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Benzo[a]pyrene and Human Embryo

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1. Introduction

Benzo[a]pyrene (B[a]P) is a typical compound of the polycyclic aromatic hydrocarbons (PAHs), compounds that are usually generated through the combustion of fossil fuels, wood, and other organic materials and are found in significant amounts in diesel exhaust, cigarette smoke, charcoal-broiled foods, and industrial waste-by-products (Boström et al, 2000). B[a]P is readily absorbed following inhalation, oral, and dermal routes of administration (Knafla et al, 2006). B[a]P absorption activates the aryl hydrocarbon receptor (AhR), which forms an active transcription factor heterodimer with the AhR nuclear translocator (ARNT), and induces the expression of a group of genes called the Ah gene battery, including the cytochrome P450 1A1 (CYP1A1), CYP1A2, and CYP1B1 genes (Shimizu et al, 2000; Nebert et al, 2000).

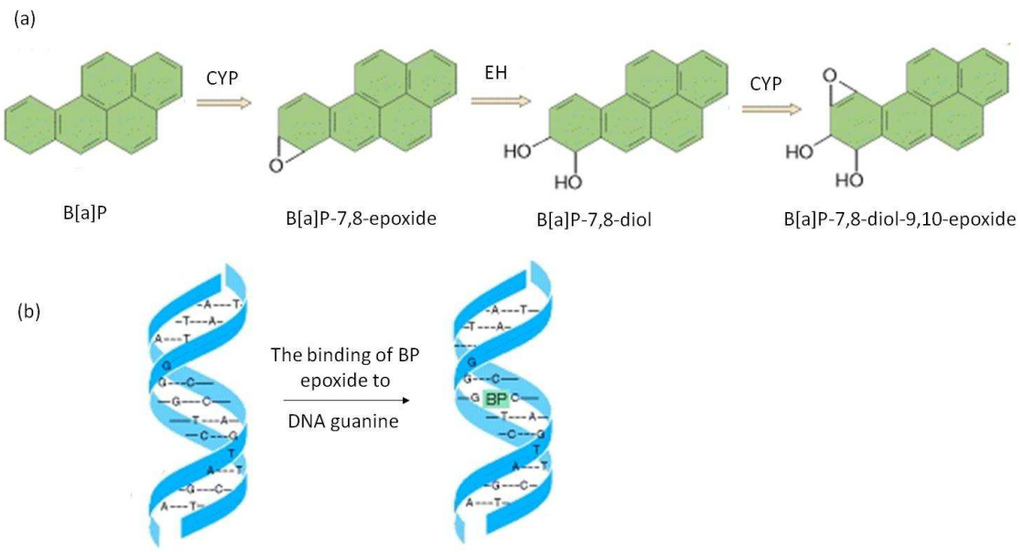

Fig. 1. The metabolic conversion of benzo[a]pyrene into a mutagen. (a) Benzo[a]pyrene goes through several steps as it is made more water soluble prior to excretion. (b) One of the intermediates in this process, B[a]P-7,8-diol-9,10-epoxide, is capable of reacting with guanine in DNA. This reaction leads to a distortion of the DNA molecule and mutations.

Several P450 enzymes are involved in key steps in the oxidation of B[a]P, and CYP1A1 has been demonstrated to be the most active in this oxidation in mammals (Chung et al, 2007). CYP1A1 activates B[a]P to B[a]P-7,8-epoxide, which through hydration by epoxide hydrolase (EH) is metabolized to (+/-)-B[a]P-trans-7,8-dihydrodiol (DHD). B[a]P-7,8-DHD may then serve as a substrate for a second CYP-dependent oxidation reaction, generating the ultimate carcinogenic metabolite r-7,t-8- dihydrodiol-t-9,10-oxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE-I) (Fig 1a). In the nucleus, the diol- epoxides may covalently bind to DNA, mainly forming deoxyguanoside-DNA adducts, which may result in misreplication and mutagenesis (Kaina, 2003) (Fig 1b).

