Mutagenic and antimutagenic activity of food compounds
Application of a dynamic in vitro gastrointestinal model

Exposure of humans to potential mutagenic and carcinogenic food compounds through the diet is unavoidable. On the other hand, there is epidemiological evidence for antimutagenic and anticarcinogenic properties of food as well (such as vegetables and fruit). The assessment of carcinogenic and cancer preventive properties of food compounds is generally restricted to genotoxicity assays available for the evaluation of manmade chemicals. Specific processes related to the gastrointestinal tract, such as digestion and bioaccessibility and interactions between various food components received little attention in the assessment of (anti)mutagenic and (anti)carcinogenic dietary compounds. A dynamic in vitro gastrointestinal model (TIM system), which simulates the human physiological conditions in the digestive tract, was used to study these processes.

The aim of the studies described in this thesis was to investigate whether this dynamic in vitro gastrointestinal model, in combination with in vitro genotoxicity assays, is a suitable tool for the assessment of (anti)mutagenic activity of food compounds.

In this TIM system the availability for absorption of food mutagens, such as heterocyclic aromatic amines (HAA) present in prepared meat, was studied. Furthermore, the mechanisms involved in the antimutagenic activity of green tea and black tea and their interaction with HAA were investigated. The addition of a food matrix, such as meat, milk or breakfast, influenced the availability for absorption and (anti)mutagenic activity of HAA and tea.

The antimutagenic activity of tea was also studied in a crossbreed dlb-1/lacZ transgenic mice model. However, a convincing antimutagenic effect of green and black tea in the small intestine could not consistently be demonstrated in vivo, in which B(a)P was used to induce mutations in the endogenous dlb-1 gene and in the lacZ transgene in the same animal.

Besides the presence of mutagens in the diet, mutagens can also be formed in the human body, e.g. at a low pH present in the stomach. The intragastric formation of nitrosamines, by a reaction of amine (derived from various fish species) and nitrite (produced by salivary bacteria after consumption of nitrate), was investigated under various human physiological conditions in the gastric compartment of the TIM system. Higher levels of nitrosamines were formed than expected on the basis of other in vitro models, but lower amounts than based on urinary excretion of nitrosamines in human studies. The nitrosation reaction was effectively inhibited by the addition of ascorbic acid (vitamin C) or green or black tea, which corresponds to in vivo studies.

In the large-intestinal-model it was demonstrated that inter individual differences were observed in the conversion of the glucosinolate into isothiocyanate, a metabolite which possibly has anticarcinogenic properties, by the human colonic microflora.

In conclusion, the dynamic in vitro gastrointestinal model, in combination with in vitro genotoxicity assays, is a useful tool for the assessment of mutagenic and antimutagenic activities of food compounds and suitable for mechanistic studies. The use of this in vitro gastrointestinal model will contribute to the further reduction of the number of laboratory animal studies.

10 key-words
- gastrointestinal model
- intestine
- gut
- bioavailability
- mutagenicity
- antimutagenicity
- food compounds
- tea
- transgenic mice
- nitrosodimethylamine
- microbial bioconversion
- glucosinolates
- alternative to laboratory animals