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Particle size determines the anti-inflammatory effect of wheat bran in a model of fructose over-consumption: Implication of the gut microbiota

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ABSTRACT

We investigated the impact of the particle size of wheat bran on gut dysbiosis and inflammation induced by a fructose overload. Mice received drinking water with or without fructose (30%) and a standard diet supplemented with or without 5% of wheat bran fractions characterized by different average particle sizes (1690 μm versus 150 μm) for 8 weeks. Fructose increased *Enterobacteriaceae* associated with higher expression of key inflammatory genes in the liver. The two wheat bran fractions differently affected specific gut bacteria known to be involved in the regulation of the gut barrier function and/or inflammatory processes. Moreover, wheat bran with small particle size was the sole fibre that reduced hepatic and systemic inflammatory markers upon high fructose intake. The anti-inflammatory effects of wheat bran may be dependent on their particle size and could be related to the changes in caecal *Enterobacteriaceae*.

1. Introduction

Consumption of refined sugars has increased over the past decades. In particular, the intake of sugars like fructose has increased substantially in the Western countries. This is largely through its use as a sweetener in beverages and in the diet with the production of “sweet corn-based syrups” known as “high-fructose corn syrups” (Bray, Nielsen, & Popkin, 2004; Cordain et al., 2005; Pereira et al., 2017). The overconsumption of fructose has been implicated as a contributing factor in the development of metabolic diseases such as in non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) (Lim, Mietus-Snyder, Valente, Schwarz, & Lustig, 2010; Matteoni et al., 1999; O'Sullivan et al., 2014; Vila et al., 2011). Growing evidence supports that increased intestinal permeability participates in fructose-induced development of NAFLD and chronic inflammation. In fact, the acceleration of fructolysis in the intestine may cause local inflammation and reduce tight junction proteins (such as occludin and zonula occludens 1 (ZO-1)) expression in intestine, leading to an increase in intestinal permeability (Zhang, Jiao, & Kong, 2017). Alteration in the gut barrier function results in the translocation of bacterial products like lipopolysaccharides (LPS) in the portal blood flow that leads to a condition defined as “metabolic endotoxemia” (Cani et al., 2008; Farhadi et al., 2008; Ruiz et al., 2007; Thuy et al., 2008). Furthermore, high levels of circulating inflammatory cytokines, which are often observed in fructose-fed animals or patients may impair intestinal mucosal integrity and increases metabolic endotoxemia (Zhang et al., 2017). The liver due to its anatomical links to the gut is continuously exposed to gut-derived endotoxins delivered via portal vein and thus functions as the body first line of defense (Mouzaki et al., 2013). LPS activates toll-like receptors (TLR) resulting in the stimulation of lipid peroxidation and the production of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) or interleukin-6 (IL-6), and reactive oxygen species

Abbreviations: AMP, Antimicrobial peptides; AX, Arabinoxylan; CD, Clusters of differentiation; IFN-γ, Interferon gamma; IL, Interleukin; LPS, Lipopolysaccharides; MCP1, Monocyte chemotactic protein 1; Nox1, NADPH oxidase 1; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; ROS, Reactive oxygen species; TLRs, Toll-like receptors; TNF-α, Tumor necrosis factor alpha; WBs, Wheat bran with reduced particle size; WB, Wheat bran; ZO-1, Zonula occludens-1

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(ROS) which have been implicated in the development of liver inflammation and fibrosis (Spruss et al., 2009). In particular, fructose-induced endotoxemia activates Kupffer cells via TLR4, which may be partially involved in the development of NAFLD, and subsequently trigger nuclear factor-kappa B (NF-κB) activation and TNF-α overproduction (Zhang et al., 2017). Meanwhile, ROS production also participates in endotoxin-dependent development of NAFLD. Elevation of plasma LPS and TNF-α levels of animals with high fructose diet, are blunted by treatment with antibiotic or inoculation with faecal samples from control donor rats (Di Luccia et al., 2015). Moreover, growing evidence in this context suggests that the onset of fructose-induced NAFLD is associated with the development of small intestine bacterial overgrowth and gut microbiota alteration, and is counteracted by antibiotic treatment in mice (Bergheim et al., 2008; Payne, Chassard, & Lacroix, 2012; Sabate et al., 2008; Schnabl & Brenner, 2014; Shanab et al., 2011). These findings suggest that the intestinal microbiota is one of the key components in the progression of NAFLD and hepatic inflammation (Le Roy et al., 2013; Payne et al., 2012; Spruss et al., 2009). More recently, it has been shown that high intake of fructose in humans (40 g/day) creates intestinal discomfort, linked mainly to gut fermentation, in healthy subjects and even more in patients having inflammatory bowel syndrome (Major et al., 2017). This “fructose intolerance” has been attributed to the fact that fructose is poorly digested, and can thus be fermented in the colon (Fedewa & Rao, 2014). It is well recognized that gut microbiota is considered as an environmental factor involved in the control of metabolic alterations and inflammatory disorders (Delzenne & Cani, 2011; Sonnenburg & Backhed, 2016). This bacterial community plays a pivotal role in human nutrition and health by promoting the supply of nutrients, preventing pathogen colonization and shaping and maintaining normal mucosal immunity (Baumler & Sperandio, 2016). Exciting research is now starting to unravel how the composition of the microbiota can offer either resistance or assistance to invading pathogenic species (Baumler & Sperandio, 2016).

