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Diabetes, obesity and gut microbiota

Amandine Everard, M.Sc., Pharm,
Patrice D. Cani, PhD, Professor *

Université catholique de Louvain, WELBIO (Walloon Excellence in Life sciences and BIOtechnology), Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Av. E. Mounier, 73 Box B1.73.11, B-1200 Brussels, Belgium

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A B S T R A C T

The gut microbiota composition has been associated with several hallmarks of metabolic syndrome (e.g., obesity, type 2 diabetes, cardiovascular diseases, and non-alcoholic steatohepatitis). Growing evidence suggests that gut microbes contribute to the onset of the low-grade inflammation characterising these metabolic disorders via mechanisms associated with gut barrier dysfunctions. Recently, enteroendocrine cells and the endocannabinoid system have been shown to control gut permeability and metabolic endotoxaemia. Moreover, targeted nutritional interventions using non-digestible carbohydrates with prebiotic properties have shown promising results in pre-clinical studies in this context, although human intervention studies warrant further investigations. Thus, in this review, we discuss putative mechanisms linking gut microbiota and type 2 diabetes. These data underline the advantage of investigating and changing the gut microbiota as a therapeutic target in the context of obesity and type 2 diabetes.

Introduction

In 1947, Jean Vague was the first to propose the android obesity phenotype as a common feature in metabolic abnormalities associated with type 2 diabetes and cardiovascular disease [1]. Many years later, many international organisations and expert groups [2–5] have agreed on most of the essential

* Corresponding author. Université catholique de Louvain, Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Av. E. Mounier, 73 Box B1.73.11, B-1200 Brussels, Belgium. Tel.: +32 2 764 73 97; fax: +32 2 764 73 59.
E-mail address: patrice.cani@uclouvain.be (P.D. Cani).

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components of the metabolic disorders that are commonly associated with obesity and have defined them as metabolic syndrome. Although these symptoms differ in terms of the number and type of criteria, the definition of metabolic syndrome includes obesity, glucose homeostasis disorders (e.g., type 2 diabetes, impaired fasting glucose, glucose intolerance, and insulin resistance), lipid homeostasis disorders (i.e., dyslipidaemia) and cardiovascular diseases risk factors (e.g., hypertension and fibrolysis disorders) [6].

Today, the clinical management of obesity is based on targeting obesity, insulin resistance and associated disorders. Therapeutic, nutritional and behavioural managements are proposed. While a weight loss of 5–10% of the initial body weight can enhance insulin sensitivity in overweight/obese individuals who are insulin resistant, only some metabolic abnormalities return to the levels seen in insulin-sensitive subjects [7,8]. Whereas, to date, drugs have not been particularly effective for the treatment of obesity, recent findings devoted to understanding the biochemical pathways related to the development of obesity have provided new targets.

Among these new targets, growing evidence supports the idea that the increased prevalence of obesity and type 2 diabetes cannot be attributed solely to changes in the human genome, nutritional habits, or the reduction of physical activity in our daily lives [9]. In the vast majority of adults, both the qualitative and quantitative composition of food intake varies considerably from meal to meal and from day to day, whereas adiposity and body weight are remarkably constant despite various short-term variations in the energy balance. It is worth noting that when recording food intake and activity within a period including several meals, most individuals are able to compensate their cumulative energy intake with their energy expenditure with great precision [10]. Such an active process stabilises the amount of energy stored as fat in the body. However, an excess of energy intake by less than 1% compared with the daily energy expenditure can lead to a detrimental increase in body weight and metabolic complications over the long term (several years) [11]. Consequently, all the mechanisms influencing calorie ingestion and subsequent harvesting should contribute to a balance in the body weight; however, the majority of molecular targets involved in this process are unknown.

Gut microbiota as novel key organ involved in metabolism

One specific environmental factor evolving with us from birth and our dietary habits has been shown to contribute to energy homeostasis. This factor, the so-called gut microbiota, has also been shown to be involved in several intestinal biological functions, such as the defence against pathogens, immunity, the development of the intestinal microvilli and the degradation of non-digestible polysaccharides [12,13]. Several elegant reports have suggested that the gut microbiota exerts a crucial role in the development of fat mass and altered energy homeostasis. The earliest evidence supporting this hypothesis was from a study revealing that germ-free mice (mice raised in the absence of any microorganisms) are leaner compared with mice that harboured microbiota since birth. Importantly, the conventionalisation of germ-free mice with a gut microbiota induced an increase in fat mass and insulin resistance. This study revealed the gut microbiota to be an environmental factor that regulates fat storage [14]. One of the proposed mechanisms is that the gut microbiota has the capacity to increase the energy harvested from the diet. Moreover, its ability to modulate host signalling pathways could influence the host energy balance and host metabolism [14–17]. We [18] and others have demonstrated that the gut microbiota plays a major role in the onset of insulin resistance and type 2 diabetes by triggering low-grade inflammation (Fig. 1) [17–19]. Although not included in the definition of metabolic syndrome, low-grade inflammation is a common feature characterising obesity and several metabolic disorders. However, how the gut microbiota contributes to the development of low-grade inflammation remains to be understood.

Among the potential mechanisms, we recently found that in pathological conditions, such as obesity and type 2 diabetes, the gut microbiota can control the host metabolism and contributes to development of low-grade inflammation (Fig. 1) [18,20–24]. We have contributed to the discovery of key elements linking the gut microbiota to host metabolism, low-grade inflammation and metabolic disorders in obesity and type 2 diabetes [18,21,22]. Among the mechanisms, we defined gut microbiota-derived lipopolysaccharide (LPS) as a key molecule involved in the early development of inflammation and metabolic diseases (Fig. 1) [18,21]. Indeed, LPS is a powerful proinflammatory