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# 苯并[a]芘对生殖系统的毒性作用及其机制研究进展

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**摘要**: 苯并[a]芘(benzo(a)pyrene, BaP)作为多环芳烃(polycyclic aromatic hydrocarbons, PAHs)的成员,是最早发现也是最具有代表性的环境污染物,通过空气、食物、水源等途径进入人体,引起细胞氧化应激损伤、DNA 损伤和基因异常表达导致细胞死亡。研究表明雄性与雌性动物经 BaP 染毒后,其生殖器官、生殖细胞甚至激素水平均会受到影响,进而影响受精卵形成和胚胎发育,造成不良妊娠结局。因此,近年来 BaP 的生殖毒性受到广泛关注,其作用机制包括改变胞内活性氧水平、诱导细胞 DNA 损伤以及调控生殖发育相关基因、类固醇合成相关基因和促凋亡基因影响生殖发育。BaP 作为环境毒物,不仅可以影响生态环境的稳定性,还可以影响生物的生殖发育,损害生态环境中的物种多样性,从长远来看,BaP 的不良影响不但会威胁到陆地与海洋生物种群的稳定,还会破坏陆地和海洋生态系统的功能。本文将从生殖健康、配子与合子形成以及胚胎发育的角度,详细阐述 BaP 染毒对生殖系统的毒性作用与机制,为预防 BaP 引起的生殖危害、减少不良妊娠结局提供理论依据,旨在为 BaP 的环境毒性行为和对生物的毒性研究提供有效借鉴,为合理预防和缓解因接触 BaP 等环境毒物而带来的健康影响提供参考。

**关键词**: 苯并[a]芘(BaP);生殖细胞;生殖毒性;生殖器官;激素;细胞毒性
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# Research Progress on Toxic Effects of Benzo (a) pyrene on Reproductive System and Its Mechanism

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**Abstract**: Benzo(a)pyrene (BaP), as a member of the polycyclic aromatic hydrocarbons (PAHs), is the earliest discovered and most representative environmental pollutant. It enters the human body through the air, food, and water, causing cellular oxidative stress damage, DNA damage, and abnormal gene expression, leading to cell death. Studies have shown that when male and female animals are exposed to BaP, their reproductive organs, cells, and hormone

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levels are affected, which in turn will affect the formation of fertilized eggs and embryonic development, resulting in adverse pregnancy outcomes. Hence, the reproductive toxicity of BaP has received more attention in recent years. Its mechanism of action on reproductive development includes alteration of intracellular reactive oxygen species levels, induction of cellular DNA damage, and modulation of genetic changes related to reproductive development, steroid synthesis and pro-apoptosis. BaP, as an environmental toxicant, could influence the stability of the ecological environment, the reproductive development of organisms and destroy the diversity of species in the ecosystems. In this review, we will detailly elaborate on the toxic effects and mechanisms of BaP on the reproductive system, and provide a theoretical evidence for prevention reproductive harm caused by BaP and the reduction of adverse pregnancy outcomes, with the aim to providing an effective reference for the study of BaP's toxicity to the environment and organisms, and for the rational prevention and mitigation of the health effects of exposure to BaP or other environmental toxins.

**Keywords**: benzo(a)pyrene; germ cell; reproductive toxicity; genital organ; hormone; cytotoxicity

PAHs是由2个或2个以上的稠环芳烃组成的有机化合物[1],由于其化学性质稳定且具有疏水性[2],因此多环芳烃可以在环境中稳定存在,是常见的环境污染物,广泛存在于油炸烧烤食物、香烟烟雾[3]、汽车尾气[4]、煤炭燃烧[5]等中。人类可以通过空气、饮用水、食物等不同方式暴露于多环芳烃[6]。此外,多环芳烃的亲脂性有利于它们在水生生物的脂肪中积累[7],并随着食物链进入人体,对人类健康产生威胁。

BaP是多环芳烃中最具有代表性也是毒性最大的致癌物[8],可以诱发肺癌[9]、乳腺癌[10]等癌症,危害人类健康。BaP广泛存在于人类生活环境中,2019年公布的美国毒物和疾病登记机构物质优先清单中,BaP被列为第8名,在污染的空气[11]、土壤[12]、水源[13]、食物[14]中均可以检测到BaP。近年来,越来越多研究表明BaP与胚胎畸形[15]和不良妊娠[16]有着密切的联系。在妊娠早期暴露于BaP会导致小鼠胎儿畸形率增高[17]。此外,一项病例对照研究表明,接触BaP与早孕流产之间存在联系,妊娠女性发生流产的风险与血中BaP-DNA加合物的浓度成正比,这进一步说明BaP除了致癌性也具有生殖毒性。

目前对于BaP的研究多聚焦于其诱发癌症[18-19]尤其是肺癌[20]这一方面,虽有研究表明BaP具有生殖毒性,其生殖毒性机理尚未研究透彻。本综述的目的是总结BaP生殖毒性相关文章,讨论BaP导致生殖毒性的潜在分子机制。

## 1 BaP在生殖方面的主要致毒途径(The main toxic pathway of BaP in reproduction)

近些年研究发现,BaP发挥其致毒作用主要有3种途径:(1)通过氧化应激影响细胞正常代谢;(2)BaP可以与DNA形成加合物,进而导致DNA损伤;(3)BaP可以通过调控基因表达,发挥其毒性作用。BaP致毒途径是多种机制相辅相成。由于生殖对繁育后代具有重要意义,因此研究BaP的生殖毒性已成为科学家们的研究重点,下文将重点总结BaP的生殖毒性机制。

