Probiotics and Obesity

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Introduction

High energy intake and sedentary lifestyle are the main reasons for the worldwide obesity epidemic and related disorders such as type 2 diabetes, fatty liver disease and cardiovascular diseases. Recently, the intestinal microbiota has been proposed to play a role in obesity development [1]. This suggestion was based on several observations. Overweight subjects harbored a higher proportion of Firmicutes and, correspondingly, a smaller proportion of Bacteroidetes than normal-weight subjects [2]. These 2 phyla cover >90% of all bacterial cells in the human intestine. Weight reduction in obese subjects leads to a decrease of Firmicutes and a concomitant increase in Bacteroidetes [1]. Essentially the same observation has been made in mice [3]. Interestingly, the ability of obese mice to extract energy more efficiently from the diet than lean mice could be transferred to germ-free mice by transfer of their gut microbiota [2].

Conflicting Findings

Two recent human studies [4, 5] could not confirm the above findings. This discrepancy might be due to differences in the methods used for the analysis of the fecal microbiota. In contrast to the 2 original studies

from the group of Gordon et al. [1, 2], who characterized the composition of the fecal microbiota by extensive 16S rRNA gene sequence analysis, the authors of the 2 recent human studies [4, 5] applied 16S rRNA-targeted oligonucleotide probes for the quantification of major bacterial groups. However, the probes used in these trials do not detect members of the Erysipelotrichaceae, a bacterial family within the Firmicutes, which was shown in mice to be largely responsible for the increase in Firmicutes observed in response to a high-fat diet [6].

How Does the Gut Microbiota Affect Host Energy Metabolism?

Possible explanations for the ability of the gut microbiota to affect obesity development include an improved energy harvest from the diet, stimulation of fat storage by influencing lipoprotein lipase activity mediated by fasting-induced adipose factor [7] and a fat-induced systemic low-grade inflammation [8] accompanied by endotoxemia and insulin resistance [9] (fig. 1). The latter mechanism has been proposed on the basis of numerous experiments conducted in the mouse. Cani et al. [8] observed that a high-fat diet leads to increased levels of lipopolysaccharides (LPS) in the serum. LPS is a com-

Fig. 1. Role of the intestinal microbiota in fat-induced changes in the regulation of nutrient absorption, fat storage and inflammatory status of the host.

ponent of the cell wall of gram-negative bacteria causing endotoxemia. LPS in conjunction with a high-fat diet was also demonstrated to enhance the symptoms of fatty liver and other criteria of the metabolic syndrome.

Metabolic endotoxemia led to an increase in the concentration of proinflammatory cytokines in various tissues. Interestingly, mice lacking CD14 were protected against the LPS-induced inflammation. CD14 is a receptor on the cell surface of immune cells, which binds LPS and in cooperation with the Toll-like receptor 4 triggers a proinflammatory response. CD14-deficient mice had an improved insulin sensitivity and glucose tolerance [9]. Experimental models revealed that not only CD14 deficiency but also Toll-like receptor 4 deficiency or treatment by antibiotics can attenuate symptoms of the metabolic syndrome following overfeeding and induction of obesity [10, 11].

Changes in the Gut Microbiota Correlate with an Improved Glucose Tolerance

The feeding of mice with a high-fat diet not only led to increased serum LPS levels but also to a decrease of bifidobacteria in cecal contents [12]. Supplementation of the

high-fat diet with oligofructose resulted in increased concentrations of bifidobacteria. This prebiotic effect was accompanied by normalization of the serum LPS concentrations and correlated with an improved glucose tolerance and insulin sensitivity.

How Do Bifidobacteria Bring about These Changes?

Cani et al. [13] demonstrated in mice that oligofructose supplementation, which stimulates bifidobacterial growth, lowers the high-fat-induced permeability of the gut epithelium and thereby the uptake of LPS from the gut lumen. The decreased permeability of the gut epithelium was accompanied by the normalization of the expression levels of tight-junction proteins, such as zonula occludens 1 and occludin, which play a major role in the control of the permeability of the epithelial layer in the gut. The decreased permeability of the epithelium correlated with lower concentrations of proinflammatory cytokines. Glucagon-like peptide 2 was shown to mediate these effects triggered by oligofructose. The authors propose that oligofructose stimulates intestinal bifidobacteria, which in turn enhance the expression of tight-junction proteins resulting in a diminished permeability (fig. 2). Consequently uptake of LPS from the gut lumen

Fig. 2. Role of endogenous bifidobacteria in lowering gut permeability, serum LPS and inflammatory status. Whether exogenous (probiotic) bifidobacteria have the same effect has not yet been investigated.

is reduced and the LPS levels in the serum are prevented from increasing and triggering a proinflammatory response [14].

Could the Supplementation with Probiotic Bifidobacteria Have the Same Effect as Endogenous Bifidobacteria?

The ability of endogenous bifidobacteria to induce the expression of tight-junction proteins and thereby reduce the permeability of the intestinal epithelium for LPS

prompts the question whether the oral supplementation with probiotic bifidobacteria could have the same effect. In this context it is interesting to note that it has already been demonstrated that secreted peptide bioactive factors from a *Bifidobacterium infantis* strain increased the transepithelial resistance and the expression of the tight-junction proteins zonula occludens 1 and occludin [15]. This led to a normalization of gut permeability and to an attenuated inflammatory response in an animal model for colitis.

Final Remarks

It has been recognized that obesity is accompanied by low-grade inflammation. There are good indications that the intestinal microbiota undergoes changes in response to a high-fat diet resulting for example in a decrease of bifidobacteria. Decreased proportions of bifidobacteria correlate with an increased permeability of the gut epithelium, which leads to higher serum LPS concentrations evoking a proinflammatory response. However, it has to be emphasized that the importance of these observations for the situation in humans is completely unclear. Whether the oral application of exogenous bifidobacteria could help improve symptoms of the metabolic syndrome needs to be investigated.

Disclosure Statement

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