World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:10, No:07, 2016

Resveratrol Ameliorates Benzo(a)Pyrene Induced Testicular Dysfunction and Apoptosis: Involvement of p38 MAPK/ATF2/iNOS Signaling

Authors : Kuladip Jana, Bhaswati Banerjee, Parimal C. Sen

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 along with carcinogenesis in skin, prostate, ovary, lung and mammary glands. Our study was focused on elucidating the molecular mechanism of B(a)P induced male reproductive toxicity and its prevention with phytochemical like resveratrol. 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 Wistar 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 Reactive Oxygen Species (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 p38 mitogen activated protein kinase (p38MAPK), cytosolic translocation of cytochrome-c, upregulation of Bax and inducible nitric oxide synthase (iNOS) with cleavage of poly ADP ribose polymerase (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 steroidogenic acute regulatory protein (StAR), cytochrome P450 IIA1 (CYPIIA1), 3β hydroxy steroid dehydrogenase (3β HSD), 17β hydroxy steroid dehydrogenase (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. Next we investigated the role of resveratrol on B(a)P induced male reproductive toxicity. Our study highlighted that resveratrol co-treatment with B(a)P maintained testicular redox potential, increased serum testosterone level and prevented steroidogenic dysfunction with enhanced expression of major testicular steroidogenic proteins (CYPIIA1, StAR, 3β HSD,17β HSD) relative to treatment with B(a)P only. Resveratrol suppressed B(a)P-induced testicular activation of p38 MAPK, ATF2, iNOS and ROS production; cytosolic translocation of Cytochome c and Caspase 3 activation thereby prevented oxidative stress of testis and inhibited apoptosis. Resveratrol co-treatment also decreased B(a)P-induced AhR protein level, its nuclear translocation and subsequent CYP1A1 promoter activation, thereby decreased protein and mRNA levels of testicular cytochrome P4501A1 (CYP1A1) and prevented BPDE-DNA adduct formation. Our findings cumulatively suggest that resveratrol prevents activation of B(a)P by modulating the transcriptional regulation of CYP1A1 and acting as an antioxidant thus prevents B(a)P-induced oxidative stress and testicular apoptosis.

Keywords : benzo(a)pyrene, resveratrol, testis, apoptosis, cytochrome P450 1A1 (CYP1A1), aryl hydrocarbon receptor (AhR), p38 MAPK/ATF2/iNOS
Conference Title : ICTAP 2016 : International Conference on Toxicology and Applied Pharmacology
Conference Location : Paris, France
Conference Dates : July 25-26, 2016