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Interplay between gut microbiota, its metabolites and human metabolism: Dissecting cause from consequence

A.V. Hartstra [a], M. Nieuwdorp [a, b, c], H. Herrema [a, *]

[a] Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[b] VUmc Diabetes Center, Department of Internal Medicine, Free University Medical Center, Amsterdam, The Netherlands
[c] Wallenberg Laboratory, University of Gothenberg, Gothenberg, Sweden

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ABSTRACT

Background: Alterations in gut microbiota composition and bacterial metabolites have been increasingly recognized to affect host metabolism and are at the basis of metabolic diseases such as obesity and type 2 diabetes (DM2). Intestinal enteroendocrine cells (EEC's) sense gut luminal content and accordingly secrete hormones that modulate glucose and lipid metabolism and affect satiety. It has become evident that microbial metabolic products significantly affect EEC function.

Scope and approach: In this review, we will discuss current insights in the role of the gut microbiota and its metabolites in development of obesity and DM2 and elaborate on interventions that modulate EEC action.

Key findings and conclusions: Studies including fecal transplantation and Roux-en-Y gastric bypass (RYGB) in humans and animal models suggest that the gut microbiota and its metabolites causally contribute to development of obesity and DM2. Emerging evidence suggests that the gut microbiota and its metabolites can modulate secretion of EEC hormones that regulate appetite and insulin secretion. Dispersed intestinal expression and low abundance make EEC's difficult to study. Since current intestinal sampling methods in humans are mostly limited to the colon, this leaves a large part of EEC function understudied. It would therefore be relevant to develop means to extend sampling methods throughout to entire GI tract.

1. Gut microbiota and development of obesity and DM2

Both the industrialized and developing world have experienced an obesogenic shift in caloric intake, nutritional composition and lack of exercise (Cecchini et al., 2010; Gregg et al., 2014). Obesity is a predisposing factor for development of chronic disorders such as cardiovascular disease (CVD) and type 2 diabetes (DM2). These pathologies are major causes of morbidity and mortality and carry significant economic burden. The growing obesity pandemic is therefore a major threat to human health and strategies to improve this condition are greatly needed. It has been proven difficult to achieve long-term life style changes to maintain a healthy body weight (Friedman, 2004) and the current relatively unsuccessful pharmaceutical treatment strategies imply that there are no simple solutions to this problem. Although obesity can be defined as an imbalance between intake and output of energy, the development of obesity and obesity–related disorders entails very complex and multifactorial mechanisms. In the past decade, it became evident that dysbiosis between the intestinal microbiota and host contributes to development of pathologies such as obesity and DM2 (Sekirov, Russell, Antunes, & Finlay, 2010; Tremaroli & Backhed, 2012). Animal studies have opened up crucial clues in the quest to mechanistically unravel microbiota impact on host metabolism. The human translatability of these studies, however, remains a challenging aspect of this undertaking (Kostic, Howitt, & Garrett, 2013; Nguyen, Vieira-Silva, Liston, & Raes, 2015). In this review, we will illuminate the contribution of the microbiota and microbiota-derived metabolites to regulation of metabolism and satiety. We will highlight insights obtained from fecal transplantation and gastric bypass studies and focus specifically on the role of intestinal enteroendocrine cells (EEC's) as enhancers of microbiota-mediated regulation of metabolism (summarized in Fig. 1).

* Corresponding author. Department of Vascular Medicine, Room G1-149, Academic Medical Center, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands.
E-mail address: h.j.herrema@amc.uva.nl (H. Herrema).

