Valorisation

The present thesis describes the potential of gut microbial-derived short-chain fatty acids (SCFA) as key players in host substrate and energy metabolism in humans. We investigated whether SCFA have beneficial effects on body weight control and insulin sensitivity via an increase in energy expenditure and fat oxidation, as well as the production of appetite-regulating hormones and inflammatory cytokines. The valorisation potential of these studies will be described in terms of societal and economic relevance and implications for specific target groups, future research and possible applications for industrial development.

The present report of the World Health Organization (WHO) indicated alarming numbers for the worldwide prevalence of obesity, indicating that more than 39% overweight (>1.9 billion adults, > 50% in Europe) and 13% (>600 million, > 20% in Europe) clinically obese adults. Moreover, of great concern is that more than 42 million children under the age of 5 were overweight or obese in 2013 and numbers are rising. Obesity is associated with a serious number of comorbidities such as cardiovascular disease, mental disorders (i.e. depression), certain forms of cancers, and type 2 diabetes mellitus. Overweight/obesity is thereby the fifth leading cause of death and the increasing prevalence has besides public health issues also major socio-economic consequences.

Obesity is a chronic metabolic disorder resulting from an energy imbalance, in which a long-term surplus of energy intake over energy expenditure (that is, positive energy balance) leads to the storage of excess energy as body fat. Putative mechanisms linking obesity to insulin resistance and type 2 diabetes mellitus are described in this thesis, including obesity-associated adipose dysfunction and related lipid overflow and chronic low-grade inflammation.

Preventing and counteracting this positive energy balance is getting more and more difficult for obese individuals. This is mainly driven by the increased access and exposure to energy-dense foods and the increase in sedentary lifestyle especially in our Western Hemisphere. However, in the obese state even modest weight loss might lead to considerable beneficial health effects, i.e. the US Diabetes Prevention Program indicated that every kilogram of weight loss reduced the risk of developing diabetes by 16%. Therefore, the outcomes of the acute studies of this thesis - that colonic SCFA might beneficially impact body weight control via an increase of energy expenditure and fat oxidation, as well as the increase in satiety-stimulating hormones - is of substantial relevance for the prevention and treatment
of obesity and related metabolic disorders. Next, we found in these studies that whole-body lipolysis and circulating pro-inflammatory markers are attenuated, and that whole-body fat oxidation is increased, which are identified as putative key factors in the pathophysiology of obesity-related insulin resistance.

Thus, SCFA were identified as important metabolites in the crosstalk of gut microbiota and peripheral tissue metabolism, indicating that modulation of SCFA metabolism through targeted diet or lifestyle interventions might contribute to the prevention of chronic metabolic disease. Increasing the effectiveness of lifestyle interventions in the prevention of obesity and related insulin resistance might significantly impact public health and health care costs. In the longer-term study, we, however, could not confirm these findings of the acute studies to more chronic beneficial metabolic health effects using a specific fibre. The reasons therefore are discussed in this thesis and the findings of this study providing several interesting leads for future strategies, which might be more effective.

The studies of this thesis are funded by TI Food and Nutrition (TIFN), a public-private partnership on pre-competitive research in food and nutrition. The collaboration of this project involved experts of international food industries, research institutes and universities. Thus, this thesis should been seen in the context of the TIFN Gastrointestinal Health project ‘microbiota, metabolism and energy harvesting’. The overall aim of the project was to further elucidate the role of the gut microbiota, gut physiology and human energy and substrate metabolism by combining state-of-the-art human phenotyping and detailed characterization of gut microbiota composition and functionality. The specific focus was on the interaction between microbial-derived or colonically administered SCFA and liver, adipose tissue and skeletal muscle metabolism.

In this project state-of-the-art human intervention studies were performed to elucidate the significance of the gut microbiota and its products, in particular SCFA and bile acids, in body weight control and insulin sensitivity. Besides the research presented in this thesis, the project included studies investigating the knockdown of gastrointestinal microbiota by means of antibiotics, SCFA dynamics after ingestion of 13C-inulin, measurement of SCFA fluxes across gut and liver and faecal transplants from lean donors in subjects with metabolic syndrome.

All results gained within this TIFN project will be available for the public through publications in international peer-reviewed journals and via the media. The food industrial partners have contributed to the project through funding and the
interaction and exchange of relevant knowledge and data during frequent meetings and presentations. This interaction has given leads to further studies with food products known to result in putative beneficial and targeted changes in SCFA production. In addition, the project was of great value in the translation of scientific knowledge into food products that may improve the metabolic profile and the prevention of obesity-related metabolic disorders.

The relationship between the gut microbiome and metabolic disorders is a rapidly growing area and almost on a daily basis intriguing new data have been published in the recent years. However, our understanding regarding which microbes are ‘beneficial’ and how these microbes interact with the host metabolism, especially in humans, is still in its infancy and researchers in this field might still be considered as frontiers. This thesis identified SCFA, the microbial products produced by their fermentation of complex non-digestible carbohydrates, as important key regulators of the crosstalk between the gut microbiota and the whole-body substrate and energy metabolism in humans. The findings are in keeping with recently published studies in SCFA-supplemented animals as well as a limited amount of human studies, in which supplementing dietary fibres demonstrated beneficially effects on metabolic health.

To conclude, the acute studies described in this thesis have shown that colonic SCFA have great potential to beneficially modulate body weight control and insulin sensitivity and maybe of importance in chronic metabolic disease. As indicated above, these findings may give leads for the development of nutritional strategies and food products modulating SCFA production in a target manner, thereby preventing obesity and obesity-related metabolic disturbances. Furthermore, this thesis also provides interesting leads for further research, such as the relevance of gut microbiota manipulation with respect to metabolic phenotypes, the colonic SCFA production sites and insight in physiologically relevant SCFA absorption rates and fluxes.