### 1.1 氧化应激(Oxidative stress)

BaP进入细胞后,通过AHR途径诱导细胞发生氧化应激反应,其主要过程为:BaP刺激细胞质中的一种转录因子——芳香族化合物受体(aryl hydrocarbon receptor, AHR)[21],使其转入到细胞核后,再与芳香族化合物受体核转运蛋白(aryl hydrocarbon receptor nuclear transporter, ARNT)结合形成异二聚体[22],结合在下游靶基因上,激活细胞色素P450目标基因的异常表达,包括细胞色素P450 1A1(cytochrome P450 family 1 subfamily A member 1, CYP1A1)、细胞色素P450 1A1(cytochrome P450 family 1 subfamily A member 2, CYP1A2)、细胞色素P450 1B1(cytochrome P450 family 1 subfamily B member 1, CYP1B1)[21, 23],进而引起细胞产生大量活性氧(reactive oxygen species, ROS),使机体发生氧化应激反应,如果体内的活性氧产生过多,超出了细胞的清除能力,会影响细胞的正常代谢甚至会破坏细胞结构。低、高剂量的BaP均可导致小鼠卵母细胞功能障碍,降低精卵结合与融合率,这与线粒体ROS水平增加和卵膜脂质过氧化密切相关[24]。Zhang等[25]发现BaP可以削弱雌鼠的繁殖能力,通过增加雌鼠卵母细胞中ROS,扰乱纺锤体组装,染色体配对,阻滞卵母细胞减数分裂过程。BaP诱导的氧化应激不仅仅通过产生ROS这一条途径,还可以通过降低过氧

化氢酶(catalase, CAT)、抗坏血酸过氧化物酶(ascorbate peroxidase, AP)、谷胱甘肽过氧化物酶(glutathione peroxidase, GPX)、超氧化物歧化酶(superoxide dismutase, SOD)、谷胱甘肽还原酶(glutathione reductase, GR)等抗氧化酶的活性[26−27]以及促进炎症细胞因子表达[28]导致氧化应激的发生,最终引起细胞功能受损。

1.2　BPDE 引起 DNA 损伤(BPDE induces DNA damage)

BaP 进入体内经过一系列氧化代谢反应,生成二羟环氧苯并[a]芘(BaP-7,8-dihydrodiol-9,10-epoxide, BPDE),进而发挥其毒性,Penning[29]认为生成 BPDE 的主要途径是在细胞色素 P450 酶的催化下,BaP 末端的苯环上发生单加氧化反应,生成 BaP-7,8-环氧化物(BaP-7,8 epoxide),在环氧化物水解酶作用下转化为 BaP-7,8-二氢二醇(BaP-7,8 diol),该过程循环往复最终形成致癌物——BPDE[30−32]。BPDE 可以与 DNA 共价结合形成加合物,造成 DNA 损伤。Shiizaki 等[33]提出一个关于 BaP-DNA 加合物成因的假设,即 CYP1A1 是 BaP 被激活形成 BPDE 反应中的关键酶,这与 Bukowska 等[32]提出的观点一致。Einaudi 等[34]通过建立 BaP 染毒的雌性小鼠模型,发现 BaP 可以导致卵母细胞与卵丘细胞 DNA 损伤,并且他们认为导致 DNA 断裂的主要原因是由于细胞中的修复机制对 BPDE-DNA 加合物切除和修复导致的。Zhan 等[35]研究表明 BaP 形成的 DNA 加合物可以干扰 DNA 复制,进一步引起胚胎的 DNA 损伤,影响胚胎的发育。Zhan 等[35]进一步研究发现 DNA 加合物与 ROS 共同造成基因组严重损伤,还可以引起卵裂球的端粒功能障碍,最终引起胚胎的异常。Miao 等[36]发现 BaP 会引起猪卵母细胞纺锤体组装缺陷进一步引起减数分裂停滞,而导致这一结果的原因可能是 DNA 加合物引起的。Zhang 等[25]将小鼠卵母细胞暴露于 BaP 后,发现纺锤体的组装、染色体的排列和着丝点-微管附着均被破坏,这可能与 DNA 加合物的形成有关联,与 Miao 的设想一致。

1.3　基因表达调控(Regulation of gene expression)

基因表达调控是生物学研究的重要内容之一,在细胞分化发育的不同时期,基因表达的种类和强度各不相同,共同决定着细胞的形态与功能;细胞为了适应环境变化改变自身的基因表达有利于生存,因而基因表达调控十分重要。海洋污染问题日趋严重,BaP 具有水生生物生殖毒性,是造成海洋污染的重要原因之一,受到广泛关注。有研究发现 BaP 生殖毒性的潜在分子机制是通过调控相关基因表达。数字基因表达技术表明 BaP 对雄性栉孔扇贝睾丸中的生殖基因有影响,其中热休克蛋白 90、细胞色素 P450 3A、凋亡抑制蛋白 3 个基因的改变会引起睾丸组织损伤,此外 BaP 与性激素合成和睾丸发育相关基因有密切联系[37]。Albornoz-Abud 等[38]研究表明苯并芘可以通过调控 GH/IGF 轴发挥其生殖毒性,急性暴露于 BaP 会导致尼罗罗非鱼睾丸中内分泌相关基因:胰岛素样生长因子 1(insulin-like growth factor 1, *IGF1*)和生长激素受体基因 1(growth hormone receptor 1, *GHR1*)基因表达降低,并造成发育问题。BaP 通过基因调控引起的生殖毒性不仅仅在海洋生物中体现,陆地生物也同样受这一机制调控。BaP 通过影响父本基因,最终影响胚胎发育。用 BaP 染毒的雄性小鼠进行体外受精后,发现在 8-细胞期和囊胚期存在基因表达异常,包括调控细胞周期以及 DNA 修复的基因[39]。妊娠黄体可以分泌雌孕激素,在生殖系统中发挥重要作用,黄体的发育与血管内皮生成因子有着密切联系[40]。苯并芘可以使血管内皮生成因子相关基因,如血管生成素-1(angiopoietin-1, *Ang-1*)、血管内皮细胞生长因子受体(vascular endothelial growth factor, *VEGFR*)、内皮细胞 TEK 酪氨酸激酶表达下调,并增加抗血管生成因子血小板反应蛋白(recombinant thrombospondin 1, *THBS1*)的表达,还影响了对黄体血管系统建立至关重要的基因 *Notch1*、*DLL4*、*Jag1* 和 *Hay2* 的表达,破坏了黄体血管网络系统的形成,最终影响了妊娠过程中黄体的内分泌功能[41]。

