by fermentation acts on the brain to decrease appetite and promote neurogenesis. It also acts on adipose tissue, gastrointestinal tract, lungs, and cells responsible for immunity, *i.e.* regulatory T cells (Treg), exerting anti-inflammatory and anti-carcinogenic effects, degradation of triglycerides in adipose tissue (protection against obesity and alleviation of excessive insulin sensitivity in adipose tissue), inhibition of epigenetic enzymes, *i.e.* histone deacetylase (HDAC9), and activation of Treg (alleviation of bronchial asthma). A line of mechanisms include a combination of intracellular signaling of fatty acid receptors that use acetic acid as a ligand (G protein-coupled seven transmembrane receptors (GPCRs), *i.e.* GPR41, GPR43) and inhibition of HDACs involved in epigenetic modification.

Butyric acid also acts on immunocompetent cells, *i.e.* Treg, distributed in the gastrointestinal tract, suppresses HDACs, and promotes secretion of interleukin-18 (IL-18) via SCFA receptors such as GPR109A, thereby suppressing inflammation and carcinogenesis in the gastrointestinal tract. Of note, butyrate plays an extremely important role as a major nutrient source for gastrointestinal epithelial cells and is also essential for the construction of the gastrointestinal barrier.

Propionic acid also enhances Treg function via GPR43 and other factors, and promotes the secretion of gut-derived hormones, *i.e.* Peptide YY (PYY), GLP-1, thereby contributing to improve glucose metabolism, suppress excessive appetite, and exert anti-inflammatory effects in a wide variety of tissues.

While a series of short-chain fatty acids produced by fermentation by beneficial intestinal bacteria exemplify a variety of health-promoting effects, when certain intestinal bacteria proliferate due to unhealthy lifestyle or dietary disturbances, gut microbiota-derived toxic substances (ammonia, nitroso compounds, hydrogen sulfide, amines, indole) and inflammatory cytokines (IL-6, TNF-α, IL-23, IL-17, *etc.*) induce liver cancer and colon cancer[14)]. For example, imidazolpropionic acid derived from histidine induces insulin resistance, and it has also attracted attention that part of the insulin sensitizing effect of metformin is mediated by its suppressive impact on the imidazolpropionic acid. Furthermore, choline and carnitine derived from red meat and liver are converted into trimethylamine by fermentation, and when metabolized to trimethylamine oxide (TMAO) in the liver, they act as potent inflammatory stimulants and are also deeply involved in the progression of atherosclerosis and cardiovascular diseases, tissue fibrosis, and mitochondrial dysfunction. In fact, TMAO, acting as an intravascular inflammatory agent, increases platelet aggregation, inhibits the reverse transport of HDL-cholesterol, and eventually contributes to the accumulation of cholesterol-phagocytosed foam macrophages (foam cells) in vessel walls.

On the other hand, 4-cresol, which has recently been attracting attention as a beneficial fermentation metabolite, is derived from tyrosine and phenylalanine, and contributes to the alleviation of hyperglycemia and liver steatosis via increased insulin secretion. Experimentally, subcutaneous administration of 4-cresol to obese-diabetic mice on a high-fat diet was shown to increase insulin secretion and ameliorate hyperglycemia via promoting proliferation of pancreatic β cells. Furthermore, some bile acids that escape reabsorption from the gastrointestinal tract are metabolized into secondary and tertiary bile acids, and secondary bile acids in particular activate bile acid receptors distributed throughout the body, namely the farnesoid X-activated receptor (FXR) and G protein-coupled bile acid receptor (TGR5). FXR signaling is accompanied by increased secretion of FGF15 and FGF19, and TGR5 signaling is accompanied by increased secretion of GLP-1, both of which act on the brain to suppress food intake, increase energy expenditure, and contribute to a line of anti-inflammatory effects (***Fig. 3***, quoted and modified from Ref. 14)[14)].

Dysfunction of the gut-brain axis: A plausible mechanism of fermentation failure

Experiments in rodents have shown that continuous intake of animal fat increases obesity-prone gut microbiota, while continuous intake of fish oil and polyunsaturated fatty acids contributes to the maintenance of a less fattening microbiota[15)]. Importantly, continuous overconsumption of

