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Benzo(a)pyrene induces oxidative stress, pro-inflammatory cytokines, expression of nuclear factor-kappa B and deregulation of wnt/beta-catenin signaling in colons of BALB/c mice

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ABSTRACT

The incidence of colonic toxicity has been epidemiologically linked to the consumption of foods contaminated with benzo(a)pyrene (B[a]P). The present study investigated the effects of B[a]P on biomarkers of oxidative stress, inflammation and wnt-signaling in colon of BALB/c mice following exposure to 62.5, 125 and 250 mg/kg of B[a]P for 7 days by oral gavage. Exposure to B[a]P significantly decreased the colonic antioxidant enzymes activities and glutathione level with concomitant significant increase in myeloperoxidase activity, nitric oxide and lipid peroxidation levels. Colon histopathology results showed treatment-related lesions characterized by atrophy, mucosal ulceration and gland erosion in the B[a]P-treated mice. Immunohistochemistry analysis showed that B[a]P treatment increased the protein expression of nuclear factor kappa B, pro-inflammatory cytokines namely tumor necrosis factor alpha and interleukin-1β, as well as cyclooxygenase-2 and inducible nitric oxide synthase in the mice colon. Altered canonical wnt-signaling was confirmed by strong diaminobenzidine staining for p38 mitogen activated protein kinase, β-catenin expression and absence of adenomatous polyposis coli following B[a]P administration. The present data highlight that exposure to B[a]P induces colon injury via induction of oxidative and nitrosative stress, inflammatory biomarkers and dsyregulation wnt/β-catenin signaling, thus confirming the role of B[a]P in the pathogenesis of colonic toxicity.

1. Introduction

Benzo(a)pyrene (B[a]P) is an environmental and food-borne pollutant often generated during industrial processes, anthropogenic activities including burning of municipal refuse, cigarette smoke, automobile emissions as well as culinary processes namely frying, roasting and curing (ATSDR, 1995; Lee and Shim, 2007; Adedara et al., 2015a). One of the major routes of exposure is through consumption of B[a]P-contaminated diet (Archibong et al., 2008). Thus, predisposing the epithelial intestinal cells to be the first point of contact with B[a]P following oral ingestion. B[a]P exhibits its deleterious effects after being metabolically oxidized into biologically reactive epoxides by CYP1 isoforms of cytochrome P450 monooxygenases (Archibong et al., 2008). Moreover, B[a]P is well documented as a potent mutagenic, carcinogenic and pro-oxidative agent in experimental animals (Wijnhoven et al., 2000; Wester et al., 2012). It is bio-transformed to reactive metabolites such as B[a]P-7,8-epoxide, BaP-7,8-dihydrodiol 9,10-epoxide and quinones which subsequently damage the DNA and generate excessive reactive oxygen (Archibong et al., 2008).

Benzo[a]pyrene metabolism takes place basically in all tissues, with high metabolic capacity in the hepatocytes. Exposure to B[a]P has been linked to genotoxicity in human cell line (Genies et al., 2013) and carcinogenesis with severe damage to reproductive, hematopoietic, hepatic, and renal tissues in experimental animals (Knuckles et al., 2001). The primary role of the colon is to remove water, salts and nutrients from partially digested food and subsequently, pushes the residue to the rectum and anus for egestion. Hence, the sensitivity of colon to xenobiotics toxicity results from its ability to concentrate the chemicals it contains. In fact, the colon has been reported to metabolically activates B[a]P into its reactive electrophilic metabolites (Harris et al., 2009; Mantey et al., 2014). Several experimental investigations in mice demonstrated that exposure to B[a]P or in combination of with dextran sulfate sodium

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