综上所述,在 3 种 BaP 发挥致毒作用的机制中(图 1),BaP 诱导生殖发育相关基因表达异常或提高促凋亡基因表达起主导作用,也是目前研究较为透彻的机制(图 2),下面将从雄性生殖、雌性生殖以及胚胎发育 3 个角度详述 BaP 的毒性机制。

## 2　BaP 的雄性生殖毒性(Male reproductive toxicity of BaP)

2.1　BaP 对雄性激素的毒性(Toxicity of BaP to androgens)

BaP 作为内分泌干扰物主要影响睾酮水平[42],睾酮主要是由睾丸间质细胞合成分泌的,其主要成分为类固醇。BaP 可以降低睾酮的转化率[43]和(或)睾酮的浓度[44]。有研究表明睾丸巨噬细胞分泌的白介素 1$\beta$(interleukin-1$\beta$, IL-1$\beta$)和肿瘤坏死因子 $\alpha$

(tumor necrosis factor $\alpha$, TNF$\alpha$)通过抑制类固醇生成急性调节蛋白(steroidogenic acute regulatory protein, STAR)表达进一步抑制间质细胞合成睾酮[45]。Zheng 等[46]发现 BaP 通过增加 IL-1$\beta$ 的表达,显著抑制雄性大鼠睾酮的产生,他们还发现 BaP 可以改变睾丸巨噬细胞亚群,激活 ED2$^+$睾丸巨噬细胞并促进了 IL-1$\beta$ 的产生,最终抑制雄性大鼠睾酮合成。此外,3$\beta$-羟基类固醇脱氢酶(3$\beta$-hydroxysteroid dehydrogenase, 3$\beta$-HSD)与细胞色素 P450 胆固醇侧链裂解酶(cholesterol side-chain lyase P450scc, P450scc)在间质细胞合成睾酮中起着重要作用[47],其表达改变时会影响睾酮水平;STAR 表达的下调也可以导致睾酮合成减少[48-49]。雄性大鼠用 BaP 灌胃 90 d 后,检测到 BaP 下调间质细胞中的 STAR、3$\beta$-HSD 以及细胞色素 P450 17A1 (cytochrome P450 family 17 subfamily A member 1, CYP17A1)表达,并上调 P450scc 表达,进而降低大鼠睾丸间质细胞生成睾酮的能力[50]。Sheweita 等[51]发现 BaP 降低类固醇合成酶 CYP17A1 和 17$\beta$-羟基类固醇脱氢酶(17$\beta$-hydroxysteroid dehydrogenase, 17$\beta$-HSD)蛋白表达,使大鼠血浆睾酮浓度降低。Banerjee 等[52]进一步验证了 BaP 通过抑制类固醇生成蛋白表达,如细胞色素 P450 Ⅱ A1(cytochrome P450 family Ⅱ subfamily A member 1, CYP Ⅱ A1)、STAR、3$\beta$-HSD、17$\beta$-HSD,进一步降低血清睾酮水平,2021 年 Daoud 等[53]再一次证实了上述观点。Yang 等[54]发现 BaP 也可以通过影响 3$\beta$-HSD、CYP17 和 17$\beta$-HSD 表达进一步扰乱雄性栉孔扇贝的激素水平。Booc 等[55]研究发现 BaP 可降低雄性底鳉的睾酮水平,与其他动物不同的是 BaP 并非通过调控类固醇相关基因表达造成这一结果,而是可能通过精原细胞包囊大小进而影响睾酮水平。综上所述,BaP 主要通过改变类固醇生成相关基因与酶的表达,抑制睾酮的生成,对雄性的生殖发育产生不利影响。

