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Red meat-derived endogenously formed N-nitroso compounds and colon cancer (#41)

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Short Abstract

Introduction

In Germany, around a half million cancer cases per year are newly diagnosed. Colorectal cancer is the second most frequent cancer type in women and the third most frequent cancer type in men. Although the methods to detect colorectal cancer have strongly improved in the last ten years, the number of newly diagnosed colorectal cancer cases and the number of colorectal cancer-associated death cases have remained quite constant or slightly decreased in the last 20 years in Germany. Risk factors contributing to the development of colorectal cancer are, among others, a fiber-poor, fat-rich diet (including a high amount of red meat), a high consumption of alcoholic beverages, smoking, a genetic predisposition, chronic inflammatory bowel disease and low physical activity. The available epidemiological evidence led the International Agency for Research on Cancer (IARC) in Lyon, France, to conclude that the consumption of red meat is probably carcinogenic to humans (i.e. IARC Group 2A) and the consumption of processed meat is carcinogenic to humans (i.e. IARC group 1). The consumption of red meat leads to the formation of nitroso compounds in the human gut, and it has been postulated that endogenously formed nitroso compounds might contribute to the development of colorectal carcinomas. In the present lecture, the evidence for the above-mentioned hypothesis as well as recent data on the DNA damaging and cell transforming activity of nitrosyl heme, one of the main endogenously formed nitroso compounds, will be presented.

Results

The consumption of red meat is known to stimulate the formation of nitroso compounds in the gut of volunteers [1] and the amount of endogenously formed nitroso compounds depends on the amount of ingested red meat, i.e. it increases "dose"-dependently [2, 3]. It has been postulated that these endogenously formed nitroso compounds can lead to the alkylation of guanine at the O^6-position, resulting in the formation of the pro-mutagenic DNA lesions O^6-methylguanine and O^6-carboxymethylguanine [4]. In fact, Lewin *et al*. [4] showed that O^6-carboxymethylguanine adducts were detected in exfoliated cells present in faeces of volunteers having consumed a high amount of red meat and that the amount of fecal nitroso compounds correlated positively with the percentage of cells staining positive for O^6-carboxymethylguanine. At that time, Lewin *et al*. [4] hypothesized that O^6-carboxymethylguanine adducts were not repaired, and that the formation of these adducts, along with other related and potentially not repaired adducts, could lead to gene mutations and, subsequently, to the development of colorectal cancer, i.e. a cascade of molecular events that could explain the association of red meat consumption with the development of colorectal cancer.

More recently, the DNA damaging potential of nitrosyl heme, a lead compound among the endogenously formed nitroso compounds in which a NO group is bound to the iron atom in the heme molecule, and hematin, the heme molecule in which an hydroxyl group is bound to the iron atom, were compared in the Comet assay. Hematin and nitrosyl heme led to a concentration-dependent increase in the tail intensity of the comets formed, whereby hematin proved to be more potent than nitrosyl heme. The ability of nitrosyl heme and hematin to induce gene mutations was analyzed in the hypoxanthine-guanine phosphoribosyl transferase assay. The assay revealed that both compounds were mutagenic, but only nitrosyl heme lead to a statistically significant increase in the number of induced mutations. The cell transforming activity of nitrosyl heme and hematin was tested in the BALB/c 3T3 cell transformation assay: Only hematin led to a concentration-dependent increase in the number of transformed cell foci.

Conclusion

Earlier studies clearly showed that: 1) nitroso compounds were formed in a concentration-dependent manner in the gut when red meat was consumed by volunteers; 2) nitroso compounds led to the formation of O^6-carboxymethylguanine adducts in exfoliated cells present in faeces of these volunteers; 3) the amount of fecal nitroso compounds correlated positively with the percentage of cells staining positive for O^6-carboxymethylguanine. Very recent mechanistic experiments revealed that hematin and nitrosyl heme, one of the lead compounds among the endogenously formed nitroso compounds, possess genotoxic potential, whereby only hematin led to the malignant transformation of cells in an internationally validated assay. Taken together, these results suggest that the heme molecule present in red meat could contribute to the development of colorectal cancer in humans and the iron moiety in the heme molecule plays a critical role in the malignant cell transformation process. Based on the pesented results and in accordance with the German Nutrition Society, it is recommended that the consumption of red meat and meat products is limited to an amount of 600 g per week.

Notes

References

1. Bingham, S.A. *et al.* (1996) Does increased endogenous formation of *N*-nitroso compounds in the human colon explain the association between red meat and colon cancer? Carcinogenesis 17: 515-523.
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4. Lewin, M.H. *et al.* (2006) Red meat enhances the colonic formation of the DNA adduct O^6-carboxymethyl guanine: implications for colorectal cancer risk. Cancer Res. 66: 1859-1865.

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