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Biological Actuality

Role of gut microflora in the development of obesity and insulin resistance following high-fat diet feeding

Rôle de la flore intestinale dans le développement de l'obésité et de l'insulinorésistance lors d'une alimentation hyperlipidique

P.D. Cani [a,b,*], N.M. Delzenne [a], J. Amar [c], R. Burcelin [b,**]

[a] *Unit of Pharmacokinetics, Metabolism, Nutrition and Toxicology, université catholique de Louvain, avenue E. Mounier, 73/69, 1200 Brussels, Belgium*
[b] *Institute of Molecular Medicine Rangueil (I2MR), Inserm U858, IFR31, hôpital Rangueil, B.P. 84225, 31432 cedex 4 Toulouse, France*
[c] *Inserm 558, faculté de médicine, 37, allées Jules-Guesde, 31000 Toulouse, France*

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Abstract

A recent growing number of evidences shows that the increased prevalence of obesity and type 2 diabetes cannot be solely attributed to changes in the human genome, nutritional habits, or reduction of physical activity in our daily lives. Gut microflora may play an even more important role in maintaining human health. Recent data suggests that gut microbiota affects host nutritional metabolism with consequences on energy storage. Several mechanisms are proposed, linking events occurring in the colon and the regulation of energy metabolism.

The present review discusses new findings that may explain how gut microbiota can be involved in the development of obesity and insulin resistance. Recently, studies have highlighted some key aspects of the mammalian host-gut microbial relationship. Gut microbiota could now be considered as a ''microbial organ'' localized within the host. Therefore, specific strategies aiming to regulate gut microbiota could be useful means to reduce the impact of high-fat feeding on the occurrence of metabolic diseases.

Résumé

Un nombre croissant d'évidences suggère que l'augmentation de la prévalence de l'obésité et du diabète de type 2 n'est pas seulement la conséquence de modifications génétiques, d'habitudes alimentaires ou de la sédentarité. La flore intestinale joue également un rôle prépondérant dans le maintien de la santé. À ce sujet, des données récentes suggèrent que la modulation de la flore intestinale pourrait affecter le métabolisme de l'hôte et par conséquent modifier le stockage énergétique. Plusieurs mécanismes expliquent le lien entre les événements se produisant dans la partie basse de l'intestin et le maintien de l'homéostasie énergétique. Cette revue discute des découvertes récentes permettant d'expliquer comment la flore intestinale serait impliquée dans le développement de l'obésité et de l'insulinorésistance. Plus récemment, de nouvelles études ont mis en évidence les aspects moléculaires faisant le lien entre l'hôte et la flore intestinale. Dès à présent, les bactéries de l'intestin peuvent être considérées comme un véritable « organe microbien » placé au sein de l'hôte et dont les caractéristiques qualitatives et quantitatives seraient des clés de régulation du métabolisme nutritionnel. Par conséquent, les stratégies spécifiques visant à modifier la composition de la flore intestinale pourraient constituer un des moyens à notre portée afin de réduire l'impact de l'alimentation sur l'apparition des maladies métaboliques.

Keywords: Gut microflora; Obesity; Type 2 diabetes; Inflammation; LPS; Insulin resistance; Pre/probiotics

Mots clés : Flore intestinale ; Obésité ; Diabète de type 2 ; Inflammation ; LPS ; Insulino résistance ; Pré/probiotiques

* Corresponding author.
** Corresponding author.
E-mail addresses: patrice.cani@uclouvain.be (P.D. Cani), burcelin@toulouse.inserm.fr (R. Burcelin).

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1. Introduction

Obesity and type 2 diabetes are two metabolic diseases resulting from a combination in variable association of genetic and environmental factors [1]. These two metabolic diseases are characterised by a low grade inflammation associated with the development of insulin resistance [2,3]. Whereas the impact of a point mutation, in a key mechanism, could lead to obesity and type 2 diabetes, the molecular events allowing environmental factors to provoke the same pathological consequences, are poorly understood.