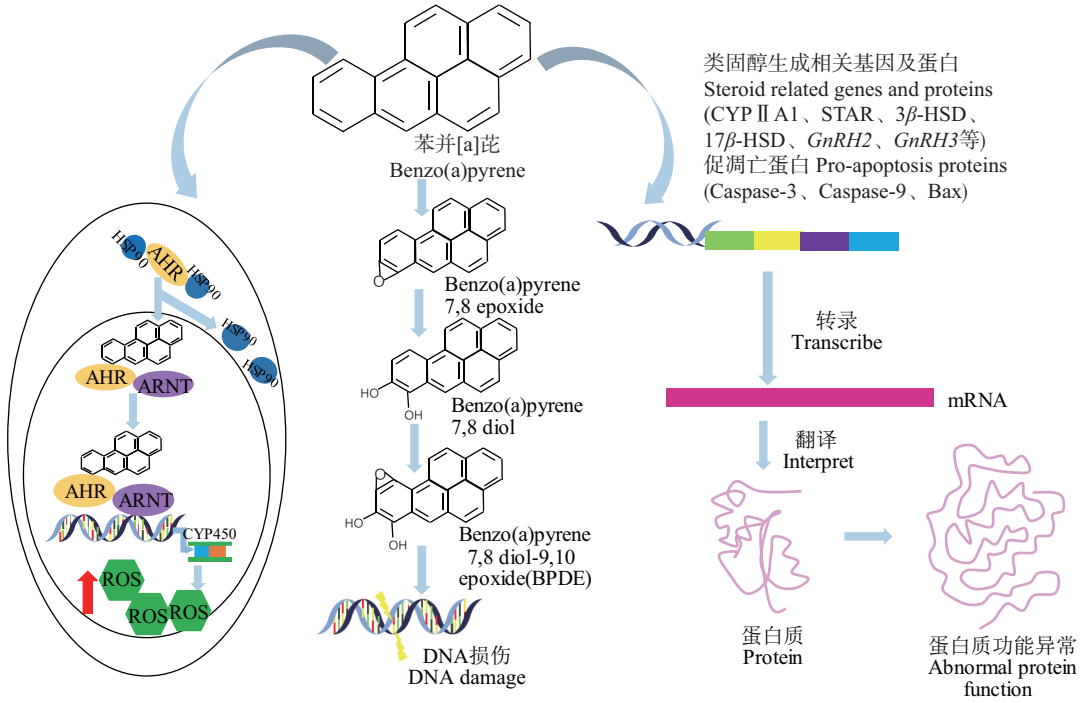


**图 1 BaP 致毒途径机制**

注:AHR 表示芳香族化合物受体,ARNT 表示芳香族化合物受体核转运蛋白,HSP90 表示热休克蛋白 90,CYP450 表示细胞色素 P450,CYP17A1 表示细胞色素 P450 17A1,STAR 表示类固醇生成急性调节蛋白,3$\beta$-HSD 表示 3$\beta$-羟基类固醇脱氢酶,17$\beta$-HSD 表示 17$\beta$-羟基类固醇脱氢酶,Caspase-3 表示半胱氨酸蛋白酶-3,Caspase-9 表示半胱氨酸蛋白酶-9,Bax 表示 Bcl-2 相关 X 蛋白。

Fig. 1 Mechanism of BaP toxicity pathway

Note: AHR represents aryl hydrocarbon receptor, ARNT represents aryl hydrocarbon receptor nuclear transporter, HSP90 represents heat shock protein 90, CYP450 represents cytochrome P450 family, CYP17A1 represents cytochrome P450 family 17 subfamily A member 1, STAR represents steroidogenic acute regulatory protein, 3$\beta$-HSD represents 3$\beta$-hydroxysteroid dehydrogenase, 17$\beta$-HSD represents 17$\beta$-hydroxysteroid dehydrogenase, and Bax represents Bcl-2 associated X protein.

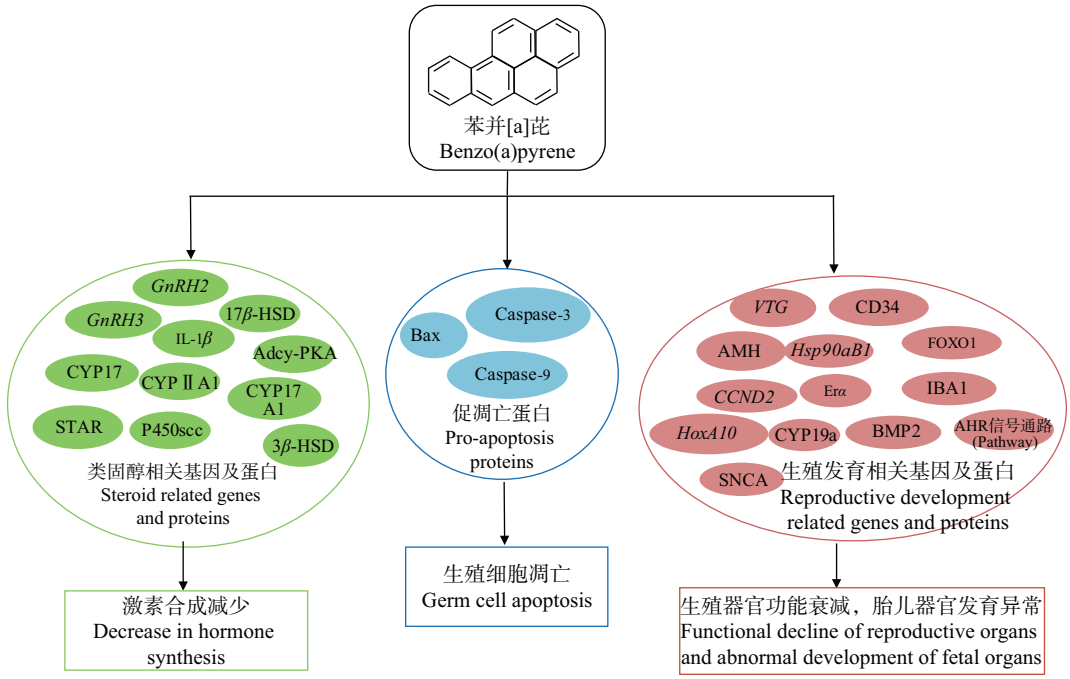


**图 2　BaP 通过基因调控引起生殖毒性**

注:*GnRH2* 表示促性腺激素释放激素,*GnRH3* 表示促性腺激素释放激素,IL-1*β* 表示白介素 1*β*,CYP17A1 表示细胞色素 P450 17A1,STAR 表示类固醇生成急性调节蛋白,3*β*-HSD 表示 3*β*-羟基类固醇脱氢酶,17*β*-HSD 表示 17*β*-羟基类固醇脱氢酶,CYP1A1 代表细胞色素 P450 1A1,P450scc 代表细胞色素 P450 胆固醇侧链裂解酶,Adcy-PKA 代表上游腺苷环化酶-蛋白激酶,Caspase-3 表示半胱氨酸蛋白酶-3,Caspase-9 表示半胱氨酸蛋白酶-9,Bax 表示 Bcl-2 相关 X 蛋白,*Hsp90aB1* 代表 90 kDa 热休克蛋白 aB1,*VTG* 代表卵黄蛋白原,CD34 代表分化簇 34,AMH 代表抗缪勒管激素,*CCND2* 代表细胞周期蛋白 D2,FOXO1 代表叉头框蛋白 O1,*HoxA10* 代表同源盒基因,BMP2 代表骨形态发生蛋白-2,IBA1 代表离子钙结合衔接分子 1,SNCA 代表重组人 α-突触核蛋白,CYP19a 代表细胞色素 P450 家族 19 亚家族 a。

Fig. 2　BaP causes reproductive toxicity through gene regulation

Note: *GnRH2* represents gonadotropin-releasing hormone 2, *GnRH3* represents gonadotropin-releasing hormone 3, IL-1*β* represents interleukin-1*β*, CYP17A1 represents cytochrome P450 family 17 subfamily A member 1, STAR represents steroidogenic acute regulatory protein, 3*β*-HSD represents 3*β*-hydroxysteroid dehydrogenase, 17*β*-HSD represents 17*β*-hydroxysteroid dehydrogenase, CYP1A1 represents cytochrome P450 family 1 subfamily A member 1, P450scc represents cholesterol side-chain lyase P450scc, Adcy-PKA represents adenylate cyclase-protein kinase, Bax represents Bcl-2 associated X protein, *Hsp90aB1* represents recombinant heat shock protein 90 kDa alpha B1, *VTG* represents vitellogenin, CD34 represents cluster designation 34 , AMH represents anti-Müllerian hormone, *CCND2* represents cyclin-D2, FOXO1 represents forkhead box O1, *HoxA10* represents homeobox A10, BMP2 represents bone morphogenetic protein-2, IBA1 represents ionized calcium-binding adapter molecule 1, SNCA represents recombinant human alpha-synuclein, CYP19a represents cytochrome P450 family 19 subfamily a.

