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Nitrosylation of the red meat compound heme does not increase its genotoxic, mutagenic and cell transforming potential

Tina Kostka[1, 2], Jörg Fohrer[3], Claudia Guigas[4], Karlis Briviba[4], Nina Seiwert[2], Jörg Fahrer[2], Pablo Steinberg[1, 4], Michael T Empl[1]

[1] Institute for Food Toxicology, University of Veterinary Medicine Hannover, Hannover, Germany
[2] Division of Food Chemistry and Toxicology, Department of Chemistry, Technical University of Kaiserslautern, Kaiserslautern, Germany
[3] Department of Chemistry, Technical University of Darmstadt, Darmstadt, Germany
[4] Max Rubner-Institut, Federal Research Institute of Nutrition and Food, Karlsruhe, Germany

The consumption of processed and red meat is associated with a higher risk of developing colorectal cancer (CRC). While heme may be responsible for the red meat-mediated higher CRC incidence, the influence of processed meat on CRC development is less known. The addition of curing salt (sodium nitrite) to meat induces the formation of *N*-nitroso compounds, mainly nitrosylated heme (NO-heme). Due to the high reactivity of nitric oxide, it is hypothesized that NO-heme may actually possess the highest carcinogenic potential in processed red meat. Therefore, NO-heme was toxicologically characterized and compared to non-nitrosylated heme.

NO-heme was synthesized by nitrosylation of hemin, followed by purification and chemical characterized. Both compounds, i.e. heme as well as NO-heme, showed significant and dose-dependent genotoxic effects in Caco-2 cells with a fairly higher number of DNA strand breaks being induced by heme. Heme and NO-heme were highly mutagenic in mammalian cells in the HPRT test, but not in a bacterial reverse mutation assay using various *S. typhimurium* strains. In the Balb/c 3T3 cell transformation assay, a significant difference between both substances was detected, with heme but not NO-heme inducing malignant cell transformation. In conclusion, both heme compounds were genotoxic and mutagenic, while the effects of NO-heme were generally lower than those induced by heme alone. This lower toxicity of NO-heme may results from its chemical instability and degradation, which causes the formation of the malaria pigment β-hematin.

Up to now, β-hematin has never been described as a component of the human diet or been associated with CRC development. Its potential endogenous formation and the contribution of β-hematin to the toxic effect of heme will be investigated in future studies.