

The gut and the heart: a concise narrative review

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Abstract

Foods have a wider role besides simply satisfying hunger, and the gut may be the source of several diseases. The human gut is populated by 100 trillion microorganisms and the most abundant phyla are the Firmicutes (60 a 80%), such as the lactobacilli, and the Bacteroidetes (20 a 40%), such as the genus Bacteroides. The obesity epidemics may be related to the constant availability of food, less physical exercise, and influences on the gut microbiota such as type of food ingested (low fiber, high calorie, and high fat). The beneficial effects of the gut microbiota result partly from products derived from the fermentation of nondigestible carbohydrates (fibers), which generate short chain fatty acids, which in turn influence hormones that stimulate insulin secretion, improve insulin receptor sensitivity, promote satiety and inhibit glucagon secretion. Obese individuals have increased intestinal permeability and LPS release may promote, through metabolic endotoxaemia, an inflammatory state, such as seen in type II diabetes mellitus and obesity. Chronic heart failure results in a decreased perfusion of the gastrointestinal tract, with edema, dysmotility and malabsorption, which facilitates LPS release, which may induce negative inotropic effects, myocardial hypertrophy, fibrosis and apoptosis via tumor necrosis factor (TNF)- α , interleukin (IL)-1 and IL-6. Trimethylamine-N-oxide (TMAO) is a microbiota derived metabolite and is pro-atherogenic.

Eating healthy and making judicious use of antibiotics may promote cardiovascular health via effects on the gut microbiota.

Key words: gut, heart, microbiota, obesity, cardiovascular events, heart failure, prebiotics, probiotics, antibiotics

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Introduction

“Let food be thy medicine and medicine be thy food” and “All disease begins in the gut” are sayings attributed to Hypocrates, 460 B.C. The concept that foods have a wider role besides simply satisfying hunger, and that the gut may be the source of several diseases is not new (1). Despite this, the interest of the general public or that of the scientific community on this issue is relatively contemporaneous. Recent studies have boosted the production and commercialization of the so-called functional foods, including probiotics and prebiotics. Prebiotics are nutritional substrates that promote the growth of microbes that confer health benefits in the host. Probiotics are live microbes that confer health benefits when administered in adequate amounts in the host. Some formulations are synbiotics, that is, they contain a combination of prebiotics and probiotics.

Basics

The human microbiota is complex and dynamic. It is present in the skin surface, in the oral cavity, in the nasopharynx, genitourinary tract and the gastrointestinal tract. It exceeds 10 times the number of somatic cells and 150 times the number of bacterial's (and other microorganisms') genes (the microbiome) compared to the human genome. The microbiota is more heavily concentrated in the colon, and is mainly composed of bacteria, some archae, eukaryotes and viruses. However, it is estimated that only 30% of the human gut microbiota has been characterized, as current microbiological methods are unable to detect most of them. The human gut is populated by 100 trillion (10¹⁴) microorganisms and the most abundant phyla in humans and mice are the Firmicutes (60 - 80%), such as the Lactobacilli, and the Bacteroidetes (20

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- 40%), such as the gender *Bacteroides*.(2).

Gut colonization is influenced by the mode of birth and by lactation (or its absence) and microbiota composition stabilizes at the age of 3 years. Subsequently there are various influencing factors, such as geographical, diet, age, use of prebiotics, probiotics, and antibiotics. Despite these influences, many microbial species persist, especially those acquired early in life (2).

The beneficial effects of the gut microbiota result partly from products derived from the fermentation of non-digestible carbohydrates (fibers), which generate short chain fatty acids (SCFA), the most important of which are acetate, propionate and butyrate. These serve as energy sources to peripheral tissues, to the liver and to the colonic epithelium. SCFA are natural ligands to the G protein, which is attached to the GPR43 receptor, which in turn is expressed in several tissues, such as adipocytes, endocrine and immunologic cells. When SCFA bind to the GPR43 receptor in colonocytes, they stimulate GLP-1 (glucagon-like peptide-1) secretion, an incretin that is produced by the gut and stimulates insulin secretion, improves insulin receptor sensitivity, promotes satiety and inhibits glucagon secretion. Mice who overexpress GPR43 in fat tissue remain lean even when fed a high-fat diet; they weigh less, have less white fat tissue and smaller adipocytes. Consequentially they have better glucose tolerance and adequate lipid metabolism (3, 4).

SCFA act on several intestinal peptides; for example, the oral administration of butyrate, and to a lesser degree, that of propionate, results in a significant increase in plasma levels of gastric inhibitory peptide (GIP), GLP-1, PYY, insulin and amylin, and the general effect of this is the slowing down of digestion and of the intestinal transit, which promotes satiety and increases plasma insulin levels. Acetate increases leptin release from adipocytes and stimulates the lipolysis rate and the lipogenesis; it also increases propionate and butyrate actions on PYY and GLP-1(4).