### 2.2　BaP 对精子的毒性(Toxicity of BaP to sperm)

#### 2.2.1　BaP 减少精子生成(BaP reduces spermatogenesis)

哺乳动物雄性生殖器官主要有睾丸、附睾、输精管等,其中睾丸的主要作用是生成精子和产生雄性激素,BaP 主要通过损害睾丸进一步影响精子生成。BaP 通过氧化应激或基因调控介导睾丸细胞凋亡,影响睾丸功能受损,减少精子数量。Banerjee 等[52]证实 BaP 激活 P38 蛋白激酶(P38 mitogen activated protein kinase, P38MAPK)通路来增加睾丸细胞内 ROS,并降低细胞中的抗氧化酶活性[56],使睾丸细胞氧化应激损伤,减少精子的生成。Sheweita 等[51]研究发现 BaP 通过降低睾丸组织中抗氧化酶 CAT、SOD、GPX 的活性,增加 ROS 水平,导致睾丸细胞线粒体膜破裂,进而引起睾丸组织凋亡。BaP 还可通过 AHR 途径降低睾丸中 CAT、SOD 活性,升高 $H_2O_2$ 含量,诱导睾丸细胞氧化应激,影响睾丸功能[57]。上述均为 BaP 对小鼠的生殖毒性,Tian 等[58]发现 BaP 通过可引起雄性栉孔扇贝精巢氧化应激损伤,进一步减少精子生成。此外,BaP 可以通过基因调控诱导睾丸细胞凋亡,提高睾丸细胞内的凋亡蛋白半胱氨酸蛋白酶-3(Caspase-3)和半胱氨酸蛋白

酶-9(Caspase-9)表达;促进细胞色素 C 转位到细胞质,启动线粒体凋亡途径,导致睾丸细胞凋亡,进一步导致精子生成减少[52, 59]。

BaP 不仅通过影响睾丸功能减少精子生成,而且可以直接影响精子生成过程。Verhofstad 等[60]的研究表明在精子发育各个阶段均可以检测到 BPDE 导致的精子 DNA 损伤,这也是精子数量减少的原因之一。BaP 可以导致雄鼠精子功能缺陷以及生育能力下降,并且 Mohamed 等[61]的实验证明了 BaP 的生殖毒性具有遗传性,但毒性随着子代数增加逐渐减弱。BaP 可以减少精母细胞和次级精母细胞进入中晚期粗线期,阻止减数分裂过程的完成,导致精子生成减少[62]。此外,BaP 诱导的氧化应激会降低精原细胞的存活率,并且通过下调基质金属蛋白酶(matrix metalloproteinase, MMP)水平以及上调促凋亡因子 Caspase-3 和 Caspase-9 表达促进精原细胞凋亡[63]。BaP 作为广泛存在于生态系统中的环境污染物,不仅使陆地雄性动物精子生成异常,还影响水生生态系统中的雄性动物的精子生成。BaP 可以通过基因调控扰乱雄性栉孔扇贝的精子发生相关基因:细胞周期蛋白 D2(cyclin-D2, *CCND2*),联会复合体 3、核呼吸因子 1 和水通道蛋白 9,进一步减少精子生成[54]。斑马鱼胚胎暴露于 BaP 后,其睾丸中生殖细胞特异基因的启动子发生甲基化上调,进一步下调相关基因表达,最终抑制精子生成,影响雄性斑马鱼的生殖能力[64]。

2.2.2 BaP 降低精子活力(BaP reduces sperm motility)

BaP 可以损害睾丸和附睾的内分泌功能,从而导致储存的精子活力下降[65-67]。睾丸的质量和大小与精子的数量和活力成正比[68],雄性小鼠用 BaP 连续灌胃 60 d,检测到小鼠的睾丸质量明显降低,精子的活力也随之降低[69]。小鼠暴露于 BaP 后,其睾丸支持细胞和间质细胞均凋亡,进而影响精子发生过程,最终导致精子活力减弱[69]。畸形精子的活力及存活率显著低于正常精子,BaP 暴露会导致精子形态异常,畸形精子大幅增加,主要异常表现为无尾、双头、中段弯曲[57]。Xu 等[59]验证了 BaP 可导致精子活动力降低,精子头、尾部畸形率以及总畸形率均显著升高。最新研究表明 BaP 改变睾丸激素水平引起雄性交配强度减弱,降低精子质量,引起畸形精子增多[70-71]。有研究表明精子短端粒可能是导致男性不育的原因之一[72],Ling 等[73]研究发现 BaP 可以使精子端粒变短,且与剂量成反比。