2. Effects of benzo[a]pyrene on reproduction

Adverse reproductive effects were observed in several studies with B[a]P. Exposure of male and female zebrafish to B[a]P impaired reproduction in zebrafish (Hoffmann and Oris, 2006). Intraperitoneal administration of B[a]P to rat embryos has resulted in stillbirths, resorptions, and malformations; decreases in follicular growth and corpora lutea; and in testicular changes (Luijten et al, 2008). Subcutaneous injections of B[a]P produced increased resorptions in rats and direct embryonal injection led to decreased fetal survival in mice (Pereraa et al, 2005). In utero exposure to B[a]P has produced adverse reproductive effects in mice (Legraverend, et al, 1984). Dietary administration of doses as low as 10 mg/kg during gestation caused reduced fertility and reproductive capacity in offspring (Mackenzie and Angevine, 1981) and treatment by gavage with 120 mg/kg/day during gestation caused stillbirths and malformations (Legraverend et al, 1984).

2.1 Benzo[a]pyrene and male fertility

Spermatogenesis is carefully controlled to produce mature spermatozoa from spermatogonial stem cells in three major stages – the mitotic stage, the meiotic stage and the maturation stage (Verhofstad et al, 2010). Germ cells are susceptible for the induction of mutations during mitotic and meiotic divisions, because cell turnover is a prerequisite for fixation of DNA damage into mutations (Somers et al, 2002). Changes in the DNA sequence can be induced by exposure to chemicals during life, but may also be inherited via mutations in the spermatogonial stem cells, in that way increasing the risk of developing abnormalities or diseases in the offspring (Vilarino-Guell et al, 2003). B[a]P related DNA damages were observed at all stages of spermatogenesis (Zenzes et al, 1999), which were associated with significantly decreased sperm counts (Verhofstad et al, 2009).

Although B[a]P has been studied with respect to sperm DNA adducts (Kao et al, 1998) and apoptosis (Whitfield et al, 2002), few studies have evaluated its possible effect on sperm motion characteristics. Because the motion characteristics, hyperactivation status, and acrosomal reaction of spermatozoa indicate functional status and fertilizing potential (Cheo et al, 1997), it is worthwhile to note whether B[a]P has any effect on these parameters (Fig 2). A study of adult male F-344 rats showed that subchronic exposure to inhaled B[a]P contributed to reduced testicular and epididymal function (NTP, 2000). Moreover, some studies have proved that escalating hypermotility of spermatozoa occurs with increasing concentrations of B[a]P as a result of premature capacitation (Zenzes, 2000). B[a]P treatment can significantly decrease the percentage of halo formation, and the hyperactivation status

attained due to B[a]P treatment induces false acrosomal reactions in the spermatozoa (Yauk et al, 2008).

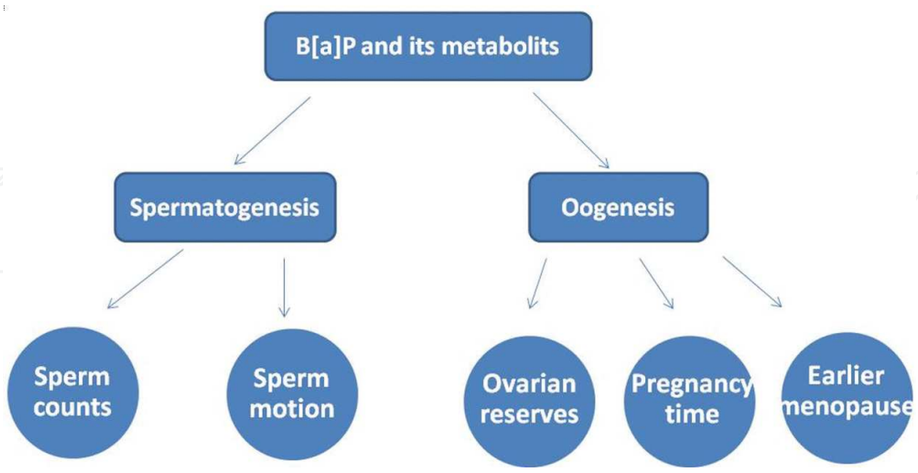

Fig. 2. Influence of benzo[a]pyrene on male and female fertility.

