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Review

Gut Microbiota and Obesity: Focus on Hormone Regulation and Appetite Control

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Abstract

The prevalence of obesity has continued to rise worldwide over the past decade. Chronic and excessive intake of unhealthy diets can alter the gut microbiota composition. This altered gut microbiota affects gut hormone secretion through their metabolites. Microbiota-mediated gut hormone levels can affect the host appetite. Probiotic strains, which are known for their beneficial functions, are associated with the improvement of gut microbiota and body weight control. This review provides detailed mechanisms of microbiota-mediated gut hormone secretion which is closely related to food intake and fat accumulation. Results show that gut dysbiosis negatively influences the sensitivity of leptin and insulin in hypothalamic neurons as well as gut hormone secretion. It can cause excessive energy intake and storage. Probiotics intervention improves intestinal microflora balance and ameliorates appetite-regulating hormonal activities, thereby preventing excessive food intake and obesity. The therapeutic efficacy of probiotic strains on obesity through appetite control would provide new insights into the prevention and control of obesity.

Key words: Gut Microbiota; Obesity; Gut Hormone; Appetite; Dysbiosis; Probiotic Treatment.

1. Introduction

The worldwide prevalence of obesity has doubled since 1980 and has shown a continuous augment that 5.0 % of children and 12.0 % of adults are defined as obese (1). Obesity increases the risk of developing several chronic diseases, including type 2 diabetes mellitus, hypertension, and even certain types of cancer (2). Efforts toward the prevention and early treatment of obesity have therefore drawn extensive attention around the world. The primary inducer of obesity and its associated disorders is the imbalance between energy intake and expenditure (3). Appetite acts as a positive regulator of energy balance. The excessive increased appetite is responsible for the worsening of body weight gain and an eating disorder, which eventually contributes to obesity (4). Mounting evidence has demonstrated that gut microbiota play an important role in food intake by regulating gut hormones. Gut hormones ghrelin (5), cholecystokinin (CCK) (6), peptide YY (PYY) (7), and glucagon-like peptide-1 (GLP-1) (8) are mainly produced by enteroendocrine cells (EEC). Leptin (9) and insulin (10) are produced by adipocytes and pancreatic beta-cells, respectively. A variety of bacterial derivatives including short-chain fatty acids (SCFAs), lipopolysaccharide (LPS), secondary bile acid (BA) act on gut hormone production which encodes information about satiety state and transmits it into the central nervous system (8, 11-14). In this review, we focused on gut hormones regulating appetite circuits in the brain via activating central and peripheral neurons. We summarized the physiological roles of bacterial metabolites in the gut hormones production and described their signaling pathways (Figure 1). This review provides detailed mechanisms of microbiota-mediated gut hormone activities and new insights of probiotic intervention on obesity treatment via appetite control.

2. Gut hormones regulation and appetite control

Gut hormones can activate appetite circuits in the brain. Hypothalamus and brainstem are mainly responsible for appetite regulation by receiving hormonal signals from the gut (15). In the hypothalamus, there are two neurons responsible for appetite control with opposing effects. Neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP) stimulate food intake, while neurons expressing pro-opiomelanocortin (POMC) inhibit eating behavior (Figure 1). Both neurons project signals into the paraventricular nucleus (PVN). Once receiving satiety signals from the gut hormones, POMC neurons produce α-melanocyte-stimulating hormone (α-MSH) which binds to melanocortin-4 receptors (MC4R) in the PVN, resulting in reduced food intake. On the other hand, activation of NPY/AgRP neurons not only stimulates the orexigenic Y1 and Y5 receptors in the PVN but also interrupts the anorexigenic α-MSH signal by blocking MC4R in PVN, leading to increased appetite (15).

2.1. Leptin

Leptin, a 167-amino-acid product of the obese gene, is an anorexigenic hormone mainly produced by adipose tissue and transmits satiety signals to the central nervous system (9). Leptin reduces food intake by upregulating anorexigenic signals such as POMC, MC4R and downregulating orexigenic signals such as NPY and AgRP (15). Both overweight people and preclinical animal models showed a higher level of leptin than lean groups. Besides, plasma leptin levels are highly correlated with body mass index (BMI) (16). Interestingly, a high level of leptin in the obese group failed to transmit satiety signals due to leptin resistance (17, 18). Therefore, enhancing leptin sensitivity and leptin production may promote body weight loss by reducing food intake.

