Microbiota-derived Short-Chain Fatty Acids and Obesity

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Microbiota-derived Short-Chain Fatty Acids (SCFAs), primarily acetate, propionate and butyrate, are metabolites produced by gut microbiota via dietary non-digestible carbohydrates (CHO) fermentation. Maternal very low-calorie ketogenic diet (VLCKD) during pregnancy and lactation stimulates the growth of diverse species of SCFA-producing bacteria, which may induce epigenetic changes in infant obese gene expression and modulate adipose tissue inflammation in obesity.

Keywords: VLCKD ; infant gut microbiota ; obesity ; adipose tissue ; SCFAs ; pregnancy ; lactation

1. Introduction

SCFAs play a significant role in CHO and lipid metabolism. Butyrate and acetate are used as precursors for lipid synthesis (cholesterol, long-chain fatty acids), whereas propionate is used as precursor for hepatic gluconeogenesis [1][2]. Lactate is an organic acid produced by *Bifidobacterium* and lactic acid bacteria (LAB), which acts as an intermediate metabolite and a substrate for butyrate formation [2][3].

There is a potential synergistic effect of butyrate with very low-calorie ketogenic diet (VLCKD) in inducing ketosis [4]. βOHB is produced in the liver from free fatty acids (FFAs) during fasting or starvation and serves as a transporter of fuel to peripheral tissues [5]. βOHB and butyrate share a degree of function and structure similarity. They have a wide range of cellular signalling roles, including regulate gene expression by epigenetic modifications, lipid metabolism and gut homeostasis [5][6][7], and their actions have therapeutic potential in many diseases such as obesity [8] and asthma [9].

The gut microbiota is a critical component during pregnancy and lactation where maternal diet may influence both the mother's and the infant's gut microbiota diversity and richness [10][11]. A well-planned diet including a variety of protein-rich plant foods, dietary fibre and omega-3 polyunsaturated fatty acid (PUFA) during pregnancy and lactation is recommended [12], which may tend to produce high amounts of fecal SCFAs by SCFA-producing bacteria [10][13]. Maternal intake of protein, high fat and omega-3 PUFA may influence the infant gut microbiota through the epigenetic mechanisms for histone acetylation and DNA methylation [14][15]. Maternal gut microbiota and its metabolites, in which SCFAs are the major products generated by the fermentation of microbiota-accessible carbohydrates (MACs), may exert regulatory effects on host energy metabolism [16][17] and the infant immune system [16][18][19]. Breast milk constitutes the main source of seeding microbes in the neonate gut [20]. It plays a key role for vertical transmission of microbes from mother to infant via the entero-mammary pathway. This route proposes that microbiota can be transferred from the maternal gut lumen by dendritic cells (DCs) to the mammary glands through the blood/lymphatic systems, and then move to the newborn and subsequently colonize the gut [21][22]. SCFA-producing gut bacteria have the ability to stimulate SCFA production in breast milk via the systemic circulation [23], which in turn enters the infant intestinal tract through the breast milk [9].

Childhood obesity has become one of the most significant global health challenges over the last decades [24]. Unfortunately, the prevention of obesity may need to be addressed at its origin, which is complex and multifaceted with no single factor domain as a determinant. The range of contributing factors comprise epigenetics, genetics, parental/infant body mass index (BMI), smoking during pregnancy, early antibiotic use, birth by caesarean section, an unhealthy diet, formula feeding and microbiota [25][26][27][28][29][30]. Among these, the infant gut microbiota has received great interest in the past few years. Infancy is a key period in the development of the gut microbiota, with the colonization rate of commensal species increasing after birth [31]. However, obesity influences gut microbial diversity and composition and may lead to dysbiosis, which dysregulates metabolic homeostasis [32]. Gut microbiota composition varies greatly between obese and non-obese infants. Epidemiologic evidence from infant studies has demonstrated lower proportions of SCFA-producing bacteria such as *Bifidobacterium* and *Bacteroides* spp. in the gut microbiota of obese children compared to lean counterparts [25]. Furthermore, infants of obese mothers have significant alterations in their gut microbiota composition, which may lead to a later-life obesity risk. The transmission of obesogenic microbes from mother to infant has the greatest

potential for childhood obesity, with a higher abundance of fecal *Lachnospiraceae* (e.g., *Coprococcus*, *Ruminococcus*) in vaginally and emergency cesarean-delivered infants which mediated the association between maternal overweight/obese and childhood obesity at ages 1 and 3 years [33].