The obesity epidemics

The obesity epidemics may be related to the constant availability of food along the last centuries, or more recently, and importantly, along the last decades. This was accompanied by a progressive decline in physical activity. These two factors have led to energy imbalance in human beings. As part of the evolutionary development, man has remained physiologically prone to protect his energy stores by accumulating fat tissue.(5). Besides these fairly simple considerations, other issues are at stake: there is a striking difference in quality and diversity of the microbiota in lean and fat individuals, men and mice. These differences come by different eating habits: diets with high sugar and fat content (so called the western diet) lead to the predominance of Firmicutes and to a decrease of Bacteroidetes. In the phylum Firmicutes, *Lactobacilli* predominate, but species variation may be associated with fatness, for ex. *L. reuteri*, or to slimness,

ex. *L.gasseri*. Some studies in obese men show an increase in the number of Actinobacteria and Prevotella. An increase in *Methanobacterium smithii*, of the Archaea phylum, has been noted in anorexic patients (4-6). The high fiber diet in less developed societies, associated with less sugar, fat and calorie intake, bring about greater variety of the gut microbiota in these populations. Obese mice and men have a deranged intestinal permeability and LPS release may promote, through metabolic endotoxaemia, an inflammatory state, such as seen in type II diabetes mellitus and obesity (2,4,5,7).

Cardiovascular events and microbiota derived TMAO

Trimethylamine-N-oxide (TMAO) is a microbiota derived metabolite and it is pro-atherogenic in men and mice. TMAO results from the metabolism of ingested choline and L-carnitine; choline is present in eggs, red meat, fish, shrimps, milk and vegetables such as broccoli, cauliflower and quinoa; L-carnitine is present essentially in red meat. Choline taken orally is metabolized to trimethylamine (TMA) by gut bacteria; TMA is absorbed and metabolized in the liver to TMAO by monooxygenases. Plasma levels of TMAO have a positive correlation to cardiovascular risk. A study on the relationship of TMAO and the incidence of cardiovascular (CV) events (death, myocardial infarct or stroke) was done on 4007 patients who had angioplasty, with a 3-year follow up. Even when traditional risk factors for CV disease were adjusted, elevated TMAO levels could predict major CV events. The link between microbiota and CV disease pathophysiology was established. On the other hand, 3,3-Dimethyl-1-butanol (DMB) is a molecule that inhibits TMA production derived from choline. DMB is found in some foods such as balsamic vinegar, olive oil and grape seeds. This may partially explain the beneficial effects of the so called Mediterranean diet, which is little atherogenic. Despite evidences, it is not clear whether the modification of the gut microbiota precedes metabolic changes or simply coincides with them, and causality cannot be ascertained (8).

Heart failure

Chronic/congestive heart failure (CHF) is an important cause of morbidity and mortality worldwide, despite advances in therapeutics. Neuroendocrine dysregulation is at its genesis, but CHF is also characterized by an important inflammatory component, accompanied by an increase in circulation cytokines and inflammatory mediators (9, 10). CHF results in a decreased perfusion of the gastrointestinal tract, with edema, dysmotility and malabsorption. The damage to intestinal permeability facilitates bacterial translocation and endotoxin release. Bacterial components, such as LPS, reach the systemic circulation, releasing tumor necrosis factor (TNF)-alfa, a cytokine with cardiosuppressive action (11). The same mechanisms may increase interleukin (IL)-1 and IL-6. The resulting inflammation may induce negative inotropic effects, myocardial hypertrophy, fibrosis and apoptosis. This gut-heart axis contributes to the worsening of CHF. Studies utilizing short courses of antibiotics have shown a decrease of toxic metabolites implicated in cardiovascular damage, such as

TMAO (12). In rats, the administration of probiotics improved cardiac function following induced myocardial infarction (13). In human individuals, the outpatient administration of probiotics for 3 months improved left ventricular ejection fraction by 5% (14). Therefore, modulation of the gut microbiota made it possible to improve acute and chronic heart dysfunction.

Potential beneficial measures in nutrition and antibiotic use for cardiovascular health:

- Decrease the oral intake of foods, which are rich in choline, so as to decrease the amount of TMAO generated.
- Increase the offer of foods, which are rich in DBB.
- Stimulate the intake of high fiber content foods, especially oligosaccharides fructanes and galactanes, which act as prebiotics (15).
- Eat the least possible high fat high sugar diets.
- Be cautious regarding the use of probiotics, as they may result in no effect or in deleterious effects, especially in immunosuppressed or severely ill patients (16).
- Make judicious use of antibiotics, since they are non-selective in eliminating gut bacteria, and may cause immediate and long lasting metabolic effects (17,18).

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