It has been reported that a high-fat diet (HFD) is associated with leptin resistance although the mechanisms remain unclear (19, 20). Lin S., et al. demonstrated that peripheral but not central leptin insensitivity occurred in mice after 8 weeks of HFD treatment. Meanwhile, significant central leptin resistance was detected after 16 weeks of HFD

treatment (20). De Lartigue G., et al. also observed a similar result in the HFD mouse model. Results showed that leptin resistance occurred in vagal afferent neurons but not in hypothalamic neurons after 8 weeks of HFD treatment, indicating that peripheral leptin insensitivity may be related to central leptin resistance (19). Furthermore, they found that bacterial LPS acted directly on vagal afferent neurons which co-express toll-like receptor 4 (TLR4) and leptin receptor *in vitro*. Besides, LPS also upregulated the suppressor of cytokine signaling-3, a negative regulator of leptin signaling, which led to leptin resistance (19). Recently, Bagarolli, R.A. group demonstrated that HFD-induced gut dysbiosis increased intestinal permeability in mice by reducing ZO-1 and Occludin expressions which play important roles in maintaining intestinal barrier homeostasis. This resulted in increased serum LPS and caused leptin resistance (18). Taken together, these data suggested that HFD may cause gut dysbiosis and destroy intestinal epithelial cells, leading to increased serum LPS. This LPS may act directly on vagal afferent neurons and induce peripheral leptin resistance by stimulating the suppressor of cytokine signaling-3, which subsequently causes central leptin resistance.

In the large intestine, gut microbiota generates SCFAs through fermentation of the undigested dietary fibers, mainly including butyrate, acetate, and propionate (21). It has been reported that SCFAs have various beneficial functions on appetite control as well as energy homeostasis (22). Roselli, M., et al. found that oral administration of probiotic mixture including *Bifidobacterium lactis* and *B. breve* could significantly promote leptin secretion by increased SCFAs production (23). Besides, Zhang XL, et al. also found that leptin production was stimulated by the administration of soymilk fermented by *B. bifidum*, *L. casei*, and *L. plantarum*, but not soymilk alone. These results suggest that metabolites of these probiotics such as SCFAs could stimulate leptin production, leading to reduced food intake and body weight loss (24).

SCFAs increase the level of leptin in the plasma through activation of free fatty acid receptors (FFAR) FFAR2/GPR43 and FFAR3/GPR41 (11, 25). Hong YH., et al. demonstrated that SCFAs-induced FFAR2 activation on adipocytes stimulated adipocyte differentiation and increased the level of leptin (25). Furthermore, Xiong et al. firstly demonstrated that SCFAs-induced FFAR3 activation on adipocytes increased leptin production (11). Nevertheless, recent studies have failed to detect the FFAR3 expression on adipocytes even though they used the same PCR primers, which suggested that the FFAR3 expression on adipocytes was quite low or undetectable (25, 26). However, in FFAR3 knockout mice, SCFAs-induced leptin secretion was attenuated by downregulated FFAR2 expression (26). These results indicate that SCFAs-induced FFAR3 activation was partially related to FFAR2. Therefore, the crosstalk between FFAR2 and FFAR3 in adipocytes still needs to be further investigated.

2.2. Ghrelin

Ghrelin is an orexigenic peptide hormone secreted from enteroendocrine X/A cells in the stomach, which can transmit the hunger signal from the periphery to the central nervous system. Ghrelin is composed of 28-amino acid. Octanoylation of serine residue located at position three of ghrelin is essential for binding to the growth-hormone-secretagogue receptor and to break through the blood-brain barrier (5). There are two pathways stimulating appetite by ghrelin have been reported so far. One is that the peripheral ghrelin can reach the hypothalamus by penetrating the brain through the blood-brain barrier and directly act on NPY/AgRP neurons in the hypothalamus. The other is that ghrelin interacts with vagal afferent neurons in nodose ganglion. Ghrelin signal is transmitted to the nucleus tractus solitaries via nodose ganglion and then relayed to NPY/AgRP neurons in the hypothalamic neurons (5, 27). The NPY/AgRP neurons have crosstalk with POMC neurons, thus

NPY/AgRP neurons activated by ghrelin suppress anorexigenic signals through inhibiting POMC neurons as well as enhance orexigenic signals through activating Y1 receptor in PVN (5, 15).

