Neuromodulatory effect of microbiome on gut-brain axis; new target for obesity drugs

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Abstract

Considering the increasing prevalence of obesity worldwide, new approaches for its control have been investigated. Recent evidences highlighted the role of the gut microbiome in weight management. Obesity-associated gut microbiota alters host energy uptake, insulin sensitivity, inflammation, and fat storage. Moreover, the gut microbiota-derived metabolites could control appetite directly by affecting the central nervous system or indirectly through modifying the gut hormones secretion. Metabolites of the gut microbiome-brain axis could be novel targets for designing drugs in obesity. They can be prescribed directly like butyrate or can be modulated by manipulating the gut microbiota through probiotics, prebiotics and other dietary components such as polyphenols. Microbiome studies are trying to identify novel microbial species as next-generation probiotics to restore healthy gut microbiota composition and combat obesity and its related complications. According to the relationships between the gut microbiota and microbial composition of other parts of the body, the mechanisms linking the gut-brain axis and the whole human microbiota should be elucidated to provide novel anti-obesity strategies.

Keywords Obesity · Human microbiota · Gut-brain axis · Metabolites

Obesity and its related comorbidities are serious health challenge worldwide [1]. There are limited efficacious pharmacological treatments to manage obesity, which each of them has different side-effects. Obesity is a multi-faceted disorder and recent evidence revealed that the gut microbiota has an effective role in obesity by regulating metabolism, adiposity, appetite and food reward signaling [2, 3]. Studies have linked obesity to intestinal dysbiosis which is caused by low microbial diversity and depletion of certain bacterial taxa. However, the role of altered gut microbiota as a cause or consequence of obesity remains controversial [4, 5]. Gut microbiota in obese individuals harvest more energy from foods compared to lean-associated gut microbiota by enrichment of fermentation enzymes and nutrient

transporters [6]. Moreover, altered gut microbiota in obesity could contribute to metabolic endotoxaemia and chronic low-grade inflammation through increased absorption of lipopolysaccharides (LPS) [7]. LPS, the major component of the outer membrane of Gram-negative bacteria, activates Toll-like receptor 4 and initiates synthesis of inflammatory cytokines in white adipose tissue leads to insulin resistance [8].

The gut microbiota is termed as the second brain because of releasing neurotransmitters. There is growing evidence that the dopamine, epinephrine, norepinephrine, gamma-aminobutyric acid, serotonin, indole metabolites and other neurotransmitters derived by gut microbiota could affect dietary preference [3, 9]. Gut microbiota-derived metabolites connect bidirectional communication axis between the gut and brain and have a role in controlling appetite directly or indirectly [3]. Gut microbiota can directly regulate eating behaviors by affecting the central nervous system (CNS) through the gut-brain-axis. Intestinal bacteria-derived metabolites modify gut hormone secretion, including glucagon-like peptide1 (GLP1) and peptide YY, leptin and ghrelin which could impact on hypothalamic neuroendocrine pathways [3, 10]. Appetite regulation is mediated by signaling through afferent nerve fibers from the autonomic nervous system to the hypothalamus, which contains orexigenic and anorexigenic peptides, cocaine amphetamine-regulated transcript and pro-opiomelanocortin neurons [11, 12]. The GLP1 receptor

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agonist drugs like liraglutide have gained interest as a potential therapeutic agent for obesity in recent clinical trials. Wang et al. observed gut microbiota alteration in mice treated with liraglutide as a result of modifying the gut transit time and gastric emptying rate. They showed decreased frequencies of some obesity-related bacterial taxa in gut microbiota composition [13]. An animal study revealed that hydrogen sulphide which produced in the colon by sulphate-reducing bacteria from sulfate prebiotic can directly stimulate the secretion of GLP1. So modulating the gut microbiota in order to increase the hydrogen sulphide production and stimulate GLP1 secretion could be nominated as a new approach for combatting obesity which needs further investigations [14].

Metabolites of the gut microbiome-brain axis are novel targets for designing drugs in obesity. As therapeutic approaches, these metabolites could be prescribed directly or the production of these metabolites could be modulated by manipulating the gut microbiota. One of the important categories of microbiota-derived metabolites is the short chain fatty acids (SCFAs) including acetate, propionate and butyrate, which produced by fermentation of non-digestible carbohydrates in a ratio of about 60:20:20 respectively [3, 15]. Butyrate as key mediator of host-microbiota crosstalk affects intracellular signaling by binding to cell surface receptors. Four G protein-coupled receptors, which have been renamed to free fatty acid receptors bind to the butyrate with different affinities [15]. These receptors found on different cell types with various functions; on enteroendocrine cells, stimulating release of GLP1, PYY and leptin, on enterochromaffin cells, inducing serotonin release, on adipocytes regulating adipogenesis and lipolysis, on norepinephrine sympathetic neurons controlling norepinephrine release and on immune cells modulating immune reactions [16]. Role of butyrate in regulation of gene expression via inhibition of histone deacetylases and its ability to cross the blood brain barrier and regulating its integrity nominated it as a neuropharmacological agent [17, 18]. Succinate, an intermediate in propionate synthesis, which produced by gut bacteria from the phylum Bacteroidetes could enhance intestinal gluconeogenesis by bonding to GPR91 receptor and thereafter activate gut-brain glucose signaling which affects adiposity and body weight at the end. Fibers and polyphenols could increase the production of succinate in the gut [19, 20].

Prevalent approaches to modulate gut microbiota and as a result stimulate production of metabolites of the gut microbiome-brain axis are using probiotics, live microorganisms, or prebiotics, non-digestible compounds feeding gut bacteria [21]. Although fructo-oligosaccharides and galacto-oligosaccharides are the most commonly used prebiotics, nowadays, studies revealed that dietary polyphenols could also promote the growth of beneficial commensal bacteria in the gut [22]. It should be noted that probiotics are not necessarily effective on the composition of gut microbiota. However, it could regulate the metabolic function of gut microbiome by altering

the expression of microbial enzymes and metabolites release. Moreover, probiotics could enhance the immune functions by modulating the integrity of the intestinal barrier [21]. Human microbiome studies have tried to identify novel microbial species as next-generation probiotics to restore healthy gut microbiota and treat obesity [23]. Next-generation probiotics developed exclusively for pharmaceutical application versus traditional probiotics which have been largely included in supplements and functional foods [23]. Moreover, regarding the effects of environmental factors including climate, geography and lifestyle on gut microbiota composition, they should also be taken into consideration when selecting intervention methods for microbiota modulation [5].

Totally, growing evidence suggests that gut microbiota can regulate the homeostatic and hedonic control of food intake and potential novel anti-obesity strategies would target gut microbiota in the future. Considering the relationships between gut microbiota and microbial composition of other parts of the body, we could investigate this issue beyond the intestinal microbiota. In this regard, the mechanisms linking the gut-brain axis and the whole human microbiota should be elucidated more to provide a promising strategy for managing obesity and its comorbidities.

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Compliance with ethical standards

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