## 3 BaP 的雌性生殖毒性(Female reproductive toxicity of BaP)

### 3.1 BaP 对雌性激素的毒性(Toxicity of BaP to estrogen)

BaP 作为一种常见的环境污染物,是海洋环境污染原因之一,影响水生动物的繁殖。雌孕激素对雌性发育有不可或缺的作用,而 BaP 作为内分泌干扰物可以降低水生动物血浆中的孕酮、雌激素和催乳素浓度[74]。为进一步探究其发生机制,Tian 等[58]用不同浓度的 BaP 处理雌性栉孔扇贝,发现 BaP 可以导致类固醇合成相关酶(3$\beta$-HSD、CYP17、17$\beta$-HSD)表达下降,并呈剂量依赖性;高浓度的 BaP 还可抑制 AHR、ARNT、CYP1A1 以及 17$\beta$-雌二醇-雌激素受体转录,2 种机制相辅相成,共同抑制雌孕激素的生成。BaP 通过干扰激素膜受体降低三疣梭子蟹的雌二醇(estradiol, E2)浓度[75]。斑马鱼胚胎暴露于 BaP 会导致成年雌鱼卵巢中 E2 水平下降,其机制为雌鱼脑中促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)基因中的 *GnRH3* 的甲基化水平显著升高,并下调 *GnRH3* mRNA 表达,从而影响 E2 的产生[76]。与斑马鱼报道相反的是 BaP 可促进雌性海马 *GnRH2* 和 *GnRH3* mRNA 的表达,并导致血浆中 E2 水平显著下降[77]。2 种相反结果可能与 BaP 的浓度、作用时间以及实验对象不同有关。Yang 等[78]发现 BaP 抑制雌性栉孔扇贝的上游腺苷环化酶-蛋白激酶(adenylate cyclase-protein kinase, Adcy-PKA)信号通路,下调促性腺激素受体转录水平,如促卵泡激素受体(follicle-stimulating hormone receptor, FSHR)和黄体生成素/绒毛膜促性腺激素受体(luteinizing hormone/choriogonadotropin receptor, LHCGR),导致类固醇生成酶(3$\beta$-HSD、CYP17、17$\beta$-HSD)表达减少,最终引起抗雌激素效应。Kennedy 和 Smyth[79]发现雌鲑鱼体内 E2 的减少并非是通过常规的 BaP 作用于类固醇机制,而是通过其他内分泌干扰机制来对抗雌激素的方式改变了血浆 E2 的浓度,这种机制有待进一步研究。综上所述,BaP 主要通过基因表达调控这一途径降低雌性体内 E2 和孕酮水平,进而影响雌性的生殖发育。

### 3.2 BaP 对卵巢的毒性(Toxicity of BaP to ovary)

卵巢是雌性生殖发育中最重要的生殖器官,具有排卵和内分泌功能,对维持雌性激素水平至关重要,暴露于 BaP 会扰乱卵巢的结构与功能,进一步

影响生育、妊娠。高剂量的 BaP 可以导致卵巢细胞退化并出现管状结构,而这些组织学变化属于癌前病变[80]。Rahmani 等[81]发现 BaP 通过氧化应激导致卵巢表面上皮内陷、细胞堆积、管状结构形成,卵巢间质出现间质水肿、出血等病理学改变,并且 BaP 诱导卵巢中 Caspase-3 表达升高,影响卵巢的生理功能,与睾丸相比,BaP 对卵巢的危害更严重,这是因为在 BaP 处理后,胎儿卵巢中促细胞凋亡蛋白 Bcl-2 相关 X 蛋白(Bcl-2 associated X protein, Bax)表达增加,并激活下游 Caspase-3 和 Caspase-9,导致卵巢细胞凋亡[82]。卵黄蛋白原(vitellogenin, *VTG*)和 *CCND2* 是雌激素介导的卵巢发育相关基因[83],BaP 可以下调 *VTG* 和 *CCND2* 表达,造成雌性栉孔扇贝卵巢受损,组织学检查发现,BaP 可引起卵巢发育延迟和卵母细胞退化,并且卵巢的病变情况随着染毒时间和染毒剂量的增加而严重[78]。研究发现 BaP 可以抑制脂联素受体 1(adiponectin receptor protein 1, AdipoR1)和脂联素受体 2(adiponectin receptor protein 2, AdipoR2)表达,进而影响卵巢功能[84]。最新研究表明,BaP 及其代谢产物 BPDE 可抑制妊娠小鼠卵巢中腺嘌呤核苷酸转运体 1(adenine nucleotide translocator 1, ANT1)的表达,进一步研究发现 ANT1 的过表达可以修复 BPDE 引起的有丝分裂缺陷,恢复卵巢功能[85]。

3.3　BaP 对雌性生殖细胞的毒性(Toxicity of BaP to female germ cells)

3.3.1　BaP 影响卵泡发生和发育(BaP affects follicular genesis and development)

卵泡发育是女性正常的生理过程,卵泡的发育情况直接关系到后代繁殖。卵泡作为卵巢的功能单位,支持卵母细胞的发育和成熟[86]。卵泡的生长发育过程相当复杂,原始卵泡经历初级卵泡、窦前、窦卵泡才能发育为成熟卵泡[87-88]。有报道称 BaP 作为卵毒物质,可以破坏原始卵泡[89],或者使原始卵泡迅速枯竭[90],BaP 还可以通过香烟烟雾进入卵泡液中,对卵泡发育产生不利影响[91]。Sobinoff 等[24]研究了 BaP 卵毒性的机制,连续用 BaP 处理雌性小鼠 7 d 会导致卵巢中的原始卵泡显著减少,卵泡闭锁,其具体机制为 BaP 通过干扰 AHR 发育信号破坏卵泡形成。有报道称 BaP 不仅可以减少或耗尽原始卵泡和初级卵泡的数量[89-90],还可以抑制卵泡生长发育,即 BaP 处理过的卵泡均发育不到窦前阶段[92]。Sadeu 和 Foster[93]将小鼠卵泡暴露于不同浓度的 BaP,发现卵泡存活率均降低,其中高浓度的 BaP 会抑制窦卵泡发育,使卵泡停滞于窦前卵泡阶段,窦卵泡比例显著减少。抗缪勒管激素(anti-Müllerian hormone, AMH)浓度增加与卵泡发育停滞有关[94-95]。有研究表明 BaP 可以通过减少 AMH 生成,促进卵泡募集到卵泡池中,最终加快卵泡枯竭的速度[96]。Sadeu 和 Foster[93]进一步探索了 BaP 诱导卵泡发育异常的关键分子途径,发现 BaP 暴露通过激活窦前、窦卵泡和成熟卵泡中 AHR 信号通路,进一步促进促凋亡因子 Bax 激活,此外,BaP 暴露还会导致 90 kDa 热休克蛋白 aB1(recombinant heat shock protein 90 kDa alpha B1, *Hsp90aB1*)基因表达上调,导致卵泡生长延迟和存活率下降。卵泡生长和卵泡发育在雌性哺乳动物生殖中有着重要地位,BaP 不但可以通过基因表达调控导致卵泡生长发育异常,还可能通过氧化应激影响卵泡发育。