2.2 Benzo[a]pyrene and female fertility

Ovarian function can be compromised by exposure to toxic chemicals (Younglai et al, 2007). In addition, the ovary itself can be affected resulting in disturbances in oocyte maturation and/or destruction of the oocyte. The mechanism of B[a]P-mediated ovotoxicity may be indirect (Fig 2), since oocytes at all stages of development are surrounded by follicular cells (Hombach-Klonisch et al, 2005). A loss in integrity of this follicular wall by B[a]P may compromise its ability to maintain oocyte viability (El Nemr et al, 1998). Extensive damages of ovarian follicles would also impair steroid hormone production which, in turn, affects the endocrine balance and results in ovarian failure (Shiverick and Salafa, 1999). The carcinogenic metabolite (BPDE-I) is a diol epoxide derivative of B[a]P which binds predominantly to the 2-amino group of DNA guanosine and forms adducts. In ovarian tissue, BPDE-DNA adducts were detected in oocytes and luteal cells in ovaries of adult women who were exposed to cigarette smoke from smoking themselves or from second-hand smoke (Wright et al, 2006).

B[a]P was reported to cross the placenta in mice, rats, and guinea pigs following maternal injection, dermal, or inhalation exposure to B[a]P (Karttunena et al, 2010). Evidence from human studies indicates that BPDE–DNA adducts have been found in the placentas of smoking mothers (Motejlek et al, 2006). In addition, prolonged time to pregnancy, earlier mean age of menopause, altered ovarian steroidogenesis, and depleted ovarian reserves, have all been observed in women who smoke compared to non-smokers (Younglai et al, 2005). Inhalation exposure of pregnant rats or mice to B[a]P resulted in decreased numbers of live pups at birth (Archibong et al, 2002; Wu et al, 2003). Injection of B[a]P to pregnant rats resulted in decreased fetal weight and increased fetal death (Bui et al, 2003). Administration of B[a]P by ingestion to pregnant rats resulted in an increased number of stillborn pups (Perera et al, 2004). Injection of pregnant mice with B[a]P also resulted in measurable changes in some enzymes in lungs (pyruvate kinase and lactic acid dehydrogenase) of exposed fetuses (Parman and Wells, 2002).

3. Mechanisms of benzo[a]pyrene on reproductive toxicity

3.1 Oxidative stress and damage

B[a]P has been proved to be able to enhance the generation of reactive oxygen species (ROS) by inducing cytochrome P450 enzymes and free radiocals produced by B (a) P metabolism (Ji and Shen, 2009). Numerous studies demonstrated that B[a]P can induce oxidative DNA damage and the formation of teratogenic ROS, and B[a]P have been postulated, at least in part, to be involved in the underlying mechanisms in the teratogenicity of B[a]P (Wells et al, 2009). Most ROS are too unstable to travel beyond the cell, which are capable of damaging every molecule present inside the cell: carbohydrates, proteins, lipids and the DNA (Kovacic and Somanathan, 2006). Teratogenicity likely depends to a large extent upon a balance between the pathogenic pathways of xenobiotic bioactivation, oxidative macromolecular damage and signal transduction on one hand, and on the other, the protective pathways of maternal elimination, embryonic detoxification of xenobiotic reactive intermediates and reactive oxygen species, and embryonic pathways for the detection and repair of oxidative DNA damage (Jeng et al, 2005). Accordingly, embryopathic risk is theoretically determined by the balance between the pathogenic and embryoprotective pathways. The risk of ROS-mediated teratogenesis can be enhanced by either genetic or environmental determinants that increase embryonic xenobiotic bioactivation or decrease one or more of the antioxidants, so the teratologically relevant processes of embryopathic xenobiotic bioactivation and reactive intermediate detoxification, ROS formation and their associated protective pathways involving antioxidants and antioxidative enzymes, and pathways for the repair of oxidative DNA damage, all lie exclusively within the embryo.

3.2 Apoptosis and cell cycle

B[a]P has been shown to induce apoptosis and necrosis in various cell types (Ko et al, 2004; Patil et al, 2009). There are two major mitochondria-dependent pathways involved in apoptosis. One is mediated by Bax, a proapoptotic member of the Bcl-2 family. After receiving death signals, Bax is activated and inserts into the mitochondrial membrane, causing cytochrome c release, which triggers downstream apoptotic pathway, including apoptosome formation, caspase cascade activation, and nuclear degradation (Teijido and Dejean, 2010). B[a]P has been shown to activate apoptotic pathways in a number of studies using mammalian cell lines (Jiang et al, 2011). Other study with B[a]P in JEG-3 (human trophoblastic) cells found no evidence of apoptosis based on analysis of cell cycle phase distribution, DNA fragmentation, or Bax or Bcl-2 levels, which may due to concentration or cell type specific (Drukteinis et al, 2005).