A high level of ghrelin stimulates food intake which induces body weight gain, suggesting that the downregulation of ghrelin could be beneficial to prevent weight gain (4). Ghrelin production is suggested to be mediated, in part, by bacteria living in the stomach. *Helicobacter pylori* is a Gram-negative bacterium that lives in the human stomach. *H. pylori* is detected in more than 50% of adults around the world. *H. pylori* infection is correlated with gastric diseases including gastritis, gastric ulcer, and gastric cancer (28). Interestingly, a clinical study showed that the level of ghrelin in plasma among *H. pylori*-positive subjects was significantly lower than *H. pylori*-negative subjects (28). In addition, plasma ghrelin levels in healthy people increased significantly after eradication of *H. pylori*, leading to markedly increased food intake and body weight gain (29). These data suggested that *H. pylori* could be associated with the decreased plasma ghrelin level and reduced food intake. Interestingly, compared with Asians, the Western population has a lower prevalence of *H. pylori* but a higher prevalence of obesity (30). This association indicates that *H. pylori* might have a role in weight loss through a reduction of ghrelin levels in healthy individuals although the associated infection often causes gastric diseases.

Bando M., et al. suggested that interleukin-1b (IL-1b) can directly reduce ghrelin production by binding to ghrelin-producing cells which express IL-1 receptor type 1 (31), although the previous study had failed to detect IL-1 receptor in the ghrelin-producing cells (32). Wang L., et al. demonstrated that intravenous injection of LPS and IL-1b in rats showed an inhibitory effect against ghrelin production. However, the intravenous injection of IL-1 receptor antagonist significantly attenuated the suppressive effect of LPS. This indicated that LPS may inhibit the ghrelin secretion by inducing IL-1b production (12). Interestingly, *Lactobacillus helveticus* which was resistant against gastric juice and acidic condition (33), also stimulated IL-1b production in macrophages *in vitro (*34). In the chicken blood monocytes test, TLR9 agonist CpG-oligodeoxynucleotide significantly upregulated IL-1b *in vitro* (35). Besides, CpG-motifs were also detected in certain probiotics such as *L. helveticus (*36). Taken together, certain probiotics such as *L. helveticus* might reduce a ghrelin level in the stomach through an increased level of IL-1b stimulated by CpG-motifs, leading to reduced food intake.

Torres-Fuentes C., et al. recently reported that both SCFAs and the supernatant of SCFAs-producing bacterial inhibited the ghrelin signaling *in vitro*. They demonstrated that SCFAs disrupted ghrelin-mediated calcium mobilization, inhibiting the ghrelin signaling *in vitro*. This result suggested that circulating SCFAs may affect the ghrelin pathway in nodose ganglion neurons which express both FFAR3 and ghrelin receptors (37).

2.3. Cholecystokinin

CCK is an anorexigenic hormone released by intestinal I-cells in the duodenum in response to dietary lipid and protein through G-protein coupled receptor GPR40 and calcium-sensing receptor, respectively. CCK directly acts on vagal afferent neurons which primarily project to the nucleus tractus solitaries and activate subsequent pathways that control appetite (6). The reduced CCK sensitivity and a low level of CCK have been found in obese individuals (6, 38). According to Duca FA.'s research, CCK plays a major role in satiety transmission which is dietary lipids-mediated (39). Their study showed that the deficiency of CCK-mediated satiety signals during a high-fat diet caused excessive calorie intake and body weight gain (39). Therefore, improvement of the sensitivity and concentration of CCK is beneficial for obesity treatment.

The CCK secretion by intestinal I-cells can be stimulated by the activation of toll-like receptors including TLR4, TLR5, and TLR9. The bacterial LPS, flagellin, and CpG-motifs activate TLR4, TLR5, and TLR9 in intestinal I-cells respectively

(40). These ligands are normally found in pathogenic bacteria, thus bacterial infection could induce excessive CCK production, provoking nausea, and emesis. Interestingly, however, a high number of CpG-motifs (GTCGTT, optimal for human TLR9) has been also detected in several probiotics such as *L. plantarum*, and *L. rhamnosus* (36), suggesting that these probiotic strains may stimulate CCK secretion and reduce food intake. Furthermore, increased CpG-motifs by probiotics could ameliorate mucosal functions and the immune system for human health[36). In the zebrafish larvae, the administration of *L. rhamnosus* upregulated CCK gene expression through modulation of gut microbial composition and increased free fatty acids concentration which stimulates CCK production (41). Meanwhile, it is also possible that a large number of CpG-motifs of *L. rhamnosus* may promote CCK production. Belguesmia Y., et al. also found that *L. acidophilus* and *L. gasseri* enhanced CCK secretion significantly in STC-1 cells in vitro (42). These data suggest that certain *Lactobacillus* species may reduce food intake through stimulation of CCK production, leading to weight loss. Future study is needed to clarify their impact on appetite and body weight in proper animal models.

