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SEARCH FOR DIETARY CONSTITUENTS WHICH PROTECT TOWARDS HETEROCYCLIC AROMATIC AMINES (HAs)

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The increasing evidence for the involvement of food borne HAs in the aetiology of human cancer has stimulated intense efforts to identify dietary constituents which protect against these compounds. About 280 articles on this topic have been published in the last 20 years, most of them were antimutagenicity studies with indicator cells that require addition of exogenous activation mix. The experimental models do not adequately reflect protective mechanisms that are active in vivo and may give misleading results. Therefore we developed protocols for improved test systems namely single cell gel electrophoresis (SCGE) assays with human derived liver (HepG2) cells which possess enzymes involved in the metabolism of the HAs, and SCGE assays with laboratory rodents which enable to measure induction of DNA-migration in organs which are targets for tumour induction by HAs. To verify if DNA-protective effects were paralleled by anticarcinogenic properties, foci assays were used which allow to monitor in parallel the induction of preneoplastic lesions in liver and colon. We used these models to investigate the effect of cruciferous vegetables (cress, Brussels sprouts, red cabbage) and their breakdown products and found indeed protection on the level of DNA-damage and foci inhibition. These effects could not be attributed to isothiocyanates which are considered to be the active principles of *Cruciferae*. The fact that pronounced effects were seen already with small amounts of crude vegetable juices, which supports the assumption that protective effects can be expected in humans as well. Enzyme measurements indicated that the inhibition of DNA-damage elicited by the vegetables is due to induction of UDPGT which plays a key role in the detoxification of amines.

Human intervention studies provide evidence that Brassica consumption in humans lead to a change in the pattern of HA induced urinary mutagenicity and that this phenomenon might also be causally related to increased glucuronidation. However with Brussels sprouts we saw also protective effects when the juices were given in the animal experiments after exposure to the HAs; the mechanisms involved in these suppressing mode of action are still unclear. Another important, hitherto neglected factor which plays a crucial role in the health effect of the HAs is the composition of the intestinal microflora. We found that presence of the intestinal micro organisms causes a strong enhancement of the DNA-damaging effects of HAs. At present we attempt to elucidate the underlying mechanisms and characterise intestinal micro organisms which affect the carcinogenic and mutagenic activities of HAs and red cabbage (Reliant). The induction of GST was about 3-fold for red cabbage (Roxy), 1,8-fold and 2,5-fold for Brussels sprouts (Cyrus) and for red cabbage (Reliant) whereas broccoli (Montop) and white cabbage (Kilor) were negative. In a second study series the impact of different food processing methods was evaluated using red cabbage (Roxy). No correlations between GST induction and gender, GST and GST genotypes could be established. It is known from epidemiological studies that impaired GST is associated with increased rates of specific forms of cancer in humans (lung-, prostate-, breast-, testicular-, esophageal-, and colon cancer), therefore the induction of GST by vegetable diets could be protective against genotoxic carcinogens moreover since in epidemiological studies consistently decreased cancer risks are associated with increased uptake of Brassicas.

We also investigated the effect of red cabbage on the urinary excretion of meat induced urinary mutagenicity. Red cabbage was consumed for five days, then a hamburger meal was consumed. The urinary mutagenicity was measured in Ames tests with *S. typhimurium* 1024 and a pronounced decrease in urinary mutagenicity was seen after the vegetable diet. Results from chemical analyses (Prof. Mark Knize, Livermore, U.S.A.) with the heterocyclic aromatic amine PhIP suggest that the shift in mutagenicity might be due to enhancement of glucuronidation reactions. Overall the results from our studies suggest that cruciferous vegetables affect the metabolism of carcinogens in humans.