Cell cycle regulation has been increasingly recognized as one of the important mechanisms required for the teratogenicity of B[a]P during the past several years. As reported, B[a]P induces cell cycle arrest in MCF-7 (human breast carcinoma) and HELF (human embryo lung fibroblasts) cells, and altered expression of genes that affect cell cycle regulation (Khan and Dipple, 2000; Gao et al, 2005). Moreover, cell cycle phases showed an accumulation of cells in the G1 and G2 phase after B[a]P exposure (Vaziri et al, 1997; Zhu et al, 2005). It has also been shown that BPDE, the metabolite of B[a]P, can induce a G2/M accumulation (Wang et al, 2003). In line with these findings, G1-S arrest was observed in testis of B[a]P exposed male mice(Verhofstad et al, 2010). B[a]P produces growth inhibition involving

G2/M arrest in JEG-3 trophoblastic cells (Drukteinis et al, 2005). Expression of G2/M phase genes showed a trend towards a higher induction of these genes in testis of mice after B[a]P exposure.

We and other have demonstrated that B[a]P could stimulate cell proliferation through certain signaling pathways (Jiao et al, 2008; Gao et al, 2007; Tannheimer et al, 1998). In addition, B[a]P-induced cell proliferation is accompanied by increased G1/S transition (Gao et al, 2006; Jia et al, 2006). Cyclin D1 serves as a key sensor and integrator of extracellular signals of cells in early to mid-G1 phase, involved in regulation of cell proliferation and differentiation (Neumeister et al, 2003). Cyclin D1 in complex with its partner, cyclin-dependent kinase 4 (CDK4), phosphorylates the product of the retinoblastoma gene, the retinoblastoma protein (pRb), a well known tumor suppressor. The phosphorylated pRb releases the E2F family that plays an integral role in cell cycle progression by inducing the expression of gene required for S phase entry (Wang et al, 2004). In a previous study, we found that B[a]P exposure also induces cyclin D1 overexpression in HELFs (Du et al, 2006; Ye et al, 2008). Exposure of HELF cells to B[a]P obviously induced cyclin D1 transcription in a dose- and time-dependent manners (Jiao et al, 2008). Cyclin D1/CDK4-E2F-1/4 pathways are also involved in the cell cycle changes in B[a]P-treated HELFs, but these pathways have different patterns in response to low dose and high dose B[a]P treatment: in cells treated with 2 μmol/L B[a]P, cyclin D1 positively regulates the expression of E2F-1, whereas CDK4 negatively regulates the expression of E2F-4; in cells treated with 100 μmol/L B[a]P, both cyclin D1 and CDK4 negatively regulate the expression of E2F-4 (Ye et al, 2008). All the above studies have demonstrated that cell cycle changes are involved in the teratogenicity of B[a]P.

3.3 Aberrant signaling pathways

Oxidative and genotoxic stress induced by B[a]P, activate checkpoint mechanisms for cell cycle control and apoptosis involving the p53 pathway and $p21^{CIP1}$ in mammalian cells (Pääjärvi et al, 2008). The importance of DNA damage detection is supported by the enhanced teratogenicity of B[a]P in p53 knockout mice (Nicol et al, 1995). We noted that primary sensors of DNA damage and stress appear to be the phosphotidyl-inostitol-3-(PI-3) kinases such as DNA-dependent protein kinase (DNA-PK), ATM (ataxia-telangiec-tasiamutated), and/or ATR(ATM related), with activation of p53 involving phosphorylation on serine 15 (Laposa et al, 2004; Bhuller and Wells, 2006).We previously found that PI-3K pathway was implicated in activator factor 1 (AP-1) transactivation induced by B[a]P (Gao, et al., 2007). C-Jun, a primary member components of AP-1 families, have been proved to be required for B[a]P-induced cell cycle alternation (Jiao et al, 2008). The conventional position of the c-Jun protein in the signaling transduction cascades is close to mitogen activated protein kinase (MAPK) family (Kennedy and Davis, 2003). Two subgroups of the MAPK family, extracellular signaling regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK), have been demonstrated to be able to activate c-Jun activation in B[a]P-treated HELF (Jiao et al, 2007). Other evidence shows that NF-κB signaling pathway might be involved during in the teratogenicity of B[a]P (Li et al, 2004).

