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Review

Obesity: An overview of possible role(s) of gut hormones, lipid sensing and gut microbiota

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ABSTRACT

Obesity is one of the major challenges for public health in 21st century, with 1.9 billion people being considered as overweight and 600 million as obese. There are certain diseases such as type 2 diabetes, hypertension, cardiovascular disease, and several forms of cancer which were found to be associated with obesity. Therefore, understanding the key molecular mechanisms involved in the pathogenesis of obesity could be beneficial for the development of a therapeutic approach. Hormones such as ghrelin, glucagon like peptide 1 (GLP-1) peptide YY (PYY), pancreatic polypeptide (PP), cholecystokinin (CCK) secreted by an endocrine organ gut, have an intense impact on energy balance and maintenance of homeostasis by inducing satiety and meal termination. Glucose and energy homeostasis are also affected by lipid sensing in which different organs respond in different ways. However, there is one common mechanism i.e. formation of esterified lipids (long chain fatty acyl CoAs) and the activation of protein kinase C δ (PKC δ) involved in all these organs. The possible role of gut microbiota and obesity has been addressed by several researchers in recent years, indicating the possible therapeutic approach toward the management of obesity by the introduction of an external living system such as a probiotic. The proposed mechanism behind this activity is attributed by metabolites produced by gut microbial organisms. Thus, this review summarizes the role of various physiological factors such as gut hormone and lipid sensing involved in various tissues and organ and most important by the role of gut microbiota in weight management.

Abbreviations: GLP-1, glucagon like peptide 1; PYY, peptide YY; PP, pancreatic polypeptide; CCK, cholecystokinin; PKC δ, protein kinase C δ; WHO, World Health Organization; IBD, inflammatory bowel disease; T2DM, type 2 diabetes mellitus; WAT, white adipose tissue; PPARγ, peroxisome proliferator activated receptor γ; TF, transcription factor; C/EBP, CCAAT enhancer–binding proteins; GR, glucocorticoid receptor; STAT5A, signal transducer and activator of transcription 5A; CREB, cAMP-response element-binding protein; TAG, triacylglycerol; NEFAs, non-esterified fatty acids; OXM, oxyntomodulin; NPY, neuropeptide Y; fMRI, functional magnetic resonance imaging; OFC, orbital frontal cortex; VTA, ventral tegmental area; GOAT, gastric o-acyl transferase; BMI, body mass index; GHS-R1a, GH-secretagogue receptor 1a; HIV, human immunodeficiency virus; CNS, central nervous system; BAT, brown adipose tissue; RBP-4, retinol binding protein-4; COX, cyclooxygenases; LOX, lipoxygenases; PGE2, prostaglandin E2; PGF2 α, prostaglandin F2 α; ECS, endocannabinoid system; IR, insulin resistance; VLDL, very low-density lipoprotein; CTMP, C terminal modulator protein; LETM1, leucine zipper/EF-hand-containing transmembrane protein 1; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; IL-6, Interleukin-6; FFA, free fatty acid; LPL, lipoprotein lipase; LCFA, long chain fatty acid; FATP1, fatty acid transfer protein 1; PPRE, peroxisome proliferator response element; FABP4, fatty acid binding protein 4; PKA, protein kinase A; PEPCK, phosphoenolpyruvatecarboxy kinase; PDH, pyruvate dehydrogenase; PDK 4, pyruvate dehydrogenase kinase 4; G3P, glycerol-3-phosphate; GK, glucokinase; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; CD36, cluster determinant 36; ACS3, acyl-CoA synthetase-3; CCKAR, CCK A receptor; OAG, 1-oleoyl-2-acetyl-sn-glycerol; GIT, gastrointestinal tract; SCFA, short chain fatty acids; GPCRs, G protein–coupled receptors; HFD, high fat diet; NAFLD, non-alcoholic fatty liver disease; DNL, *de novo* lipogenesis; LPS, lipopolysaccharides; TLR-4, toll like receptor-4; FAO, Food and Agriculture Organization.