3.3.2　BaP 影响卵母细胞功能(BaP affects oocyte function)

BaP 可使卵母细胞线粒体内 ROS 水平升高,导致精-卵结合和融合障碍,影响动物的繁殖[24,36]。BaP 可导致卵母细胞和卵丘细胞 DNA 断裂,细胞功能障碍,影响卵母细胞进一步发育,精卵融合失败[34],这也是 BaP 生殖毒性机制之一。卵母细胞的减数分裂在卵母细胞成熟与成功受精中起着重要作用[97],BaP 诱导卵母细胞减数分裂异常,卵母细胞功能障碍,不利于动物繁殖。BaP 可以阻滞猪卵母细胞减数分裂,使部分卵母细胞停滞在 MⅡ期,进一步检测发现 BaP 通过降低乙酰化 α-微管蛋白,导致微管不稳定,损害纺锤体组装,从而干扰卵母细胞减数分裂过程[36]。Sui 等[98]通过将雌鼠暴露于 BaP 检测其对子代的影响,验证了 BaP 对卵母细胞的遗传毒性:生发泡破裂(germinal vesicle breakdown, GVBD)是卵母细胞成熟的关键事件,母体暴露 BaP 会降低子代 GVBD 率[99];并且 BaP 会扰乱子代卵母细胞的纺锤体组装和染色体配对,使卵母细胞减数分裂停滞;最后,雌鼠暴露于 BaP 可导致子代卵母细胞基因组高甲基化,损害卵母细胞的发育能力。综上所述,母系 BaP 暴露损害了子代卵母细胞的进一步发育,这与上文 Miao 等[36]研究结果相一致。

## 4　BaP 对胎儿或胚胎的生殖毒性(Reproductive toxicity of BaP to the fetus or embryo)

4.1　BaP 的胚胎发育毒性(Embryonic developmental toxicity of BaP)

早有研究表明,吸烟损害身体健康,还对孕妇以

及胎儿有害[100-101]。BaP 作为香烟烟雾中的主要成分之一[102],可以通过母体进入胚胎,对胎儿的生长发育产生负面影响。高/低剂量的 BaP 均可诱导小鼠受精卵 ROS 增加,导致受精卵基因组及端粒 DNA 受损,促进受精卵凋亡,BaP 还通过降低 Nanog 或 Oct4 阳性内细胞团比率扰乱胚胎发育[35]。Xie 等[103]的研究表明 BaP 可引起牡蛎胚胎 DNA 断裂损伤,胚胎发育异常,并降低牡蛎的存活率。Wang 等[15]以人胚胎干细胞来源的类胚体(embryoid bodies, EBs)为体外模型,探究了 BaP 对胚胎的毒性作用:用不同浓度的 BaP 处理 EBs,结果显示高浓度的 BaP 可以降低 EBs 存活率,长期暴露(14 d)显著抑制所有浓度细胞的存活率。此外,BaP 通过上调促凋亡蛋白 Bax 表达,进一步激活 Caspase-3,与此同时,BaP 还上调细胞中的凋亡蛋白酶激活因子 1 表达,激活 Caspase-9 形成凋亡体,这 2 种途径均可导致 EBs 凋亡。上皮-间充质转化(epithelial-mesenchymal transition, EMT)是高度保守的细胞过程,是胚胎发育过程中的重要生理现象[104-105],BaP 可诱导 EMT 相关基因:基质金属蛋白酶 2(matrix metallopeptidase 2, *MMP2*)、基质金属蛋白酶 9(matrix metallopeptidase 9, *MMP9*)、*Snail*、*Slug*、*ZEB1* 和 *ZEB2* 的表达减少,抑制细胞分化和 EBs 发育。他们还发现 BaP 介导 EBs 中 *Vimentin* 和 *E-cadherin* 基因下调,显著抑制细胞增殖和分化,并进一步加剧 EBs 的形态异常。并且他们还证实了 Akt 的磷酸化水平和糖原合成酶激酶-3$\beta$(glycogen synthase kinase-3, GSK-3$\beta$)水平与 BaP 呈剂量依赖性下降。综上所述,BaP 可抑制 EBs 细胞生长,损伤细胞形态,并引发细胞凋亡,其机制与 EMT 过程和 Akt/GSK-3$\beta$ 信号通路的调控有关。

中/高浓度 BaP 处理海洋青鳉会导致青鳉胚胎的孵化时间明显延迟,并且高浓度的 BaP 会导致青鳉胚胎死亡,作者还发现 BaP 的胚胎毒性不仅体现在胚胎致死性,还可以导致海洋青鳉性别分化异常以及性成熟时间延长,暴露于 BaP 后,F1 代雄性海洋青鳉显著增加,造成这一结果可能与以下 2 种因素有关:首先 BaP 具有抗雌激素作用,即 BaP 可以增加睾丸和肝脏中雄激素受体的表达[106],这与 Colli-Dula 等[107]研究相一致;其次,BaP 作为内分泌干扰物,可引起生殖发育相关基因雌激素受体 $\alpha$(estrogen receptor $\alpha$, Er$\alpha$)、细胞色素 P450 家族 19 亚家族 a(cytochrome P450 family 19 subfamily a, CYP19a)和 VTG1 表达水平下降,而 Er$\alpha$[108]、CYP19a[109] 与 VTG[110]均与雌激素受体关系密切,因此 BaP 通过以上 2 种方式抑制与雌性海洋青鳉生殖发育相关基因的表达,最终引起性别比例失衡[106]。Yamaguchi 等[111]继续研究 BaP 对海洋青鳉的影响发现:BaP 还可引起胚胎体积减小,心血管发育异常等胚胎畸形,其中心脏畸形是 BaP 上调 *CYP2J* 表达导致环氧-二十碳三烯酸(epoxyeicosatrienoic acids, EETs)增加而引起的,这与 Colli-Dula 等[107]研究结果相一致。