2.4. Peptide YY

Gut hormone peptide YY is mainly produced by large intestinal L-cells and transmits satiety signals from the gut to the hypothalamus through peripheral circulation (7). Two molecular forms of PYY including PYY_{1-36} and PYY_{3-36} have been identified. PYY_{3-36} is the predominant of PYY in postprandial human serum (43). Peripheral injection of PYY_{3-36} in mice inhibited food intake and reduced bodyweight gain but not in Y2 receptor (Y2R)-null mice, which indicated that Y2R was necessary for the anorexic function of PYY_{3-36} (7). PYY acts directly on hypothalamic NPY neurons by activating of Y2R. PYY-induced Y2R activation in NPY neurons decreased *Npy* expression which projects hunger signal to ascending pathways (7). It has been reported that a lower circulating level of PYY was detected in obese people than in normal controls (44, 45). Therefore, the recovery of impaired PYY secretion in obese patients may contribute to body weight loss.

It has been reported that gut microbiota can regulate plasma PYY level by producing SCFAs and secondary bile acids which can bind to FFAR2/3 or G-protein coupled receptor TGR5 on L-cells, respectively (46-48). It is supported by Qu L., et al. who found the lower concentration of SCFAs and PYY in the diabetic rat model compared to normal controls. After oral administration of *Lactobacillus. casei* for 6 weeks, the abundance of total SCFAs-producing strains was significantly increased, leading to enhanced SCFAs production, resulting in increased PYY levels (49). Brooks L., et al. found that in normal but not *ffar2*-deficient mice, SCFAs increased PYY levels by upregulating *Pax4* which is an essential transcription factor for L-cell differentiation. This result indicated that SCFA-induced FFAR2 activation in L-cells can increase the PYY level by stimulating L-cell differentiation (46). Besides, SCFAs-induced PYY production was significantly blunted in FFAR3 knock out mice, indicating that FFAR3 also played an important role in PYY secretion. However, the underlying mechanisms are still poorly understood yet (48).

Primary BAs are physiological important steroid acids that are produced in the liver. They can promote intestinal absorption and transport of nutrients, especially lipids (50). Besides, bile acids can increase PYY production by activating TGR5 (51). In the small intestine, primary BAs are deconjugated by bile salt hydrolases which are produced by various intestinal bacteria, such as *Bacteroidetes* (52). In the large intestine, unconjugated primary BAs are transformed into unconjugated secondary BAs by gut bacteria, mainly including *Clostridium scindens* and *C. hylemonae (*52). Although secondary BAs have been reported to be correlated with colon cancer, they also play an important role in preventing intestinal infections (52). Furthermore, secondary BAs are strong activators of TGR5 compared to

primary BAs (53), indicating that secondary BAs stimulate PYY secretion in L-cells stronger than primary BAs. Bile acids should be transported to the basolateral side for binding TGR5 because the TGR5 of L-cells is basolaterally located. Primary BAs need ileal-bile acid transporter to be absorbed, while secondary BAs can be absorbed through diffusion without active transporter (13). These data indicate that gut bacteria increase the basolateral pool size of BAs that stimulates PYY secretion through activation of TGR5 on L-cells, leading to reduced food intake.

2.5. GLP-1

Intestinal L-cell that synthesizes PYY also produces another hormone, Glucagon-like peptide-1 (GLP-1), which is currently selected as a drug target for type 2 diabetes (54). Both clinical trials and animal studies have shown that GLP-1 and GLP-1 receptor agonists can reduce food intake and lead to body weight loss (55-57). This inhibition on satiety and appetite may be mediated by the synergistic effects in the gut and brain. GLP-1 acts on central and peripheral receptors that transmit anorexigenic signals to NPY/AgRP and POMC neurons (58). Gut microbiota can influence the secretion of intestinal GLP-1 through their cellular components and metabolites (8, 14).

SCFAs promote the secretion of GLP-1 by L-cells through activation of FFAR2 and FFAR3, which is similar to PYY (8, 47, 55). Patrice et al. also found that the non-digestible carbohydrates diet promoted the L-cell differentiation in male Wistar rats and induced more endogenous GLP-1 secretion (59). Probiotics with mixed bacteria such as VSL#3 were proved to alter gut flora composition in HFD mice and promoted GLP-1 secretion (55). Yadav H., et al demonstrated that butyrate was a key factor that stimulated the release of GLP-1 from intestinal L-cells (55). Zhao et al. found that dietary fiber significantly increased the diversity and abundance of SCFA-producing bacteria in a randomized clinical trial. This modified gut microflora resulted in more acetate and butyrate production that stimulated GLP-1 and PYY secretion (60). Acetate and butyrate improved glucose homeostasis by inducing intestinal GLP-1 and PYY production. Hemoglobin A1c levels were also improved which was partly due to the increase of GLP-1 production.