Adipose tissue (AT) is known to be the main contributor to immune dysregulation, metabolic diseases and low-grade chronic inflammation during obesity [34]. AT macrophages represent the major component of C-C motif chemokine ligand-2 (MCP-1) and tumor necrosis factor-alpha (TNF-α) in AT and upregulate of Interleukin (IL-6) expression, where they can induce inflammatory changes in adipocytes [35]. Pregnancy and early infancy are critical periods of increased oxidative stress (OS) and pro-inflammatory cytokines levels [36][37][38][39]. OS plays a significant role in the development of obesity and its related diseases, in which the role of dysfunctional AT is involved [40]. OS results from the shift in the balance between the reactive oxygen species (ROS)-generating systems (e.g., nitric oxide synthase) produced by mitochondria and the capability of the antioxidant system to detoxify them [41].

A high-fat maternal diet during pregnancy has been shown to cause dysbiotic gut microbiota in infants, which has been linked to obesity, leading to developmental programming that can contribute to obesity-associated chronic inflammatory diseases. Additionally, maternal high-fat diet-induced obesity during lactation may alter breast milk microbiota composition, which may in turn contribute to infant gut dysbiosis and increase obesity susceptibility later in life [10]. While an obesogenic diet or obesity during pregnancy and lactation have a significant influence on the infant gut microbiota changes, human studies linking these alterations with an increased risk of childhood obesity are controlled for potential maternal life factors such as mode of feeding, antibiotic use and mode of delivery [10]. Therefore, a better understanding of how gut dysbiosis might induce obesity in early life is needed. Indeed, the mechanisms by which VLCKD could modify obesity risk in early life remain to be understood. The maternal VLCKD composition during pregnancy and lactation may influence the infant gut SCFA-producing bacteria [9], which play key roles in regulating glucose homeostasis, appetite, inflammatory response and the immune system [42][43]. Nutritional ketosis induced by VLCKD has a suppression effect on hunger and appetite [44], in which appetite-regulating gut hormones promote weight loss, increase circulating FFAs, reduce food intake and regulate energy homeostasis [44][45], through an increase of hypothalamic malonyl-CoA cellular levels [46]. The VLCKD during pregnancy and lactation may include olive oil, coconut oil, butter, cream cheese, sour cream, eggs, fish, lamb, ham, beef, poultry, low-CHO nuts and non-starchy vegetables [47][48][49], which are potential sources of dietary fibre, protein, polyphenols, saturated fatty acid (SAT), monounsaturated fatty acid (MUFA) and PUFA. SCFAs are involved in the mechanism linking the VLCKD during pregnancy and lactation to the infant gut microbiota, which may modulate allergic asthma in infants [9]. Given the fact that SCFAs influence obesity-related asthma [50], it is perhaps the case that SCFAs from VLCKD-infant gut microbiota interactions may have potential therapeutic implications for reducing obesity.

2. Ketone Bodies and SCFAs as Epigenetic Modifiers in Obesity

Epigenetic changes constitute the key contributing factor of obesity during early development [30][51], in which heritable changes in gene expression result from histone modifications, DNA methylation and non-coding RNAs, without modifying the DNA sequence [52]. Genetic and/or environmental factors (e.g., nutritional changes, metabolic surgery, exercise) are thought to drive these epigenetic changes, in which several obesity-related traits, revealing cytosine-phosphate-guanine dinucleotides (CpG)-related sites (e.g., GNASAS1, MEG3, INSIGF2) are involved in altering DNA methylation in blood cells of the offspring [30]. Exposure to low a glycaemic index diet among obese pregnant women has been shown to induce DNA methylation changes at 771,484 CpG sites located in NFIC, TBCD and IL17D genes in the offspring cord blood [53]. Maternal obesity and high-fat intake during gestation may affect trans-generational epigenetic modifications. This is achieved through DNA methylation and chromatin alterations in adipogenic gene transcription, in which key epithelial to mesenchymal transcription (EMT)-related transcription factors (Slug, Zeb1, Zeb2, Snail, Twist) are involved, leading to increased obesity risk in the fetus [54]. Pre-and postnatal high-fat diets alter the gut microbiota in the offspring as well as DNA methylation and histone modification that result in changing adipogenesis-related gene expression such as adiponectin, leptin and peroxisome proliferator-activated receptor (PPAR-γ), leading to increase obesity and metabolic diseases later in life [55]. A few human studies investigating the epigenetic changes of early postnatal nutrition showed thatCpG3 methylation of leptin (LEP) and retinoid X receptor alpha (RXRA) obesity-related genes in infants are increased or decreased, depending on the duration of breastfeeding, and as a result, activate the PPAR-induced DNA demethylation in WAT, which drives changes in breast milk fatty acid (BM FA) composition [56]. A long-term folic acid supplementation of 400 µg/day (>6 months) and the dietary intake of betaine in pregnant and/or lactating women are shown to increase cord blood LEP and RXRA methylation in infants [57][58]. However, the impact of other dietary and supplemental methyl-group donors on these methylation changes have not yet been studied, given that methyl-donor intake through diet and supplementation may alter DNA methylation patterns in gene and disease susceptibility in humans [59][60].