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1. Introduction

According to the World Health Organization (WHO), episode of obesity has more than doubled since 1980. In 2014, over 1.9 billion adults, 18 years and older, were overweight, including 600 million obese. About 39% of adults aged 18 years and above were overweight in 2014, and 13% were obese. Most of the world's population lives in countries where overweight and obesity kill more people than underweight [1]. The above mentioned data suggest that obesity presents an ever increasing threat to global health. Thus it becomes important to look into the different factors such as diet, physiological responses to diet, lifestyle and majorly the role of microbiome constituent of the individual in the regulation of body weight and maintaining energy homeostasis. The role of the GI tract as the largest endocrine organ and its secretion of several gut hormones such as ghrelin, cholecystokinin (CCK), peptide YY(PYY), and glucagon like peptide-1 (GLP-1) plays a vital role in maintaining energy balance and body weight regulation. Elevation of lipid affects the energy and glucose homeostasis. Different organs such as gut, brain and liver respond in different ways, through several biochemical, molecular, neuronal and physiological responses that alter appetite and hepatic glucose production [2]. The factors responsible are ambiguous but the formation of esterified lipids (long-chain fatty acyl-CoAs) and the activation of certain protein kinases (PKC δ) are involved in these organs [2]. Thus it becomes important to examine the role of lipid sensing in different organs and to study their effect on obesity.

Gastrointestinal microbes play a very important role in human health and diseases. The human intestine is the home for complex plethora of microbes ranging from 10^{13} to 10^{14} microbial cells [3,4]. These gut flora have a wide metabolic activity associated with it and can be truly termed as a virtual organ within an organ [5]. The major functions associated with these commensals are protective, structural and metabolic functions. The protective functions include development of humoral components of the gut mucosal immune system [4,5] and modulating development of T-cell repertoires [6,7]. The structural functions include the barrier fortification and apical tightening to tight junction [5,8]. The metabolic activity associated is both adaptable and renewable [8]. There is now enough evidence to suggest that dysregulation of normal flora might give rise to many inflammatory diseases such as obesity, inflammatory bowel disease (IBD), type 2 diabetes mellitus (T2DM), arthritis and cancer [9]. Obesity is a major disease caused due to dysbiosis of gut microbiota and energy imbalance. This review also focuses on the mechanism associated with physiological action of lipids in face of excessive fat exposure and leading to impaired signaling pathways controlling food intake and energy balance, assessing the role of probiotics in gut microbiota modulation along with lipid signaling involved in various organs. The role of beneficial bacteria such as probiotics in maintaining homeostasis will also be evaluated [9].

2. Cellular Mechanism Involved in Obesity

The accumulation of white adipose tissue (WAT) leads to the development of several metabolic disorders including obesity [10]. Obesity is the result of imbalance between energy intake and its expenditure. There are two possibilities associated with the fat mass accumulation, either adipogenesis or an increase in the size of adipocytes [11].

2.1. *Adipogenesis*

The differentiation of pre-adipocytes into mature adipocytes which is also known as adipogenesis has been extensively investigated particularly by using murine 3T3-L1 preadipocyte cell line [12]. There are several temporal cascades which are required for the differentiation of adipocytes. Among them, peroxisome proliferator activated receptor γ (PPARγ) is considered as the band master of cascade orchestra for adipocyte differentiation [12–14]. Thus adipogenesis proceeds through the activation of at least two waves of transcription factors (TFs) (Fig. 1). The first is induced directly by the adipogenic cocktail, and includes TFs such as the CCAAT enhancer–binding proteins C/EBP β and δ—as well as the glucocorticoid receptor (GR), signal transducer and activator of transcription 5A (STAT5A), and the cAMP-response element-binding protein (CREB). These factors in turn activate TFs of the second wave, which initiate the adipocyte gene program. The major player of the second wave includes PPARγ2 and C/EBPα [15,16].

2.2. *Lipid Storage*

The fate of lipid in a mature adipocyte has a major influence on obesity. The storage of lipid in a mature adipocyte is the result of four distinct processes which includes uptake of metabolic substrate, lipogenesis, lipolysis and lipid export [11]. As far as metabolic substrate is concerned the primary substrates utilized by adipocytes include glucose, triacylglycerol (TAG) and non-esterified fatty acids (NEFAs) [17]. The process of lipogenesis involves both imported and newly synthesized NEFA, which serve as a substrate for conversion into stored TAG droplets, which are further stabilized by associating with perilipin [18], and combine to form a storage depot. The action of lipolysis is associated with lipases and this occurs with the dissociation of perilipin from the lipid droplet which allows the cytosolic lipases to perform its function [18], producing diacylglycerol and monoacylglycerol as a result of sequential breakdown of stored TAG. However the export of NEFA is not fully understood but appears to involve the action of one or more membrane bound flipper proteins [19,20]. Thus the increased fat mass as a result of lipid accumulation may result from increased substrate uptake, increased lipogenesis, decreased lipolysis, decreased export or any combination of these processes.

3. Gut hormones and Obesity

The GI tract is the largest endocrine organ secreting more than 20 different hormones in the body. Gut hormones perform various roles which include digestion and absorption along with the prime role of nutrient uptake. These have fine tuning between appetite and energy expenditure through