Bile acid receptors, including farnesoid X receptor (FXR) and TGR5, belong to the main targets of metabolic disease transformation and intervention research. Bile acids are known to stimulate the secretion of GLP-1 secretion (61). This effect was possibly mainly mediated by TGR5 which was located on the basolateral L-cell membrane (62, 63). Results found that INT-767, as the dual FXR and TGR5 agonist, has beneficial effects on GLP-1 secretion inducing *Tgr5* gene expression, increasing Ca^{2+} level and cAMP activity in HFD-induced obese mice (64). However, activation of FXR reduced FFAR2 expression and signaling transduction, attenuating SCFAs-induced GLP-1 secretion (65).

Indole, another important bacterial metabolite, can affect GLP-1 secretion in L-cell. Chimerel et al. reported that indoles inhibited voltage-gated K^+ channels, promoted $Ca2^+$ entry, and thus strongly stimulating GLP-1 secretion (66). Nevertheless, their work also showed that indoles could slow down ATP production by blocking NADH dehydrogenase, resulting in a sustained decrease of GLP-1 secretion. Hence, more explorations are needed to elucidate the complex association between indole and GLP-1 production.

LPS, the major component of Gram-negative bacterial outer membrane, are involved in the regulation of intestinal GLP-1 secretion. Lebrun et al. reported that gut bacterial LPS easily leaked into the bloodstream following the intestinal barrier injury, leading to rapidly increased plasma GLP-1 levels through toll-like receptor 4 (TLR4)-dependent manner (14). Recent studies further revealed that LPS required distal intestinal Gcg expression to maximize plasma GLP-1 level (67).

2.6. Insulin

Insulin is a protein hormone, secreted by β-cells in the pancreas. It is involved in regulating carbohydrates, fat metabolism, and controlling

blood sugar balance (10). Insulin can stimulate POMC neurons and inhibit NPY neurons, thereby reducing food intake (68, 69). It is supported by Jastreboff AM., et al. who demonstrated that individuals with insulin resistance are more likely to overeat, leading to bodyweight gain (70). In the insulin signaling pathway, neurotransmitter dopamine (DA) plays an important role in feeding behavior control (71). Insulin can directly stimulate DA transporters which inactivate DA signaling by transporting DA back into the DA nerve terminal from the synapse. Hence, insulin inhibits the effect of dopamine and suppresses appetite (71, 72). Accordingly, insulin is considered as an anorexic hormone and plays an important role in appetite control.

It has been reported that gut microbes can influence the insulin signaling pathway through several of their derivatives including SCFAs, LPS, branched-chain amino acids (BCAAs). The effects of SCFAs-activated FFAR2/FFAR3 on insulin secretion in pancreatic β-cells are controversial both *in vivo* and *in vitro (*73). Tang C et al. found that mice lacking FFAR2 and FFAR3 showed greater insulin secretion, indicating that SCFAs-activated FFAR2/3 may inhibit insulin production (74). In contrast, McNelis JC et al. demonstrated that *ffar2*-deficient mice have significantly lower insulin secretion in response to dietary glucose, suggesting that FFAR2 activation may stimulate insulin production by pancreatic β-cells (75). These discrepancies might be due to the FFAR-mediated alteration of other hormone levels including GLP-1 and leptin which can influence insulin secretion. Interestingly, it has been reported that SCFA, especially butyrate may improve insulin sensitivity. In the clinical trial, subjects who received fecal microbiota transplantation from lean donors improved insulin sensitivity through the increased prevalence of butyrate-producing strains (76). It consists of other data showing that vancomycin treatment reduced the abundance of butyric acid-producing bacteria and impaired insulin sensitivity (77). Besides, oral administration of butyrate induced the increased insulin sensitivity and weight loss in mice (78). Collectively, the improvement of butyrate-producing gut bacteria could ameliorate insulin resistance and insulin-mediated appetite control. Furthermore, Carvalho BM., et al. also showed that antibiotics-induced gut microbiota modification in HFD-induced obese mice ameliorated insulin sensitivity through a decrease in serum LPS levels and an increase in SCFA levels. After the injection of LPS, however, the increased insulin sensitivity was significantly attenuated, demonstrating that LPS is closely associated with obesity-induced insulin resistance (79).