Nutritional strategies are of growing interest as a promising tool to shape gut microbial composition, in order to improve key physiological functions in the gut, and beyond (Carmody et al., 2015; David et al., 2014). Dietary fibres, one of the most important classes of compounds in cereal grains play an important role in the control of several metabolic disturbances clustered in the metabolic syndrome (Delzenne & Cani, 2005; Fardet, 2010; Neyrinck & Delzenne, 2010). Wheat bran is a major source of dietary fibres, such as non-starch polysaccharides and lignin. Arabinoxylan (AX) is the most abundant dietary fibre in wheat bran (Broekaert et al., 2011; Neyrinck & Delzenne, 2010) and accounts for 20–30% of dry wheat bran mass, or 70% of its non-starch polysaccharides (Hemdane et al., 2016; Maes & Delcour, 2002). It is a polymer with a D-xylose backbone linked with L-arabinose. Wheat bran contains also several phytochemicals such as ferulic acid, which is the most abundant phenolic compound of the whole-grain (Vitaglione et al., 2015). It is well known that ferulic acid may be involved in anti-inflammatory effects of wheat bran or whole wheat grain demonstrated in humans (Anson et al., 2009; Mateo Anson et al., 2011; Mateo Anson, van den Berg, Havenaar, Bast, & Haenen, 2008; Vitaglione et al., 2015). Moreover, wheat bran fibre can deliver phenolic compounds into the lower gut, and the slow and continuous release of ferulic acid by the action of gut microbiota metabolism may increase circulating ferulic acid and its metabolites, thus providing an amelioration of subclinical inflammation and the long-term benefits associated with whole-grain consumption (Vitaglione et al., 2015). It is thought that processing may release bound phytochemicals from grains but the concentration and extractability of phytochemicals in relation to the exposed surface area is not well documented. However, one study demonstrated that wheat bran particle size influenced on phytochemical extractability and antioxidant properties (Brewer, Kubola, Siriamornpun, Herald, & Shi, 2014). Furthermore, particle size influences the physiological effects of wheat bran such as colonic fermentation in humans (Jenkins et al., 1999). Our previous study has demonstrated that particle size differently affects adiposity, inflammatory markers and gut microbiota composition in mice (Suriano et al., 2017). Possible beneficial effects of wheat bran fractions on gut microbiota and inflammation have never been investigated in a model of fructose overconsumption. In addition, the contribution of high fructose content to gut microbiota and gut dysfunction remains poorly explored. Therefore, the objective of this study was to evaluate in a model of fructose-induced gut dysfunction, the effects of two wheat bran fractions characterized by different particle sizes on specific gut bacteria known to be involved in the regulation of the gut barrier function and/or inflammatory processes, and to unravel how these effects may affect inflammation outside the gut.

2. Materials and methods

2.1. Animals and diet intervention

Twenty-four male C57BL6 mice (9 weeks old at the beginning of the experiment, Janvier Laboratories, France) were housed in specific pathogen free (SPF) condition in groups of 3 mice per cage in a controlled environment (12-h daylight cycle) with free access to food and water. After one week of acclimatisation, mice were divided in 4 groups (n = 6/group): a control group (CT) fed a standard diet (AIN93M, Research Diets®, composition presented in Supplementary Table 1) without supplementary sugar, a group fed a standard diet with 30% w/v of fructose (D-fructose high purity grade, VWR) in the drinking water (F group), a group fed a standard diet supplemented with 5% unmodified wheat bran (average particle size of 1690 µm) and with fructose in the drinking water (F + WB group), and a group fed a standard diet supplemented with 5% wheat bran with small particle size (average particle size of 150 µm) and with fructose in the drinking water (F + WBs group). Commercial coarse wheat (*Triticum aestivum L.*) bran was obtained from Dossche Mills (Deinze, Belgium) and it was reduced in particle size with a Cyclotec 1093 Sample mill (FOSS, Höganäs, Sweden) as previously described (Jacobs, Hemdane, Dornez, Delcour, & Courtin, 2015). The composition of the wheat bran materials including soluble fibre and insoluble fibre has been detailed in Supplementary Table S1. The free ferulic acid contents of the standard diet supplemented with WB and WBs were 2.4 mg/kg and 6.8 mg/kg, respectively whereas their Oxygen Radical Antioxidant Capacity (ORAC) were 1.98 and 2.94 mg Trolox equivalents/g, respectively (data obtained from the accredited analytical laboratory Celabor, Belgium). Food intake and water intake were recorded twice a week, and drinking water (with or without fructose) was changed twice a week. The total caloric intake was obtained by multiplying total food and water intake (g) for 3 mice per cage (n = 2) by the caloric value of the diet and fructose, i.e. 3.85 kcal/g and 4.00 kcal/g for CT and F groups, respectively, and by assuming that the mice inside the cage ate and drank the same quantities. The caloric value of the standard diet supplemented with cereal fractions was calculated considering that wheat bran fractions were completely processed by the gut microbiota into SCFA available to the host and that the maximal caloric intake through this process would be 2 kcal/g on average. After 8 weeks of dietary treatment and a 6-h period of fasting, mice were anaesthetised with isoflurane (Forene®, Abbott, Queenborough, Kent, England) before exsanguination and tissue sampling. Vena cava blood was collected in EDTA tubes and plasma was immediately collected after centrifugation (13,000*g*, 3 min) and stored at −80 °C. Mice were killed by cervical dislocation. Liver, white adipose tissues (visceral, epididymal and subcutaneous), and gut segments (from ileum, proximal colon and caecum) were carefully dissected, weighed and immersed in liquid nitrogen before storage at −80 °C. Animal experiments were approved and performed in accordance with the guidelines of the local ethics committee. The ethical code is 2014/UCL/MD/022. Housing conditions were as specified by the Belgian Law of 29 May 2013, on the protection of laboratory animals (Agreement LA 1230314).