ROLE OF DIET IN BIOTRANSFORMATION AND DNA ADDUCT FORMATION IN ENVIRONMENTAL TOXICANT-INDUCED COLON CARCINOGENESIS

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Abstract: Colorectal cancer is a contributing factor for significant mortalities in the United States, with 50,000 deaths per year and around 150,000 new cases expected to be diagnosed in this year. Consumption of well-done red meat and fats, rich in food-borne environmental toxicants such as benzo(a)pyrene [B(a)P] has also been implicated as one of the causative factors for sporadic colon cancer. Thus, on one hand, diet-induced obesity and on the other hand exposures to environmental toxicants contribute to the development of sporadic colon cancer. Therefore, the objective of this study was to investigate whether the colon polyp burden was accelerated by high fat diet consumption when exposed to toxicants. For our studies we used an adult male rat model, the Polyposis in the Rat Colon (PIRC) kindred type. Groups of PIRC rats (n = 8) were fed with AIN-76A regular diet (RD) or Western diet (WD) and received 25, 50 and 100 µg B(a)P/kg body wt. via oral gavage for 60 days. Rats that were fed with the diets alone, but no B(a)P served as controls. Subsequent to exposure, rats were euthanized; colon, liver were retrieved and polyps were enumerated. Blood samples were collected and plasma was harvested. Colon and liver samples were analyzed for expression and activities of CYP1A1, CYP1B1, UDPGT, ST and GST drug metabolizing enzymes (DME). Benzo(a)pyrene metabolite concentrations in plasma, colon and liver samples were measured using a HPLC equipped with UV and fluorescence detectors. The colon tumor counts and sizes were more in B(a)P + WD rats compared to their B(a)P + RD counterparts, and also exhibited a B(a)P dose-response relationship. Western diet consumption increased metabolic activation and reduced detoxification among rats that were given B(a)P + WD. Benzo(a)pyrene exposure through WD altered its metabolic fate in a dose-dependent manner, with 100 µg/kg dose group registering an elevated expression of B(a)P biotransformation enzymes, and greater concentration of B(a)P metabolites, compared to the 50- and 25 µg/kg dose group (P<.05). This effect was more marked for WD group compared to RD group (P<.05). These findings establish that WD causes sustained induction of B(a)P biotransformation enzymes and metabolism of this toxicant. As a consequence, B(a)P metabolites were generated to a greater extent in colon and liver. These metabolites were found to bind with DNA and form B(a)P-DNA adducts, which may have contributed to colon tumors in a long-term (subchronic) exposure regimen. In summary, our studies established that WD potentiates the development of colon tumors caused by B(a)P in the PIRC rat through pro-inflammatory action, characterized by gain in tumor number and sizes, mediated by DMEs, resulting in greater concentrations of B(a)P reactive metabolites and B(a)P-DNA adducts.

Key words: Benzo(a)pyrene, colon tumors, dietary fat, biotransformation, DNA adducts

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