Also, branched-chain amino acids have been considered as an inducer of insulin resistance. Recently, Pedersen HK., et al. observed a high level of branched-chain amino acids in the serum of insulin-resistant patients, among which the key strains were *Prevotella copri* and *Bacteroides vulgatus*. Their results showed that two weeks of *P. copri* administration in the HFD mice model caused insulin resistance by enhancing serum BCAA levels (80). In contrast, the administration of *P. copri* to mice with a high-fiber and low-fat diet improved insulin sensitivity by producing succinate which is a substrate for intestinal gluconeogenesis (81). These results suggest that the effects of certain bacterial strains such as *P. copri* on insulin sensitivity could be totally different depending on the diet style.

Furthermore, anorexigenic hormone GLP-1 and leptin are also involved in insulin regulation. Muller, T.D., et al. suggested that GLP-1 stimulates both the synthesis and secretion of insulin via multiple cAMP-dependent and PKC-dependent pathways (82). On the contrary, leptin has negative effects on insulin secretion from pancreatic β-cells (83).

3. Gut microbiota and their derivatives in appetite control

There are increasing studies on bacterial metabolites and appetite regulation. In the gastrointestinal tract, bacterial metabolites and cellular components including SCFA, LPS, ClpB,

and CpG molecular patterns could be associated with the gut hormones production, affecting the host appetite. Therefore, the abnormal concentration of bacterial metabolites may cause eating disorders which could eventually contribute to obesity.

3.1. SCFAs

Plentiful data have demonstrated that SCFAs have beneficial effects on the host immune system, energy homeostasis, and appetite control (22). In the context of obesity, SCFAs may prevent weight gain by reducing food intake through the secretion of anorexigenic hormones including PYY, GLP-1, and leptin by activating the FFAR2 and FFAR3 (26, 46, 48). It is supported by one clinical study showing that acute inulin-propionate ester supplementation increased plasma PYY and GLP-1 levels and reduced food intake compared to inulin-control. Besides, the long-term supplementation with inulin-propionate ester for 6 months strongly prevented body weight gain in obese individuals compared to inulin-control (82). This is consistent with other clinical data providing that healthy overweight-adults with oligofructose supplementation which is mainly fermented by gut bacteria into SCFAs showed weight loss over 12 weeks through decreased food intake. Meanwhile, the control group with maltodextrin showed no notable differences in food intake and body weight (83).

In contrast, it has also been reported that SCFAs could be used as an energy source, thus might increase energy harvest and promote weight gain. Bergman, E. demonstrated that daily calories absorbed from SCFAs are equivalent to ~10% of the human caloric requirements (84). This is supported by Isken F., et al. who demonstrated that long-term supplementation of highly fermentable soluble fiber for 45 weeks in the HFD-mice model increased body weight profoundly compared to control with partially fermentable insoluble fiber (85). Turnbaugh PJ. et al. also demonstrated the increased energy absorption in the obese mice through enhanced SCFAs in caecum (86). Taken together, SCFAs might be contributed to increased energy harvesting as well as reduce food intake by stimulating anorexigenic hormone production. The discrepancy between SCFAs-induced bodyweight changes might be due to their different dosage. Increased energy harvesting from SCFAs sometimes could outweigh their anorexigenic effects. Therefore, a well-designed long-term human study is needed to elucidate the impact of SCFAs on body weight.

3.2. Bacterial components

LPS, the major component of Gram-negative bacterial outer membrane, is an endotoxin that causes inflammation when entering the circulation. Different levels of endotoxin activity may be owing to variations in the detailed lipid A structure[87). People with an unhealthy diet and suffer from obesity are more likely to have chronic inflammation in their bodies. LPS may play an important role in the inflammation caused by unhealthy diets. High-fat food significantly increases insulin resistance, serum LPS, and lipid levels, leading to obesity in rats (88). Jamar et al. also reported that hyperlipidemic diets can stimulate TLR4 inflammatory pathway by promoting LPS translocation and lipopolysaccharide-binding protein activation. TLR4 inflammatory pathway modulates the feeding center in the brain (89). A study of rats has shown that chronic low-dose LPS treatment reduced vagal afferent leptin signaling and decreased CCK-induced satiety (90). Gut microbes may promote host appetite and possibly leading to obesity by releasing LPS.

