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Review

Whole cereal grains and potential health effects: Involvement of the gut microbiota

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ABSTRACT

The intakes of whole cereal grains (WCGs) have long been linked to decreased risks of metabolic syndromes (MetS) and several chronic diseases. Owing to the complex range of components of cereals, which may show synergistic activities to mediate these protective effects, the mechanisms by which the benefits of whole cereals arise are not fully understood. The gut microbiota has recently become a new focus of research at the intersection of diet and metabolic health. Moreover, cereals contain various ingredients known as microbiota-accessible substrates that resist digestion in the upper gastrointestinal tract, including resistant starch and non-starch polysaccharides such as β-glucan and arabinoxylans, making them an important fuel for the microbiota. Thus, WCGs may manipulate the ecophysiology of gut microbiota. In this review, the scientific evidence supporting the hypothesis that WCGs prevent MetS by modulating gut microbiota composition and functions are discussed, with focuses on cereal intake-related mechanisms by which gut microbiota contributes to human health and scientific evidences for the effects of WCGs on modulating gut microbiota. Once strong support for the association among WCGs, gut microbiota and host metabolic health can be demonstrated, particular cereals, their processing technologies, or cereal-based foods might be better utilized to prevent and possibly even treat metabolic disease.

1. Introduction

In a range of countries dietary guidelines recommend increased consumption of whole cereal grains (WCGs) (Mckeown et al., 2013). Consumption of WCGs has repeatedly been linked to improvements of metabolic syndrome (MetS), a cluster of several metabolic diseases including obesity, dyslipidemia, hypertension and hyperglycaemia or Type 2 diabetes, for which an epidemic is developing worldwide (Rebello, Greenway, & Finley, 2014). Whole cereal foods help prevent or reduce MetS in humans and animal models, but the demonstration of causality in this regard remains a challenge as the benefits of WCGs intake can be mediated by one or more mechanisms (Rebello et al., 2014). Compared with refined cereal grains, WCGs are rich in several potentially bioactive compounds found in the bran, the outer part of the grain (Liu, 2007; Vrieze et al., 2012). WCGs foods consist of dietary fibers, minerals, polyphenols, phytosterols and vitamins, which could show synergistic activities to mediate the protective effects via diverse mechanisms (Rosa-Sibakov, Poutanen, & Micard, 2015).

Owing to recent advances in 'omic' technologies, the available data on the composition and functions of the gut microbiota have increased exponentially over the last 10–15 years. Growing evidence has revealed that the composition and richness of the gut microbiota are linked to MetS in humans, such as diabetes, obesity, and insulin resistance. For example, compared with individuals with high bacterial richness, individuals with low taxonomic richness (23%–40% of the population) are characterized by more marked overall adiposity, insulin resistance and dyslipidemia and a more pronounced inflammatory phenotype (Le Chatelier et al., 2013). Furthermore, the composition of the gut microbiota in human may be altered in obese individuals relative to that in lean ones such as a change in the Firmicutes to Bacteroidetes ratio, and these changes are transmissible. Turnbaugh et al. (2006 & 2008) demonstrated that the colonization of germ-free mice with gut

Abbreviations: AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; ANGPTL4, angiopoietin-like protein 4; AX, arabinoxylan; CAZymes, carbohydrate active enzymes; CBMs, carbohydrate-binding modules; CVD, cerebrobascular disease; ERs, estrogen receptors; IL, interleukin; LPS, lipopolysaccharide; MetS, metabolic syndrome; FFA, free fatty acid receptor; FIAF, fasting-induced adipose factor; FXR, farnesoid X receptor; TGR5, G-protein-coupled bile acid receptor Q; GHs, glycoside hydrolases; GLP-1, glucagon-like peptide-1; GPR, G-protein-coupled receptors; HDAC, histone deacetylase; HDL, high-density lipoprotein; IGN, intestinal gluconeogenesis; LPL, lipoprotein lipase; MAPK, mitogen-activated protein kinases; MW, molecular weight; OXM, oxyntomodulin; PPARγ, peroxisome proliferator-activated receptor gamma; PYY, peptide YY; RS, resistant starch; SREBP-1c, sterol response element-binding protein-1; WCGs, whole cereal grains; NSPs, non-starch polysaccharides; SCFA, short chain fatty acid