Nowadays, the growing epidemic of obesity and type 2 diabetes prompts the scientific community to develop or identify new therapeutic targets. The excessive energy intakes, as well as the reduction of physical activity, are certainly two environmental factors classically associated with the development of metabolic diseases. Among these most common triggering events, a fat-enriched diet generates features of metabolic disorders leading to the diseases.

Over the last years, numerous attempts have been performed to determine the triggering factor which **(1)** would depend on fat feeding, **(2)** trigger a low grade inflammation and **(3)** behave over a long term period, to be part of the progressive disease. The aim of this review is to highlight how the modulation of gut microbiota affects the development of obesity and type 2 diabetes.

2. Gut microbiota and energy metabolism

The intestinal flora has been recently proposed as an environmental factor involved in the control of body weight and energy homeostasis [4–9]. The human intestine contains a large variety of microorganisms, this community consists of at least 10^{14} bacterial cells and up to 500–1000 different species. As a whole this represents overall more than 100 times the human genome [10,11], and is called the ''metagenome''. Thus, the intestinal flora can be considered as an ''exteriorized organ'' which contributes to our homeostasis with multiple functions largely diversified. The biological functions controlled by the intestinal flora are related to the effectiveness of energy harvest, by the bacteria, of the energy ingested but not digested by the host. Among the dietary compound escaping to the digestion occurring in the upper part of the human gastro-intestinal tract, the polysaccharides constitute the major source of nutrient for the bacteria. Part of these polysaccharides could be transformed into digestible substances such as sugars, or short chain carboxylic acids, providing energy substrates which can be used by the bacteria or the host. The control of body weight depends on mechanisms subtly controlled over time and a small daily excess, as low as 1% of the daily energy needs, can have important consequences in the long term on body weight and metabolism [12]. Consequently, all mechanisms modifying the food-derived energy availability should contribute to the balance of the body weight. Several studies from the group of Gordon [4,5] highlighted that the gut microbiota of obese subjects changed according to the loss of body weight occurring after a hypocaloric diet. The authors demonstrated that two groups of bacteria are dominant in the intestinal tract, Bacteroidetes and Firmicutes [4]. The quantification and characterization of each dominant group of bacteria were carried out by measuring the concentration of the bacterial 16S rRNA. The authors show that the number of Bacteroidetes bacteria depended on the weight loss whereas the Firmicutes bacteria group remained unchanged. Importantly, the bacterial lineage was constant one year after the dietary intervention for a given body weight, validating the bacterial signature of each individual. The specificity of these differences between individual and body weight is not explained. However, it could be related to the diet and in particular to the presence of dietary fibres [13–16] (Cani et al. Personal Communication). Gordon and colleagues [4,5] propose that the gut bacteria from obese subjects are able to specifically increase the energy harvested from the diet, which provide an extra energy to the host. This conclusion was drawn from work showing that the axenic mice colonized with a conventional gut flora gain weight rapidly. Indeed, axenic mice bearing the same age and genetic background than the conventional mice exhibit a 40% lower weight [8]. In the same line, the authors demonstrated that axenic mice colonized with the gut microflora derived from the conventional mice increased their fat mass by about 60% and developed insulin resistance within two weeks. The mechanisms of the apparent gain weight implied an increase in the intestinal glucose absorption, energy extraction from non-digestible food component (short chain fatty acids produced through the fermentation) and a concomitant higher glycemia and insulinemia, two key metabolic factors promoting lipogenesis. These set of experiments demonstrated for the first time that an environmental factor such as gut microbiota regulates energy storage. The results, obtained both in rodents and human, suggest that obesity is associated with an altered composition of gut microbiota. However, this study did not demonstrate that the relative change in bacterial strains profile leads to different fates of body weight gain. To test this hypothesis, the same group performed experiments were the gut microbiota from *ob/ob* was transferred to lean axenic mice. They found that after only two weeks, lean mice colonized with the microbiota from obese mice had a modest fat gain. Such mice extracted more energy from their food as compared to the mice colonized with the gut microbiota from lean mice [5]. Together, these data suggest that the differences between both groups of lean mice, in term of fat and body weight gain, might be attributable to change in gut microbiota.