When the intestinal barrier is broken, much LPS passes through the intestinal barrier and enters the bloodstream, leading to inflammation. LPS is also considered as a cause for immune stress-induced anorexia and α2-adrenoceptors may participate in this appetite suppressive effect (91). In rodent studies, secretion of leptin (92, 93) and GLP-1 (14) increased and triggered immune responses in the LPS-induced inflammation model. These findings expand traditional concepts of gastrointestinal hormones to encompass the sensing of

inflammatory stimuli and compromised mucosal integrity, linking gastrointestinal hormones secretion to gut inflammation. In the case of infection caused by large doses of LPS, the effect on host appetite is negative.

CpG-motifs are molecular patterns found abundantly in microbial genomes. It has been mainly studied in immunity due to its immunostimulatory effects (94). However, it has been reported that CpG-motifs stimulated CCK secretion by activating TLR9 in murine intestinal enteroendocrine cells (40). Besides, CpG-motifs strongly induced IL-1b production by chicken monocytes (35) which is a negative regulator of ghrelin secretion (31), suggesting that bacterial CpG-motifs may play a role in appetite control. Hildebrandt MA., et al. demonstrated that mice fed with a high-fat diet exhibited an altered gut microbiome with significantly increased *Firmicutes* and decreased *Bacteroides* which is similar to the gut microbiome observed in obese patients (95). Interestingly, CpG-motifs are rich in *Bacteroides* but relatively low in *Firmicutes (*36). The plasma levels of CCK were also significantly lower in obese individuals than in lean controls (38). Taken together, these data suggest that an increased ratio of *Firmicutes* to *Bacteroides* induced by HFD may decrease the total amount of bacterial CpG-motifs. This decreased CpG-motifs could induce a low CCK level, leading to increased host appetite. It is a possible way to understand the mechanisms between altered gut microbiota composition and low levels of CCK in obese patients.

Escherichia coli ClpB heat shock disaggregation chaperone protein has been reported that ClpB may influence host appetite as an antigen-mimetic of the anorexigenic α-MSH due to their sequence homology and anti-ClpB immunoglobulins crossreactive with α-MSH (96). Tennoune N., et al. demonstrated that the intragastric gavage in mice with *E. coli* K12 reduced food intake and body weight. However, this anorexigenic effect was significantly attenuated in mice with ClpB-deficient *E. coli* K12. It suggests that ClpB produced by *E. coli* K12 may be associated with reduced food intake (96). It is supported by recent data showing that the intragastric gavage of ClpB-producing *Hafnia alvei* increased plasma a level of ClpB protein and reduced food intake in the obese mice (97). Interestingly, a low abundance of enterobacterial ClpB gene was detected in obese humans compared with lean individuals (97). This is similar to other data showing a low prevalence of Enterobacteriaceae which are ClpB-synthesizing bacteria in obese individuals (98). These results indicated that a low abundance of Enterobacteriaceae might be associated with obesity through decreased ClpB production. On the contrary, Tennoune N., et al. also demonstrated that ClpB-immunized mice by acute injection of ClpB showed increased food intake and body weight due to the stimulated autoantibodies reactive with α-MSH. Therefore, further research is needed to elucidate the effect of ClpB on α-MSH signaling and host appetite.

4. Conclusion

To date, despite the high prevalence of obesity and related diseases around the world, effective appetite suppressants for obesity treatment are still in scarcity. Interestingly, certain probiotic strains, as the appetite suppressant, have shown great potential in improving satiety hormone signaling through modifying gut microbiota composition and their metabolites. However, the specific mechanisms remain unclear. Future studies are needed to further elucidate the molecular mechanisms of microbiota on satiety hormone signaling improvement.

Declarations

1) ***Consent to publication***
   We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2) ***Ethical approval and consent to participants***
   Not applicable.
3) ***Disclosure of conflict of interests***

