Ketone Bodies as Epigenetic Modifiers

Subjects: Nursing

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Ketogenesis and ketolysis are the main regulatory metabolic pathways of ketone bodies (KBs). These pathways are active during conditions like adherence to ketogenic diet or starvation, where carbohydrates availability is reduced, or fatty acid levels are increased. Epigenetic changes are influenced by KBs, and in particular βOHB, which regulates cellular processes through epigenetic mechanisms, and therefore serves as a strong epigenetic modifiers and exerts its anti-inflammatory effect providing potential targeted therapy in asthma.

Epigenetic Modifiers | Ketone Bodies | Asthma

1. Introduction

Low carbohydrate diets (LCDs) can be highly heterogeneous in terms of carbohydrate (CHO) content and quality, with no consensus on its precise definition [1], and for this reason it is difficult to interpret comparisons of results between studies. The very low-calorie ketogenic diet (VLCKD), a popular type of LCD, is similar to the modified Atkins regime in terms of restricting CHO while emphasizing a high-fat regimen [2]. As the VLCKD seems to be an area of growing interest in preventing and treatment of several diseases [3][4][5][6][7][8], evidence of its effect on the gut microbiota is inadequate and still ongoing in animal models and humans [9]. In fact, thevery low-calorie diet (VLCD) contributes to gut microbiota remodelling in humans [10], and "keto microbiota," which refers to a gut microbiota shaped by a ketogenic diet (KD), and may play a major role in enhancing the response of the host to therapy [11]. The low CHO, adequate protein and high-fat KD has been found to be associated with increased beneficial gut microbiota-related profiles including *Bacteroidetes* phylum in children with refractory epilepsy. However, this increase occurs with respect to reducing the overall microbial diversity, probably due to the low CHO content of the diet, which can disrupt the abundance of other beneficial microbiota responsible for degrading complex CHO [11].

The symbiotic relationship that has evolved between humans and their gut microbiota provides several benefits for humans, including regulating host immunity, producing vitamins K and B, protecting against pathogens, strengthening gut integrity and producing metabolites such as short chain fatty acids (SCFAs) [12]. The composition of the infant gut microbiota is driven by several factors, such as mode of delivery and feeding, maternal antibiotic use and nutrition and body mass index (BMI) [13]. The stability of the gut microbiota, reached between 2 to 18 years of age, is varied by phylum, with *Bacteroidetes* exhibiting the highest temporal stability [12].

2. Ketone Body Metabolism

The main metabolic pathways for ketone body metabolism include ketogenesis and ketolysis. Adherence to KD causes the body to enter the ketogenesis pathway to produce three main KBs: βOHB, acetoacetate (ACA) and acetone (least abundant) [14]. Ketogenesis takes place in the mitochondrial matrix of hepatocytes, where free fatty acids (FFAs) are released from adipose tissue during lipolysis under low insulin conditions, along with stimulating catecholamines, cortisol, glucagon and growth hormone secretion. FFAs are broken down via β-oxidation to acetyl-coenzyme A (acetyl-CoA), which is used as a precursor for the production of βOHB and ACA [14][15]. These are released into the circulation for use in extrahepatic tissues via the monocarboxylate transporter 1 (MCTI1), where the ketolysis process takes place. Once taken up by target tissues, βOHB is transformed to ACA via βOHB dehydrogenase (βDH) and ACA is transformed back to acetyl-CoA viaβ-ketoacyl-CoA transferase (βCT). Acetyl-CoA then goes through a thetricarboxylic acid (TCA) cycle to generate nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) via the oxidative phosphorylation pathway to produce adenosine triphosphate (ATP) [14][16]. The ketogenesis and ketolysis pathways are also active during starvation/fasting [14][17][18][19], and the periods of pregnancy and childbirth [17][20], where CHO availability is significantly diminished, or fatty acid levels are increased.

3. Ketone Bodies as Epigenetic Modifiers in Asthma

Epigenetic changes constitute the key regulator of gene expression and cellular metabolism, and their dysregulation may contribute to several diseases [21], including childhood asthma [22], where changes may start in utero following prenatal environmental exposures (e.g., maternal smoking, allergen, dietary supplements) or during early life [23]. Epigenetic changes in breastfed infants, particularly changes in DNA methylation patterns, may be influenced by breastfeeding, but further studies are needed to explore the role of epigenetic mechanisms in the associations between breastfeeding and asthma [24]. DNA methylation, non-coding RNA and histone modifications are the most common epigenetic mechanisms existing in childhood asthma, which can regulate gene expression through effects on chromatin structure and contribution to gene silencing [25][26].

Epigenetic changes are influenced by KBs [11], and the βOHB not only regulates cellular processes such as signaling metabolites [27], but also influences the gut microbiota and increases butyrogenesis [28], in which epigenetic mechanisms are involved [29][30]. Ketosis has been linked to epigenomic reprogramming and displays as covalent KB-induced histone post-translational modifications, including histone methylation (Kme), histone/lysine acetylation (Kac) and β-hydroxybutyrylation (Kbhb), which regulate chromatin architecture and gene expression during adherence to KD, DKA and fasting ketosis [31]. Kac and Kbhb consider the key epigenetic mechanisms for activation of βOHB to modulate immune cell function and inflammation [32]. The βOHB, an endogenous histone deacetylase (HDACs) inhibitor, has a well-known protective role against oxidative stress. In animal models, adherence to KD, which increases βOHB levels, is associated with increased histone Kac at the promoter regions of the forkhead box (Foxo3a) and metallothionein 2A (Mt2), which targets oxidative stress resistance genes activated by HDAC class I and II inhibitors [31][32][33]. In response to high levels of βOHB, histone Kbhb levels with site-specific lysine residues (H3K4, H4K8, H3K9, H4K12, H3K56) are elevated significantly in human embryonic kidney 293 (HEK293) cells during prolonged fasting, suggesting that lysine Kbhb at these residues regulates

chromatin structure and functions [29]. HEK293 cells are found to transiently transfect with ORM (yeast)-Like protein isoform 3 (ORMDL3) mRNA expression, an asthma susceptibility gene located on chromosome 17q21 in children [34]. ORMDL3 suppresses the sarco-endoplasmic reticulum Ca^{2+} pump (SERCA) leading to a decreased endoplasmic reticulum (ER) Ca^{2+} concentration and activating unfolded-protein response (UPR) signaling pathway [35]. This pathway can induce increased expression of chemokines, metalloproteases and activating transcription factor (ATF6) in lung epithelial cells, which are involved in the pathogenesis of asthma [36]. βOHB suppresses inflammation via inhibition of protein expression of ER stress response pathway (known as UPR). It also enhances both Foxp3 and manganese superoxide dismutase (MnSOD) transcription through AMP-activated protein kinase (AMPK) activation, a cellular energy sensor which regulates energy homeostasis, leading to a reduction in the level of cellular oxidative stress [37]. This suggests that βOHB may regulate histone Kbhb and protect HEK293 cells against oxidative stress via suppressing ER stress. Taken together, βOHB acts as a potent epigenetic modifier and exerts its anti-inflammatory effect providing potential targeted therapy in asthma through mechanisms for epigenetic regulation.

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