

The gut in control of health and disease

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VALORIZATION

"Valorization is the process of value creation out of knowledge by making this knowledge suitable and available for economic or societal utilization and to translate this into high-potential products, services, processes, and industrial activity." (Landelijke Commissie Valorisatie 2011:8)

The relationship between food intake and human health is complex. Food intake supplies nutrients that can be used for growth, repair, energy provision, and other functions. Food intake can also negatively influence health and contribute to the development of disease. Not only the lack of high-quality food in low-income countries, but also overnutrition in high-income countries emerges as a threat to public health. Overnutrition, i.e. total energy from food intake exceeding energy expenditure, can cause overweight and obesity on the long term. Overweight, obesity, and related disorders such as type 2 diabetes represent a rapidly growing health threat. In 2014, approximately 1.9 billion adults worldwide were overweight ($25 < \text{BMI} < 30 \text{ kg/m}^2$) and about 600 million were obese ($\text{BMI} > 30 \text{ kg/m}^2$). It has been estimated that obesity and related disorders contribute to 2 - 7% of total health care costs. As such, obesity imposes a tremendous economic burden on health care systems.^{1,2} Importantly, obesity increases the risk for type 2 diabetes, cardiovascular disease, and several types of cancer. As such, it has been suggested that growth of the obese population could lead to future declines in life expectancy.³ This thesis provides information that can be used to design intervention strategies that help to maintain a healthy body weight in order to prevent obesity-related disorders and subsequent impact on quality of life and healthcare systems.

Attempts have been made to fight obesity with the simple regimen: "Eat less, exercise more". However, the implementation of such a lifestyle intervention fails for the majority of people and will never solve the obesity epidemic. Therefore, better knowledge of human metabolism and the development of effective interventions to prevent the onset of overweight and obesity-related disorders may improve life expectancy and quality of life and reduce healthcare costs. In conclusion, the world is in dire need of effective and safe strategies enhancing energy expenditure, and fat oxidation in particular.

Studies performed over the last decades have indicated that intestinal microbiota composition and function are closely associated with health and thus with the development and progression of a variety of disorders. Several years ago, a class of compounds defined as prebiotics were recognized for their ability to manipulate gut microbiota composition and benefit the host. Especially the ability of gut microbiota to ferment otherwise indigestible food components, such as dietary fibers, into short-chain fatty acids (SCFAs) adds a unique function to the human body. *In vitro* and animal studies have shown that SCFAs are involved in energy regulation, lipid metabolism, glucose homeostasis, and inflammation.

A highly promising intervention for preventing or treating metabolic diseases such as obesity and type 2 diabetes would therefore be a change in gut microbiota composition and function to benefit human health, i.e. to influence energy expenditure and fat oxidation in particular. Results from these mechanistic *in vitro* or animal studies cannot be directly translated into the human situation, because of different microbial composition in humans, and thus cannot simply be used to redefine public health guidelines. This thesis describes several clinical trials in human subjects and attempts to better understand the role of SCFAs in human metabolism.

The studies described in this thesis are derived from an intensive collaboration between academia, industry, and government with scientists in the field of human nutrition and physiology, clinicians, and health care professionals. The close collaboration between industry and academia leads to demand-driven research that not only helps to better understand physiology but also provides information that can be used to create or optimize product formulations and/or services. It is important that academia, government and industry collaborate as the government detects and controls health issues, academia has the ability to study these issues and gain novel information, which then can be used by industry to create and market new health products.

The present thesis has shown that SCFAs, especially acetate applied in the distal part of the colon, can serve as important nutritional and/or therapeutic targets to promote human metabolism. Increasing acetate concentrations in the distal part of the colon could theoretically be achieved by developing slow-fermentable dietary fibers that take a longer time to ferment and thus the fermentation process will take in the distal part of the colon. Moreover, a slow-fermentable fiber can be modified to serve as a vector that can bind acetate in order to further increase acetate concentrations. The challenge with this approach is the difference in gut transit time between individuals. Human gut transit time ranges from 2 - 5 h for gastric emptying, 2 - 6 h for small bowel transit, and 10 - 59 h for colonic transit. One can imagine that the wide range in colonic transit time makes it difficult to develop a 'one size fits all' slow-fermentable fiber. The same holds true for special coatings that resolve when in contact with microbiota or coatings that release their content after remaining in the gut for a specific amount of time. This challenge can be bypassed by using enemas. These are extremely handy in scientific settings; however, use in daily life is not feasible, as they should be used daily for several years or decades to prevent or treat diseases. Thus, more research on product development using the information above should be initiated.