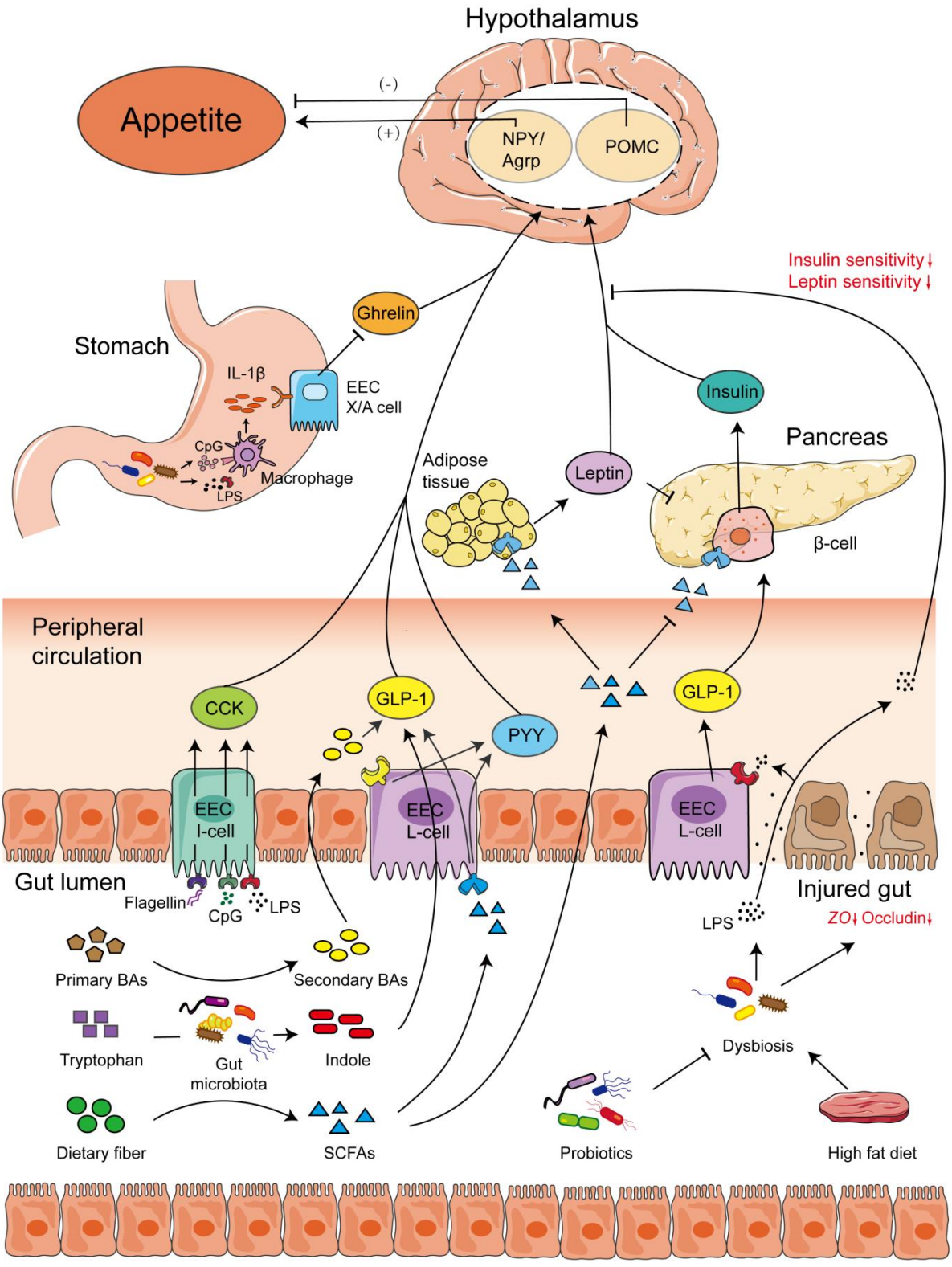

Figure 1. Schematic representation of gut microbial pathways to host appetite via control of appetite-regulating hormones.

Dietary nutrients are used by gut microbiota for growth, affecting to microbiota composition. Gut microbiotas produce a variety of metabolites, including secondary bile acids, indole, SCFA, and cellular components including LPS, flagellin, CpG-motifs. These metabolites can influence the host appetite through direct

interaction with gut hormone-producing cells including EEC cells, adipocytes, and pancreatic β-cells, or affecting indirectly by inducing cytokines. The interaction of bacterial metabolites with hormone-producing cells influences the levels of appetite-regulating hormones PYY, GLP-1, CCK, Leptin, Ghrelin, and insulin. The gut dysbiosis can cause an imbalance of these hormones and damage the intestinal barrier, leading to increased serum LPS which can impair insulin and leptin sensitivity. Appetite-regulating hormones affect the host eating behavior by transmitting the satiety state from the gut to the brain through hypothalamic orexigenic NPY/Agrp and anorexigenic POMC neurons.

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5) Availability of data and material

We declare that the data supporting the results reported in the article are available in the published article.

6) Authors' Contributions

The authors CP, BL and YD did the paper research and wrote the manuscript. LS contributed to figure drawing and manuscript review. WH helped with proofreading. GL, ZZ and ZL provided conceptualization and editing.

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8) Authors' biography

None

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