This particularly original idea that the bacteria can contribute to the maintenance of the host body weight, is characterized by numerous paradoxes. It is not clear, however, whether the small increased of energy extraction can actually contribute to a meaningful body weight gain within a short period of time, as suggested in the gut flora transplantation studies. Moreover, we and other have clearly shown that a diet rich in non-digestible fibres decreases body weight, fat mass and the severity of diabetes [17–21]. However these dietary fibres increase strains of bacteria able to digest these fibres and provide extra-energy for the host as they thus increase the total amount of bacteria in the colon [13,22,23]. This mechanism is

not completely in accordance with the ''energy harvesting theory'' according to which the fermentation of non digestible polysaccharides would provide energy substrates for the host. In addition, it is difficult to conclude that small changes in energy ingestion (1–2%) can induce sufficient quick variation in weight (within two weeks) as observed in the American studies [5–8]. Importantly, the axenic mice colonized with the gut flora from normal mice ate more than their conventional mice counterparts; therefore, the body weight gain can also be dependent of the increased food intake. A last crucial point, which cannot depend only on the role played by the bacteria to harvest energy from nutrients escaping digestion in the upper part of the intestine, concerns a study showing that axenic mice are more resistant to diet-induced obesity [6]. The authors maintained axenic or conventionalized mice on a high-fat/high-carbohydrates diet (western diet) and found that conventionalized animals fed the western diet gained significantly more weight and fat mass and had higher glycemia and insulinemia than the axenic mice. Strikingly, and opposite to the results previously observed in axenic mice fed a normal chow diet, the amount of western diet taken up by an axenic or a conventionalized mouse was similar and hence had similar fecal energy output. All those data suggest that a bacterially related factor is responsible for the development of diet-induced obesity and diabetes.

Another point remains to be elucidated, how can we attribute the low grade inflammatory process observed during metabolic diseases to the energy harvested from the gut bacteria?

3. Gut microbiota and inflammation

Obesity and type 2 diabetes are metabolic diseased characterized by a low grade inflammation [3]. In the models of high fat diet induced obesity, adipose depots express several inflammatory factors IL-1, TNF-α and IL-6 [24,25]. These cytokines impaired insulin action and induce insulin resistance. For example, TNF-α phosphorylates serine residue substrate (IRS-1) from the insulin receptor leading its inactivation [26]. Recently, it has been proposed that nutritional fatty acids trigger inflammatory response by acting via the toll-like receptor-4 (TLR4) signalling in the adipocytes and macrophages. The authors shown that the capacity of fatty acids to induce inflammatory signalling following a high-fat diet feeding is blunted in the TLR4 knock out mice [27]. Altough TLR4 is the coreceptor for the lipopolysaccharides (LPS) constituent of the Gram negative bacteria, the authors did not characterise the gut microbiota following high fat diet feeding. Therefore, we have been looking for a triggering factor of the early development of metabolic diseases, we looked for a molecule involved early in the cascade of inflammation and identified that LPS as a good candidate [28]. Furthermore, LPS is a strong inducer of inflammatory response and is involved in the release of several cytokines that are key factors triggering insulin resistance. The concept of dietary excess is more ore less associated to high-fat feeding-induced inflammation. As we identified recently LPS as a putative factor for the triggering of obesity and insulin resistance, we challenge our hypothesis in a pathological context (obesity and insulin resistance) of high-fat diet fed mice. Mice fed a high-fat diet for a short term period as two to four weeks exhibit a significant increase in plasma LPS. An endotoxemia that we characterized as a ''metabolic endotoxemia'', since, the LPS plasma concentrations were 10 to 50 times lower than those obtained during a septic shock [29]. The mechanisms allowing LPS absorption are not clear but could be related to an increased absorption during fat digestion [30]. LPS is absorbed into intestinal capillaries to be transported by lipoproteins (i.e. chylomicrons) [31–33]. We then demonstrated that high-fat diet feeding changed gut microbiota in favour of an increase in the Gram negative to Gram positive ratio. Indeed, the number of *Bifidibacterium* spp. and *E. rectale/Cl. coccoides* group were reduced, the first group of bacteria has been shown to reduce intestinal endotoxin levels in rodents and improve mucosal barrier function [34–36]. In order to determine the role of metabolic endotoxemia in the development of metabolic disorders such as diabetes and obesity, we mimicked the metabolic endotoxemia by chronically infusing a low dose of LPS to reach the same plasma LPS levels as the one measured in the high-fat diet fed mice. The four weeks chronic low dose LPS infusion mimicked the high-fat diet fed mice phenotype with a fasted hyperglycemia, obesity, steatosis, adipose tissue macrophages infiltration, hepatic insulin resistance and hyperinsulinemia. To demonstrate our hypothesis that the metabolic endotoxemia is a triggering factor in the development of metabolic diseases, we challenged LPS receptor knock out mice (CD14 knock out mice-CD14KO) with a high-fat diet and a chronic low dose LPS infusion. CD14 is a key molecule involved in the innate immune system [37]. CD14 is a multifunctional receptor constituted by a phosphatidyl inositol phosphate-anchored glycoprotein of 55 kDa expressed on the surface of monocytes, macrophages and neutrophils [38–41]. We have shown that CD14KO mice were hypersensitive to insulin even when fed a normal diet, suggesting that CD14 could be modulator of insulin sensitivity in physiological conditions. As a matter of fact, CD14KO mice resist high-fat diet and chronic LPS-induced metabolic disorders. Similarly hepatic steatosis, liver and adipose tissue inflammation and adipose tissue macrophages infiltration was totally blunted in the CD14KO mice fed a high-fat diet or infused with LPS [28]. In these sets of experiments, we showed that high-fat feeding induced a low tone inflammation which originates from the intestinal absorption of the LPS.