4. Future work

Evidence from molecular studies in vitro combined with results from complementary studies in embryo culture and in vivo suggest that B[a]P in animal models contribute to both

constitutive origins of teratogenesis as well as a broad spectrum of B[a]P and its metabolites-initiated adverse developmental outcomes, including structural birth defects, traditionally referred to as teratogenesis, as well as developmental deficits and cancer in later postnatal life.

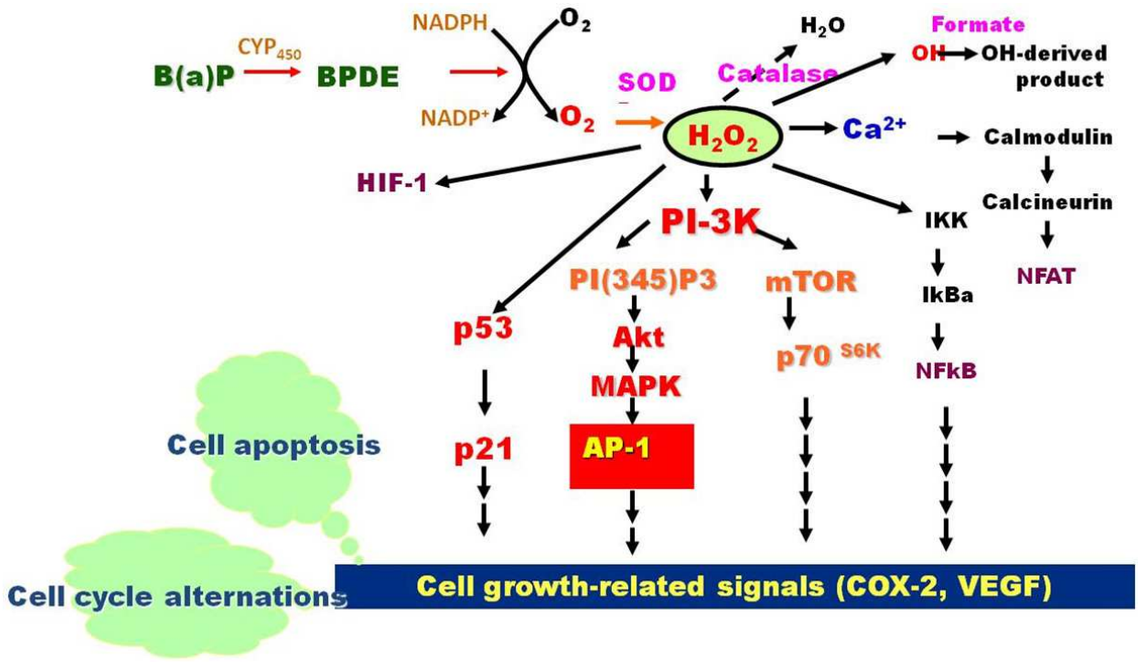

Fig. 3. Mechanism of benzo(a)pyrene-related reproduction toxicity.

At least some of probably mechanisms such as oxidative macromolecular damage, cell cycle alternation and signaling pathway aberrant activation, are involved in the the risk of teratogenesis of B[a]P (Fig 3). However, we still know relatively little about the full nature of B[a]P teratogenicity, particularly with regard to its signal transduction. It is likely that other important contributing signaling pathways remain to be discovered, and that more than one mechanism may contribute to the same adverse reproductive outcome. The results from animal studies provide a basis for similar evaluations in humans, for whom little information is available.

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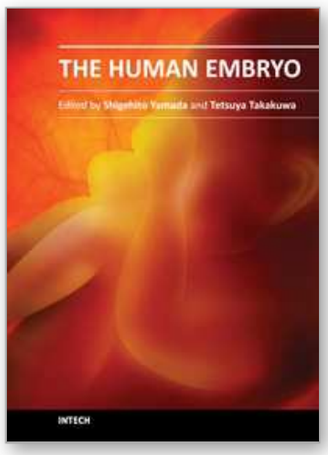

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Human embryology is now rapidly moving to a new phase due to recent innovation and advances of life science including ES and iPS technology. This new era also directs a difficult challenge for scientists in terms of technological and ethical issues for future human embryology. However, human embryology is difficult to research due to ethics involved in the collection of human materials. This book traces the early history and provides knowledge on demonstration of principles from ancient to the most recent embryo studies amidst the unresolved scientific and ethical issues. We hope this book will help the readers to understand human embryo development better.

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