DIETARY FAT POTENTIATION OF BENZO(a)PYRENE [B(a)P] BIOTRANSFORMATION, DNA ADDUCT FORMATION AND COLON TUMOR DEVELOPMENT IN Apc\textsuperscript{Min} MICE

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Abstract: Our studies thus far have shown formation of colon tumors in Apc\textsuperscript{Min} mice subsequent to ingestion of fat containing BaP, an environmental toxicant. These findings have human health relevance in that in US alone, around 60,000 lives/year are lost to colon cancer. Diet and environment have been implicated in the development of sporadic colon tumors. Since biotransformation of toxicants is the prime driving force for carcinogenesis, the objective of this study was to determine how dietary fat potentiates the development of colon tumors through altered BaP biotransformation, using a mouse model. Benzo(a)pyrene was administered to Apc\textsuperscript{Min} mice in unsaturated- (peanut oil) and saturated- (coconut oil) fats at doses of 50 and 100 \( \mu \)g/kg via oral gavage over a 60-day period. Blood, colon and liver were collected at the end of exposure period. The expression of BaP biotransformation enzymes (CYP1A1, CYP1B1 and GST) in liver and colon were assayed at the level of mRNA and activities. Tissue samples were analyzed by reverse phase-HPLC for BaP metabolites, and \( ^{32} \)P-postlabeling method for BaP-DNA adducts. BaP exposure through dietary fat altered its metabolic fate in a dose-dependent manner, with 100 \( \mu \)g/kg dose group registering an elevated expression of BaP biotransformation enzymes, greater concentration of BaP metabolites, BaP-DNA adducts and more adenomas compared to the 50 \( \mu \)g/kg dose group (\( p < 0.05 \)). This effect was more pronounced for saturated fat group compared to unsaturated fat group (\( p < 0.05 \)). Our findings establish that saturated fat causes sustained induction of BaP biotransformation enzymes and extensive metabolism of this toxicant. As a consequence, the reactive metabolites generated in colon and liver bind with DNA, form adducts resulting in colon tumors in a subchronic exposure regimen.

Key words: Benzo(a)pyrene, Biotransformation enzymes, DNA adducts, Colon tumors

Acknowledgements: This research was supported by NIH grants 1F31ES017391-01, 1RO1CA142845-01A1, RO3CA130112-01, 5T32 HL007735-14, S11ES014156, 5-G12-RR03032, and U54RR026140.