Thus altogether our data support the key idea that the gut microbiota can contribute to the pathophysiology of obesity and type 2 diabetes. We report that high-fat feeding alters the intestinal microbiota composition were *Bifidobacterium* spp were reduced. Several studies have shown that this specific group of bacteria reduced the intestinal endotoxin levels and improved mucosal barrier function [34–36], therefore, in a recent study we addressed this question: *Could the selective increase of bifidobacteria in gut microflora improves high-fat diet-induced diabetes in mice?*

We used the unique advantage of the prebiotic dietary fibres (oligofructose, [OFS]) [15] to specifically increase the gut bifidobacteria content of high-fat diet treated mice. We found

that among the different gut bacteria analysed, plasma LPS concentrations correlated negatively with *Bifidobacterium* spp [42]. We confirm that mice fed a high-fat diet exhibit a higher endotoxemia a phenomenon completely abolished in the prebiotic dietary fibres fed mice. We found that in the prebiotic treated-mice, *Bifidobacterium* spp. significantly and positively correlated with improved glucose-tolerance, glucose-induced insulin-secretion, and normalized inflammatory tone (decreased endotoxemia, plasma and adipose tissue pro-inflammatory cytokines) [42]. Together, these findings suggest that the gut microbiota contributes to the pathophysiological regulation of endotoxemia, and sets the tone of inflammation for the occurrence of diabetes/obesity. Thus, it would be useful to develop specific strategies for modifying gut microbiota to favour bifidobacteria growth and prevent the deleterious effect of high-fat diet-induced metabolic diseases.

4. Conclusion

The demonstration of the role of gut microflora in maintaining human health led the scientific community to consider the means by which the gut microflora could be manipulated. Different and complementary mechanisms can be proposed to explain the metabolic shift towards energy storage. The first described mechanism consists in the role of the gut microbiota to increase the capacity to harvest energy from the diet. The second one consists in the role of the gut microbiota to modulate plasma LPS levels which triggers the inflammatory tone and the onset of obesity and type 2 diabetes. Nevertheless, a number of questions remain: how and why the composition of gut microbiota may be associated with obesity and other nutritional disorders? How the specific modulation of bifidobacteria lowers plasma LPS levels and metabolic consequences? Can we propose specific strategies for modifying gut microbiota (in favour of i.e. bifidobacteria?) to reduce the impact of high fat feeding on the occurrence of metabolic diseases in humans? Thus, specific strategies for modifying gut microbiota would be useful tools to reduce the impact of high-fat feeding on the occurrence of metabolic diseases.

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