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microbiota from obese donors led to a significant increase in body fat content and insulin resistance. They also found that the obese microbiome had stronger capacity to harvest energy from the diet (Turnbaugh et al., 2006; Turnbaugh, Bäckhed, Fulton, & Gordon, 2008). On the other hand, a 6-week energy-restricted high-protein diet led to an increase in gene richness in the low gene count subjects. Interestingly, the increase of gene richness was associated with an improvement of the systemic metabolic status, including significant decrease in hip circumference, total fat mass, circulating cholesterol as well as a trend towards a decrease in highly sensitive C-reactive protein (Cotillard et al., 2013). The gut microbiota transplantation from healthy donors to obese human volunteers might improve the systemic insulin sensitivity within 6 weeks (Vrieze et al., 2012). In addition, genetically obese mice treated with antibiotics (ampicillin plus neomycin) showed a surprising change in the composition of microbiota and decreases in body weight and insulin resistance (Hernández et al., 2013). These outcomes suggest that the gut microbiota composition and activities associated with host metabolism and related disorders. Thus, approaches focusing on gut microbiota offer possible new routes for therapeutic interventions.

Here, we review our understanding of how WCGs can alter the composition and function of the gut microbiota in humans and other mammals. We will refer to both WCGs involved mechanisms of gut microbiota contributed to human health and to the in vitro and in vivo studies with animals and human subjects assessing impact of WCGs on gut microbiota.

2. WCGs bioactive components

The health benefits of consuming WCGs are often described as being related to their dietary fiber content. However, in addition to fiber, bioactive phytochemicals such as phenolic compounds, sterols, tocols and lignans are also abundant in WCGs (Derrien & Veiga, 2017; Liu, 2007, 2009).The most important bioactive components that have been reported to modulate gut microbiota are phenolic compounds and dietary fibers such as resistant starch (RS), β-glucan and arabinoxylans (AX). The previously reported data clearly show obvious that the content and composition of bioactive ingredients including dietary fiber and bioactive compounds vary greatly among different cereals as well as different cereal genotypes.

RS concentrations in native cereals range from 0.18 g/100 g dw (wheat) to 65.66 g/100 g dw (sorghum), depending on the species, method of flours preparation and processing conditions (Louis et al., 2004). Indeed, native cereal grains appear to contain more rapid digestive starch and slow digestive starch than RS. However, physical or chemical treatments may alter the level of RS in cereal foods or ingredients (Louis et al., 2004).The formation of RS during processing is affected by various factors including water content, pH, heating temperature and time, heating or cooling cycles, and the presence of additives such as oil and salts (Alsaffar, 2015). AX is the major non-starch polysaccharide of rye (3.11–4.31 g/100 g dw) and wheat kernel (1.2–6.8 g/100 g dw) (Fardet, 2010; Nyström et al., 2008). β-Glucans are major structural components of the endosperm cell wall of cereals, in particular barley (3.7–6.5 g/100 g dw) and oat (2.3–8.5 g/100 g dw) (Derrien & Veiga, 2017; Shewry et al., 2008). Rye contains the highest fructan levels (3.6–6.6 g/100 g dw) among cereal varieties. Lower fructan concentrations are generally found in barley grains and oat grains (Verspreet, Dornez, Ende, Delcour, & Courtin, 2015).

