6. Summary

Maillard reaction products (MRPs) arise from complex reactions between amino acids or proteins and reducing sugars *in vivo* as well as during food processing. Numerous studies have shown that MRPs are beneficial compounds, due to their antioxidant, chemopreventive and probiotic effects. On the other side certain MRPs revealed harmful effects like cytotoxicity, carcinogenicity and mutagenicity. To date no knowledge exists, if MRPs are able to modulate P-Glycoprotein (P-gp) activity or to induce P-gp expression.

Within this dissertation different model MRPs were formed by using the protocol of COST Action 919 and fractionated into water soluble and ethanol soluble MRPs. To assess the functional activity of P-glycoprotein the fluorescent dye Rhodamine 123 (RH 123) was used as a model P-gp substrate. The colon cell lines Caco-2 and LS180 were exposed to model MRPs for 48 h and subsequent changes in RH 123 accumulation were measured. In contrast to Caco-2 cells LS180 cells only express P-gp after treatment with inducers of P-gp expression. Following treatment with model MRPs a reduced uptake of P-gp substrate RH 123 could be observed only by certain water soluble model MRPs. Among them Glucose-Prolin (Glc-Pro) showed the strongest influence on cellular uptake. This effect appeared merely in LS180 cells in a time dependend manner and could be reversed by the potent P-gp inhibitor Elacridar. The influence of water soluble MRPs on the P-gp expression of Caco-2 and LS180 cells was determined by Western Blotting. A 48 h incubation of LS180 cells revealed an enhanced P-gp protein amount only in Glc-Pro treated cells in contrast to untreated cells. These findings demonstrate that the reduced RH 123 accumulation by water soluble MRPs of Glc-Pro could be explained by an induced expression of P-gp. In comparison to Caco-2 cells LS180 cells exhibit the Pregnane X receptor (PXR), the key receptor for inducing P-gp expression. Consequently water soluble MRPs of Glc-Pro assumedly induce P-gp expression with participation of PXR. In contrast none of the model MRPs showed an inhibition of P-gp in RH 123 accumulation studies and transport studies with Caco-2 monolayer.

The second purpose of this dissertation was to examine the ability of short chain fatty acids (SCFAs) to modulate P-gp activity or to induce P-gp expression. SCFAs are the main products of colonic microbial fermentation of carbohydrates. SCFAs especially Butyrate are involved in processes of cell proliferation, differentiation and apoptosis. In RH 123 accumulation and transport studies with Caco-2 monolayer no inhibition of P-gp by SCFAs in various concentrations could be detected. However, Propionate, Butyrate, Valeriate and Iso-

valeriate exhibited an influence of P-gp expression. These SCFAs were able to reduce the RH 123 accumulation after an incubation for 48 h in Caco-2 and LS180 cells. Furthermore Propionate, Butyrate, Valeriate and Isovaleriate induced growth arrest in Caco-2 and LS180 cells, that is often associated with differentiation including an enhanced P-gp expression. In addition to these findings P-gp protein levels were determined by Western Blotting after a 48 h exposure of SCFAs. Western Blot analysis confirmed that among the SCFAs only Propionate, Butyrate, Valeriate and Isovaleriate were able to induce P-gp expression. Enhanced P-gp protein contents could be observed in both colon cell lines. This implicated a role of the Vitamin D receptor (VDR) in SCFA-induced P-gp expression. In all investigations Butyrate was most effective, whereas Formiate, Acetate, Isobutyrate and Capronate showed no effects according P-gp.