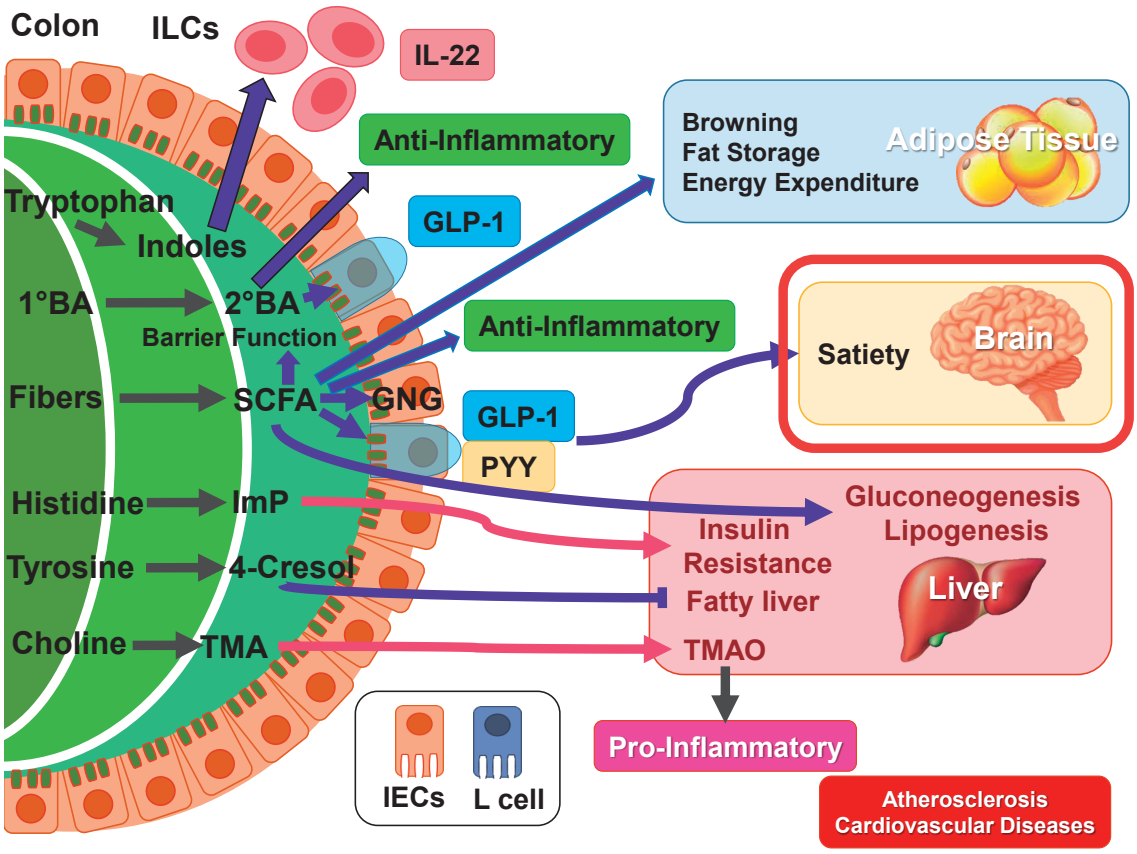

Fig. 3. **Role of gut-derived microbial metabolites in metabolic health and disease.**

1°BA, primary bile acids; 2°BA, secondary bile acids; SCFA, short chain fatty acids; GNG, gluconeogenesis in the intestinal tissue; IECs, intestinal epithelial cells; ILCs, innate lymphoid cells; IL, interleukin; GLP-1, glucagon-like prptide-1; PYY, peptide tyrosine (Y) tyrosine (Y); ImP, imidazole propionate; TMA, trimethyl amine; TMAO, trimethyl amine oxide. Quoted and modified from Reference 14.

animal fat reduces the fermentation power of beneficial intestinal bacteria, leading to a substantial drop in intestinal immune function mainly due to decreased production of SCFAs, and also a marked shrink in epigenomic regulatory functions mediated by SCFAs, which predisposes to metabolic derangement such as T2DM and obesity disease [16].

The gut microbiota of humans and mice with sustained and substantial intake of animal fats is markedly altered in a short period of time, inducing inflammation of the gastrointestinal tract, impairment of acquired as well as innate immune system, and barrier dysfunction in the gastrointestinal mucosa. Concurrently, a reduction in the size of the cecum and considerable shortening of the gastrointestinal tract occur. Disruption of the gastrointestinal barrier increases the concentration of lipopolysaccharide (LPS) and other endotoxins in the circulation, causing mild but chronic invisible inflammation throughout the body, leading to insulin resistance and obesity. In addition to excessive intake of animal fat, other triggers for dysfunction of gastrointestinal mucosal barrier have been suggested to be related to excessive intake of preservatives and colorants in foods, caffeine, and alcohol, and also abuse of antibacterial drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs).

There are two types of gut microbiota: those that are inherited from the mother and remain largely unchanged throughout the life, and those that can be easily altered by life circumstances. Compared to vaginally delivered infants, the intestinal flora of infants via the cesarean section (C-section) is considerably altered, with a predominance of metabolically and immunologically beneficial Lactobacillus species in the former and an increase in pathogenic staphylococci in the latter. It has been reported that the risk of a variety of metabolic, allergic and neuropsychiatric diseases is apparently increased in C-section infants compared to vaginally delivered infants (allergic diseases: 5 times, attention deficit hyperactivity disorder (ADHD): 3 times, autism: 2 times, obesity: 1.5 times, type 1 diabetes mellitus: 1.7 times), and the mechanistic link with abnormal balance of intestinal flora has attracted attention in scientists and clinicians [17].

In addition to this notion, an interesting finding was reported comparing the gut microbiota of thin children living in the suburbs of central Africa on a cereal staple diet with that of children living in urban Italy. In the former, Bacteroidetes (B) accounted for 75% of the microbiota and Firmicutes (F) for only 10%, whereas in the latter, Bacteroidetes accounted for 25% and Firmicutes for 50% [18].

Conclusion

Although diet and nutritional guidance up to now have mechanically determined caloric intake based on blood glucose level, body fat mass, body mass index (BMI), and level of physical activities, huge individual differences do exist in the risk of obesity and hyperglycemia even when eating similar foods. Based on these observations, evaluation of gut microbiota has recently begun to be actively utilized as part of prevention and monitoring of therapeutic effects in T2DM and obesity. The development of pharmaceuticals and functional foods targeting the improvement of microbiota balance is expeditiously exploding, and "the power of gut-brain axis" will be no doubt an increasingly key concept in the future medical field.

Conflicts of Interest

All authors state that they have no conflicts of interest.

Acknowledgments

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Author Contributions:

Writing, Masuzaki H; Analysis of intestinal flora in obese and diabetic patients, Uema T; Analysis of intestinal flora in obese and diatetic mice, Millman JF; Analysis of brain functions related to food preference, addictive behaviors, and cognitive functions, Okamoto S.

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