PROTECTIVE IMPACT OF NATURAL ARYL HYDROCARBON RECEPTOR ANTAGONIST ON BENZO(A)PYRENE INDUCED MALE REPRODUCTIVE DYSFUNCTIONS AND INFERTILITY: A TRANSLATIONAL APPROACH

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Objective: Benzo(a)pyrene (B(a)P) is an environmental pollutant that induces spermatogonial germ cell apoptosis and Leydig cell steroidogenic dysfunction. Thus it induces male reproductive toxicity. We investigated the magnitude of natural aryl hydrocarbon receptor antagonist (3,5,4′-trihydroxy-trans-stilbene, Res) against B(a)P induced male reproductive dysfunction. Natural phytochemicals with anti-oxidative and aryl hydrocarbon receptor antagonistic property, are interesting protective agents against environmental toxicant like B(a)P.
Design: The animals were gavaged B(a)P and aryl hydrocarbon receptor antagonist in combination, in different study groups daily for 60 days. Control animals received only the vehicle for the period. Blood, caudae epididymal sperm and testis were collected from the experimental animals. Testicular germ cell and Leydig cell population was isolated.
Setting: National Laboratory Research Center
Animal(s): Adult male Wistar rats.
Intervention(s): Western blot, RT-PCR, ChIP assay, Flowcytometry, Histology and TUNEL staining of tissues, Immuno-cytochemistry of cells, and ELISA were performed. Serum Testosterone, FSH and LH levels were measured. Germ cell and Leydig cell apoptosis were evaluated. The expression of different proteins related to stroidogenesis, apoptosis, oxidative stress and B(a)P signaling were studied.
Main outcome measure(s): Natural aryl hydrocarbon receptor antagonist (Res) is significantly able to protect the B(a)P induced male reproductive dysfunctions.
Result(s): B(a)P was induced oxidative stress, p53 dependent germ cell apoptosis and steroidogenic dysfunctions in testis. B(a)P exposure activated both intrinsic and extrinsic mode of germ cell apoptosis. B(a)P disturbed cellular Bax/Bcl2 rheostat, released cytochrome c, activated caspase 9 and 3. Besides that, B(a)P also altered Fas/FasL expression, activated Bid and caspase 8. In Leydig cell, Steroidogenic acute regulatory protein (StAR) expression and its promoter activation was significantly decreased by B(a)P. B(a)P was induced oxidative stress in Leydig cell and increased iNOS expression through the activation of p38MAPK and ATF2. Aryl hydrocarbon receptor antagonist (res) prevented promoter activation of cytochrome P4501A1 (CYP1A1) and subsequent B(a)P induced DNA adduct formation in germ and matured sperm cells. Res also prevented B(a)P induced sperm cell damage, morphological abnormality and apoptosis. Res modulated DAX1 and SF1 expression and thus maintained StAR gene expression and improved Leydig cell steroidogenesis. Our findings indicated that res co-treatment with B(a)P maintained testicular redox potential, prevented germ cell apoptosis, increased serum testosterone level and prevented steroidogenic dysfunctions.
Conclusions: Res being an antioxidant as well as a natural AhR antagonist, works as a double edged sword against the B(a)P induced male reproductive toxicity. Present day B(a)P induced toxicokinetics and its protection is not well elucidated in human. Res can come up with new hopes as the potential protector of reproductive health against B(a)P. It requires further studies and clinical trials to conclude on the dosage and efficiency of res as suitable protective agent against environmental reproductive toxicants in human subjects.