Pregnancy and lactation are characterized by increased markers of OS and inflammation [36][37][38][39]. OS is induced by obesity in pregnancy, which may cause decreased fertility and increased miscarriage risk [38]. The OS markers, superoxide anion, nitric oxide, carbonyl proteins and malondialdehyde, have been observed in obese pregnant women, which leads to impact fetal redox balance [36]. The OS marker, 8-hydroxy-deoxyguanosine (8OHdG), along with lactose concentrations in breast milk, are found to be associated with a weight-for-length Z-score (WLZ) trajectory among infants of lactating overweight/obese women [37]. Increased breast milk inflammatory cytokines (IL-8, IL-6, and IL-1β) have been found to be associated with increased weight gain in infants [39]. The βOHB, a surrogate marker of liver ketogenesis, has been shown to regulate gene expression by inhibiting histone deacetylases (HDACs) and activating G-protein coupled receptors (GPCRs), and this may contribute to protection against OS and increased histone acetylation by inducing gene expression of Metallothionein 2 (Mt2) and forkhead box (Foxo3a) that encode oxidative stress resistance [61]. Under prolonged fasting, histone lysine β-hydroxybutyrylation (kbhb), a type of histone post-translational modification, which regulates gene expression, is increased in human embryonic kidney 293 (HEK293) cells as a result of βOHB level elevation [62][63]. Administration of βOHB on the human gut microbiota has been found to be associated with increased butyrate and SCFAs (sum of propionate, succinate, acetate, lactate and butyrate) production [64]. Butyrate promotes histone acetylation, inhibits HDACs activity in HEK293 cells, and suppresses lipopolysaccharide (LPS)-induced pro-inflammatory gene production in human adipose microvascular endothelial cells (HAMEC), including C-C motif chemokine ligand (CCL2), IL-6, IL-8, and IL-1β [63]. It has been shown that HEK293 cells are transiently transfect with the mutant melanocortin 4 receptor (MC4R) [65][66], a rhodopsin-like GPCR expressed in the hypothalamic pro-opiomelanocortin (POMC) neurons and the gene most commonly linked to obesity [67], which is located on chromosome 18q21.31at an early age [68]. MC4R mutant variant dysfunction may decrease ligand binding and expression of the receptor at the cell surface, with a reduction in MC4R agonist α-melanocyte-stimulating hormone (α-MSH)-induced cyclic adenosine monophosphate (cAMP) production, resulting in increased obesity and hyperphagia [65][66]. Leptin and insulin act on anorexigenic POMC neurons by signalling via its receptors to increase melanocortins and inhibit the orexigenic agouti related neuropeptide (AgRP)/neuropeptide Y (NPY) neurons, resulting in enhanced processing of POMC to α-MSH, decreased food intake and enhanced energy expenditure [69]. In diet-induced obesity, elevated activation of inflammatory pathways such as nuclear transcription factor-kappaB (NF-kB) and inhibitors of nuclear factor kappa-B kinase β (IKKβ) induce levels of suppressor of cytokine signaling-3 (Socs3) mRNA in POMC neurons and disrupt leptin/insulin signalling, leading to the development of insulin/leptin resistance in obesity [69][70]. SCFAs, and in particular acetate and propionate, influence intestinal epithelial cells through binding to FFA2/GPR43 and FFAR3/GPR41 expressed in AT in humans [71][72], leading to inhibition of signalling to the orexigenic hypothalamic neurons through systemic circulation by stimulating the secretion of key gut hormones, including glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) [72][73][74], which indirectly regulate food intake and energy expenditure by increasing leptin and insulin secretion in adipocytes [72][73]. Taken together, βOHB and SCFAs act as potent epigenetic modifiers and exert anti-obesity effects providing a potential target in the treatment of obesity-induced inflammation and OS in children through interactions of leptin and insulin signalling in hypothalamic neurons, leading to regulated food intake and energy expenditure.

3. Conclusions

The VLCKD has been proven effective as a restricted dietary pattern for treating obesity. However, its influence during pregnancy and lactation on SCFA-producing bacteria in infant gut microbiota and its mechanisms of action in the treatment of obesity are still unknown. Low CHO, high-fat and moderate-protein in a VLCKD regimen would be beneficial to maintain a continuous state of ketosis. Maintaining a nutritional ketosis is characterized by increased levels of ACA and βOHB in the blood, which are the main KBs that serve as energy sources during periods where CHO stores are reduced in the liver. The βOHB and SCFAs can influence epigenetic changes in infant obese gene expression and exert potential anti-obesity and anti-inflammatory effects by targeting obesity-associated inflammation via interactions of the hypothalamic appetite-regulating hormones leptin and insulin.

SCFAs appear to be the key microbial metabolites mediating VLCKD-infant gut microbiota relationships. Further studies would be needed to assess the safety of VLCKD during pregnancy and lactation to illuminate its potential influence on infant gut SCFA-producing bacteria.

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