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Molecular Signaling Involved in the 'Benzo(a)Pyrene' Induced Germ Cell DNA Damage and Apoptosis: Possible Protection by Natural Aryl Hydrocarbon Receptor Antagonist and Anti-Tumor Agent

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Abstract : Benzo(a)pyrene [B(a)P] is an environmental toxicant present mostly in cigarette smoke and car exhaust, is an aryl hydrocarbon receptor (AhR) ligand that exerts its toxic effects on both male and female reproductive systems. In this study, the effect of B(a)P at different doses (0.1, 0.25, 0.5, 1 and 5 mg /kg body weight) was studied on male reproductive system of rat. A significant decrease in cauda epididymal sperm count and motility along with the presence of sperm head abnormalities and altered epididymal and testicular histology were documented following B(a)P treatment. B(a)P treatment resulted apoptotic sperm cells as observed by TUNEL and Annexin V-PI assay with increased ROS, altered sperm mitochondrial membrane potential ($\Delta\Psi m$) with a simultaneous decrease in the activity of antioxidant enzymes and GSH status. TUNEL positive apoptotic cells also observed in testis as well as isolated germ and Leydig cells following B(a)P exposure. Western Blot analysis revealed the activation of p38MAPK, cytosolic translocation of cytochrome-c, up-regulation of Bax and inducible nitric oxide synthase (iNOS) with cleavage of PARP and down-regulation of BCl2 in testis upon B(a)P treatment. The protein and mRNA levels of testicular key steroidogenesis regulatory proteins like StAR, cytochrome P450 IIA1 (CYPIIA1), 3β HSD, 17β HSD showed a significant decrease in a dose dependent manner while an increase in the expression of cytochrome P450 1A1 (CYP1A1), Aryl hydrocarbon Receptor (AhR), active caspase- 9 and caspase- 3 following B(a)P exposure. We conclude that exposure of benzo(a)pyrene caused testicular gamatogenic and steroidogenic disorders by induction of oxidative stress, inhibition of StAR and other steroidogenic enzymes along with activation of p38MAPK and initiated caspase-3 mediated germ and Leydig cell apoptosis.The possible protective role of naturally occurring phytochemicals against B(a)P induced testicular toxicity needs immediate consideration. Curcumin and resveratrol separately were found to protect against B(a)P induced germ cell apoptosis, and their combinatorial effect was more significant. Our present study in isolated testicular germ cell population from adult male Wistar rats, highlighted their synergistic protective effect against B(a)P induced germ cell apoptosis. Curcumin-resveratrol co-treatment decreased the expression of pro-apoptotic proteins like cleaved caspase 3,8,9, cleaved PARP, Apaf1, FasL, tBid. Curcumin-resveratrol co-treatment decreased Bax/Bcl2 ratio, mitochondria to cytosolic translocation of cytochrome c and activated the survival protein Akt. Curcumin-resveratrol decreased the expression of p53 dependent apoptotic genes like Fas, FasL, Bax, Bcl2, Apaf1.Curcumin-resveratrol co-treatment thus prevented B(a)P induced germ cell apoptosis. B(a)P induced testicular ROS generation and oxidative stress were significantly ameliorated with curcumin and resveratrol. Curcumin-resveratrol co-treatment prevented B(a)P induced nuclear translocation of AhR and CYP1A1 production. The combinatorial treatment significantly inhibited B(a)P induced ERK 1/2, p38 MAPK and JNK 1/2 activation. B(a)P treatment increased the expression of p53 and its phosphorylation (p53 ser 15). Curcumin-resveratrol co-treatment significantly decreased p53 level and its phosphorylation (p53 ser 15). The study concludes that curcumin-resveratrol synergistically modulated MAPKs and p53, prevented oxidative stress, regulated the expression of pro and anti-apoptotic proteins as well as the proteins involved in B(a)P metabolism thus protected germ cells from B(a)P induced apoptosis.

Keywords : benzo(a)pyrene, germ cell, apoptosis, oxidative stress, resveratrol, curcumin
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