The present thesis has shown that the prebiotic inulin is fermented into SCFAs, and thus might have an important nutritional implication for human health. In addition, replacing digestible fibers with fermentable fibers such as inulin attenuates the rise in blood glucose after a meal intake without affecting hunger and satiety. The lower glycemic index of inulin compared with digestible fibers also lowers caloric intake, and thus promotes

weight loss. The ingestion of up to 24 g of inulin caused no side-effects in our study subjects and was easy to consume, and can thus be considered safe and feasible for daily intake. The formation of SCFAs in the colon might have additional health effects by further increasing fat oxidation.

Results from this thesis show that long-term supplementation of the prebiotic galacto-oligosaccharides (GOS) changes gut microbiota composition, but has no effect on metabolic outcomes. It is possible that microbial imbalance (also termed dysbiosis) in our obese prediabetic population might have hampered any beneficial metabolic effects. Microbial utilization of prebiotics can only occur if the appropriate species of bacteria are abundantly present in the host's microbiota. A number of environmental factors, including mode of delivery and early feeding, antibiotic use, disease status, adult diet, and metabolic status can influence the human gut microbiota composition and possibly the effect of prebiotic supplementation. Therefore, a patient-specific treatment to target a specific microbial response is an important aspect for future research. Microbiota profiling using state-of-the art techniques, such as Human Intestinal Tract Chip (HITChip), makes it possible to map the entire microbiome. To allow for personalized medicine in the future, we need to develop affordable and scalable techniques for mapping microbiota composition but also for microbiota function. Based on the unique microbiota composition and function, a specific prebiotic can be prescribed in order to effectively improve microbiota function and subsequent metabolic parameters.

SCFAs are important for maintaining or improving colonic health. Especially butyrate enemas have the potential for treating distal colonic diseases such as the inflammatory bowel disease ulcerative colitis. On the other hand, high systemic levels of butyrate can cause side effects such as hypokalemia and nausea. We have shown that the liver has a large capacity to catabolize colonically delivered butyrate, thereby preventing a rise in systemic butyrate and making the use of butyrate enemas safe as a treatment for colonic disease. This thesis also includes a review on the role of SCFAs in colonic inflammation, carcinogenesis, as well as mucosal protection and healing. In short, *in vitro*, *ex vivo*, and animal studies show promising results of SCFA treatment in colonic diseases, while only a limited number of human studies have been performed and show little or no favorable effects of direct SCFA application when compared with placebo. However, it is possible that SCFAs support and improve the efficacy of established medical treatment, such as the use of the first class anti-inflammatory drug mesalazine. Especially in ulcerative colitis it is easy to reach the colon and its mucosa by using SCFA enemas, because ulcerative colitis is characterized by superficial mucosal inflammation predominantly in the distal part of the colon. In addition it has been suggested that combining mesalazine treatment with SCFA enemas is an effective treatment to attack colonic inflammation. Also, the combination of SCFAs with probiotics or prebiotics, or even the combination of SCFAs, prebiotics, and mesalazine, might serve as an effective treatment for inflammatory bowel disease. SCFAs

may also be used in colonic surgery, e.g. by coating surgical sutures with SCFAs to promote wound healing after surgery. Evidence on this topic is still scarce and these sutures have only been applied in animals, but the outcome of these studies are promising for future human studies.

The overwhelming load of information about healthy and unhealthy foods in the news and social media often provides the general public with confusing information and lifestyle advices. Frequently, only positive results and/or false translation of results find their way to the media, i.e. publication bias or industry bias may play a role. A recent analysis shows that industry funded randomized-controlled trials are seven times more likely to report a positive result in general and abdominal surgery than a non-industry-funded trial.⁴ A public-private partnership such as TIFN is an excellent way to fund research, as risk of publication and industry bias is diminished and data are not published in a selective way. As researchers, we should feel obliged to translate our scientific knowledge into practical guidelines, but also to highlight different aspects and negative results of our studies. Moreover, the concept of personalized medicine should be introduced to the general public, and it should be explained that a 'one size fits all' therapy does not exist. This thesis highlights that the gut microbiota and its fermentation products such as SCFAs play an important role in human metabolism, although we need to gather more information before patient-specific health recommendations can be made.

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