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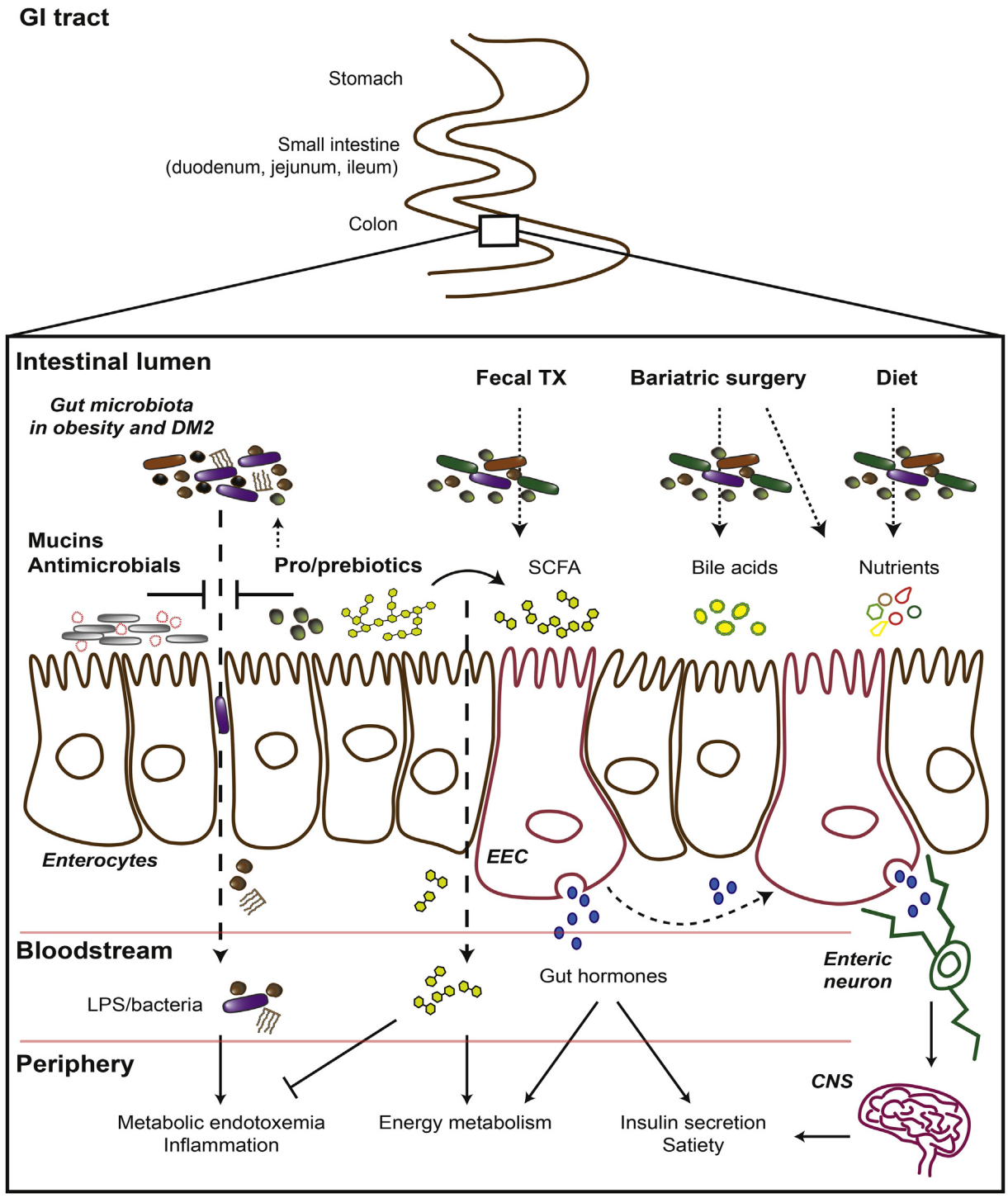

Fig. 1. Alterations in gut microbiota composition and dysbiosis between microbiota and host contribute to development of pathologies including obesity and DM2. Bacterial translocation and subsequent development of metabolic endotoxemia and initiation of inflammatory events are hypothesized to be secondary to microbiota-mediated alterations in intestinal integrity. EEC's are highly responsive to nutrients and bacterial metabolites and accordingly convey signals to the periphery in an endocrine and neuronal fashion through secretion of hormones. Altered gut microbiota composition has been associated with compromised EEC function and development of metabolic disease. Interventions that aim to modulate gut microbiota composition and metabolite production provide important means to reestablish intestinal integrity and EEC signaling events. Please see text for further details. DM2, type 2 diabetes; EEC, enteroendocrine cells; CNS, central nervous system.

1.1. Cause or consequence?

Research on the role of the gut microbiota in health and disease is booming and we have long passed the thought that the trillions of microbial cells (Qin et al., 2010) in and on our body are inert passengers. Instead, they are deeply integrated in the regulation of host metabolism (*e.g.,* digestion, immune response and feeding behavior) and a large number of metabolites present in our circulation is derived from the microbiota (Wikoff et al., 2009). It has been shown that microbiota composition changes rapidly in