DIFFERENTIAL METABOLISM OF THE ENVIRONMENTAL TOXICANT, BENZO(A)PYRENE BY SUBCELLULAR FRACTIONS OF HUMAN OVARY

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Abstract: Knowledge of the ability of the female reproductive system to metabolize environmental chemicals is critical not only from the standpoint of toxicity, but also risk assessment. Benzo(a)pyrene (BaP) is one such environmental contaminant that enjoys ubiquitous distribution. This chemical is released into the environment from automobile exhausts, cigarette smoke, burning of refuse, industrial emissions, and hazardous waste sites. In exposed animals, BaP becomes activated to reactive metabolites that interfere with target organ function and as a consequence cause toxicity. Studies from animal models from our laboratories and those of others have shown that BaP possess endocrine disrupting properties. Thus, this chemical has the potential to cause infertility and cancers of the female genital tract. Therefore, an understanding of the process by which BaP is metabolized in the female reproductive system will be of importance in the diagnosis and management of female fertility as well as cancers of the reproductive tissues. Though the metabolism of BaP by human somatic tissue preparations has been previously examined, there have been no reports of BaP metabolism by human ovarian tissues or enzymes. Therefore, the objective of our study was to characterize the metabolism of BaP by human ovarian subcellular fractions. Human ovary samples (10 individuals) were obtained from postoperative tissue removed from human subjects with uterine tumors. Only the healthy, non tumorous tissue was used. Subcellular fractions (nuclear, cytosolic, mitochondrial, and microsomal) were prepared by differential centrifugation. The tritium-labeled BaP (5µM and 10µM) were individually incubated with individual subcellular fractions and cofactors for 15 min, and the products were analyzed by HPLC. The cytochrome P450 content and P450-linked activities (CYP1B1) were also determined. Among the different fractions tested, mitochondrial BaP metabolism was higher than the rest of the fractions. The BaP metabolites identified were as follows: BaP-9,10-diol; BaP-4,5-diol; BaP-7,8-diol; 9(OH) BaP; 1(OH) BaP; 3(OH) BaP; BaP-1,6-dione; BaP-3,6-dione; BaP-6,12-dione. Greater qualitative differences were observed between individual metabolite profiles. For e.g. the diol metabolites were detected in all the samples analyzed. While the 9(OH) and 1(OH) BaP metabolite was not present in 3 out of 10 samples, the 3(OH) BaP was invariably present in the samples. Among diones, the 1, 6-dione metabolites was infrequently detected. Among the diol metabolites, the subcellular fractions preferentially formed BaP-7, 8-dihydrodiol, a precursor to the DNA-reactive BaP-7,8-dihydrodiol epoxide (BPDE). Our findings are indicate marked differences in BaP metabolite profiles among the subjects and therefore may contribute to differential susceptibilities of individuals exposed to BaP. Additionally, the finding of preponderance of BaP-7, 8-dihydrodiol is interesting, given the fact that this precursor of BPDE has been linked to BaP-induced cancer and infertility. The influence of factors such as age, nutrition, pathological status, and polymorphism of drug metabolizing enzymes notwithstanding, individuals who are exposed to BaP via cigarette smoke, occupational settings and diet are at a larger risk.

Key words: Benzo(a)pyrene, subcellular fractions, ovary, metabolism, infertility

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