In addition to dietary fiber, the main bioactive components found in cereals are phenols, sterols, tocols and betaine. Cereals contain significant amounts of polyphenols (3–1459 mg/100 g dw), especially flavonoids and phenolic acids such as ferulic, *p*-coumaric, vanillic, caffeic, and sinapic acids. Among the different WCGs, wheat is a good source of polyphenols (< 1459 mg/100 g dw) (Anthony, Edmond, & Christian, 2008; Fardet, 2010), while sorghum (3–43 mg/100 g) and oat (9–34 mg/100 g) have lower levels of them. The concentrations of phenolic acids range from 100 to 1080 μg/100 g dw, depending on the type of cereal with the exception of rice, which has very low levels of them. However, rice is rich in flavonoids (43.1–219.8 mg/100 g grain) compared with other cereals (Fardet, 2010; Shewry et al., 2008; Taylor, Belton, Beta, & Duodu, 2014). Alkylresorcinols, a mixture of phenolic lipids in several but not all whole cereals, are specifically present in rye (570–3220 μg/100 g) and wheat (200–750 μg/100 g) at significant levels (Fardet, 2010).Cereals are a moderate source of tocols and folate as they contain from 0.05 to 38.69 mg tocols/100 g and 0.01 to 0.8 mg folate/100 g. However, sorghum (22.07–38.69 mg/100 g) is a better source of tocols than other cereals. In addition, rye (0.55–0.80 mg/100 g) and barley (0.50–0.80 mg/100 g dw) are good sources of folates (De Morais, Pinheiro, Martino, & Pinheirosant'Ana, 2017). Moreover, WCGs are a rich source of sterol and betaine, which rice and sorghum have lower sterol contents. Other cereals (wheat, barley, oat and rye) have sterol contents that are similar to each other (57–115 mg/100 g dw).Wheat, barley and oat are significant sources of betaine but the amount varies significantly with the variety (11.3–291 mg/100 g dw) (Fardet, 2010).

These compounds may exhibit different health benefits via: 1) metabolized by gut microbiota directly into functional metabolites as listed in Table 1; and 2) modulate gut microbiota composition which may influence the metabolism of dietary ingredients both from cereal and non-cereal foods. In the next sections, the cereal intake- related mechanisms by which gut microbiota contributes to MetS are introduced.

3. WCGs components intake-related microbial metabolites and remodeling

3.1. Dietary fiber

Cereal-based dietary fiber that resist digestion in the upper GI tract including, RS and non-starch polysaccharides (NSPs) such as β-glucan or arabinoxylans, is an important fuel for the microbiota, it could potentially manipulate the ecophysiology of the gut microbiota via their microbial metabolites, such as short chain fatty acids (SCFAs) (Table 1) (Cantarel, Lombard, & Henrissat, 2012; Chassard & Lacroix, 2013; Yang, Martínez, Walter, Keshavarzian, & Rose, 2013). Acetic acid (C2), propionic acid (C3), and butyric acid (C4) represent 90%–95% of the SCFAs present in the colon (Ríos-Covián et al., 2016). SCFAs are mainly produced by gut microbiota as a result of carbohydrate fermentation via different metabolic pathways by specific microbiota (Table 1) (Harry et al., 2015; Koh et al., 2016; Ríos-Covián et al., 2016). For example, acetate is derived from pyruvate via the acetyl-CoA pathway and the Wood-Ljungdahl pathway mainly by enteric bacteria including *Akkermansia muciniphila*, *Bacteroides* sp., *Bifidobacterium* sp., *Prevotella* sp., and *Ruminococcus* sp. as well as acetogenic bacteria such as *Blautia hydrogenotrophica*, *Clostridium* sp., and *Streptococcus* sp. (Ragsdale & Pierce, 2008); butyrate is formed from the butyrate kinase pathway and the butyryl-CoA: acetate CoA-transferase pathway by colonic bacteria classes within the Firmicutes including *Eubacterium rectale* sp., *Roseburia* sp. within the Lachnospiraceae (*Clostridium* cluster XIVa) and *Faecalibacterium prausnitzii* within the Rumncoccaceae (*Clostridium* cluster IV) as well as other genera within several *Clostridium* clusters (Louis et al., 2004); propionate is formed by Bacteroidetes and some Firmicutes bacteria within the Negativicutes (*Veillonellaceae*) via the succinate pathway, converted from lactate to propionate in the acrylate pathway by a few members of the families Veillonellaceae and Lachnospiraceae, as well as produced by the Proteobacteria phylum and members of the Lachnospiraceae family via the propanodiol pathway (Reichardt et al., 2014).

A number of studies have implied that small amounts of these SCFAs are released into the circulation, exerting a diverse array of protective effects against host obesity and MetS through at least five possible pathways as follows (Fig. 1): **1)** SCFAs in the gut tract maintain the gut