子宫内膜蜕膜化和蜕膜血管生成是胚胎着床成功的先决条件,也是维持妊娠的关键事件[112-113],当其发生异常时,会对胚胎发育产生不利影响。da Silva Moreira 等[114]研究发现 BaP 通过影响蜕膜化和蜕膜血管生成的关键信号转导途径,进而导致胚胎发育异常。其他研究发现 BaP 诱导蜕膜化相关因子叉头框蛋白 O1(forkhead box O1, FOXO1)、同源盒基因 A10(homeobox A10, HoxA10)和骨形态发生蛋白-2(bone morphogenetic protein-2, BMP2)以及蜕膜血管生成基因分化簇 34(cluster designation 34, CD34)的表达降低,抑制蜕膜血管生成,对随后的胚胎发育和胎盘形成产生不利影响[115]。综上所述,BaP 的胚胎毒性作用机制主要为调控相关基因表达变化,引起胚胎畸形或发育异常。

### 4.2 BaP 对胎儿器官发育的毒性(Toxicity of BaP on fetal organ development)

从受精卵形成到最终分娩大约需要 40 周左右,胎儿的器官在此期间逐渐成形,这一阶段称为胎儿发育阶段,当该阶段出现异常时,会对后期胎儿成长会产生不利影响。有研究表明,BaP 可以降低胎儿体质量[116-117],进而影响到胎儿发育[118]。此外,BaP 的毒性还体现在胚胎的致畸性和胚胎发育毒性[111]。BaP 通过 AHR 途径诱导氧化应激,导致斑马鱼胚胎心脏畸形[119],BaP 还可以通过增加 ROS 水平导致胚胎肾脏受损[114]。Holloway 等[120]发现 BaP 诱导斑马鱼胚胎出现神经行为缺陷,而抗氧化剂维生素 E 可以显著改善 BaP 的神经毒性,也间接证明了 BaP 通过氧化应激导致胎儿神经发育异常。BaP 通过基因调控发挥其生殖毒性,例如 BaP 上调心血管疾病相关基因 *CYP2J* 导致海洋青鳉胚胎心血管异常[111]。Jules 等[121]发现,孕期接触 BaP 会上调子代的血管紧张素Ⅱ、血管紧张素原和内皮型一氧化氮合酶的表达,胎儿心血管系统发育受到影响。Cunha 等[122]研究发现 BaP 通过上调兴奋-收缩偶联

相关基因:钙离子转运 ATP 酶 A2(ATPase sarcoplasmic/endoplasmic reticulum $Ca^{2+}$ transporting 2, *ATP2A2*)以及心脏发育相关基因 T 盒转录因子 5 表达,导致斑马鱼胚胎出现心包水肿以及心动过缓。BaP 介导 $Na^+/K^+$-ATP 酶活性降低也是导致心包水肿的原因之一[123]。Li 等[124]研究发现 BaP 以剂量依赖方式降低 $Na^+/K^+$-ATP 酶和 $Ca^{2+}$-ATP 酶活性,进而导致心脏发育异常,这与上述研究结果相一致。

BaP 的毒性不仅作用于心脏,还可以影响骨骼发育。斑马鱼幼体短期暴露于 BaP,可使颅骨减小,而长期暴露于 BaP 会影响中轴骨骼的发育,骨骼畸形的发生率和严重程度均会增加,其发生机制为 BaP 激活 AHR2 和/或 PXR 异生和代谢途径,对细胞外基质的形成产生负面影响;BaP 还通过募集中性粒细胞与骨基质的相互作用影响成骨细胞和破骨细胞的活动[125],2 种机制共同导致胎儿骨骼发育异常。

BaP 发挥其神经毒性不仅可以通过氧化应激,还可以通过基因表达调控。雌鼠暴露于 BaP,可检测到胎儿中脑内离子钙结合衔接分子 1(ionized calcium-binding adapter molecule 1, IBA1)和重组人 α-突触核蛋白(recombinant human alpha-synuclein, SNCA)表达增加,导致蛋白质降解能力受损,黑质可见 α-突触核蛋白(alpha synuclein, α-SYN)聚集现象,BaP 还可以激活黑质小胶质细胞,导致黑质多巴胺能神经元丢失,最终对胎儿的神经发育造成不利影响[126]。

综上所述,BaP 是一种环境毒物,可以进入陆地生物和海洋生物体内,对雄性、雌性以及胎儿的生殖发育产生不利结果(图 3 及表 1)。

## 5　总结(Summary)

BaP 作为比较常见的环境毒物,通常存在于空气、土壤、水源、食物以及香烟烟雾中。因其具有疏水性以及亲脂性,人类可以通过呼吸、饮食等方式接触到 BaP,进而导致一系列疾病的发生。近些年来因污染导致的 $PM_{2.5}$、水污染以及地沟油等事件越来越受到关注,BaP 作为以上污染主要危害之一,也逐步走进公众视野。研究发现 BaP 的致毒机制主要通过氧化应激、BPDE 与 DNA 结合形成加合物以及基因调控等途径发生。以往的研究重点聚焦于 BaP 的致癌机制,虽有研究表明 BaP 具有生殖毒性,其生殖毒性机理尚未研究透彻。

BaP 的生殖毒性主要分为以下三部分,对雄性、雌性以及胚胎或胎儿的生殖毒性。其对雄性生殖毒性主要为:BaP 可以作用于睾丸间质细胞以及改变类固醇生成相关基因的表达,抑制血睾酮的生成;其氧化应激作用会损伤睾丸和附睾的功能,进一步引起精子异常;BaP 还可以通过氧化应激以及基因调控方式诱导异常精子增多,对雄性的生殖发育产生

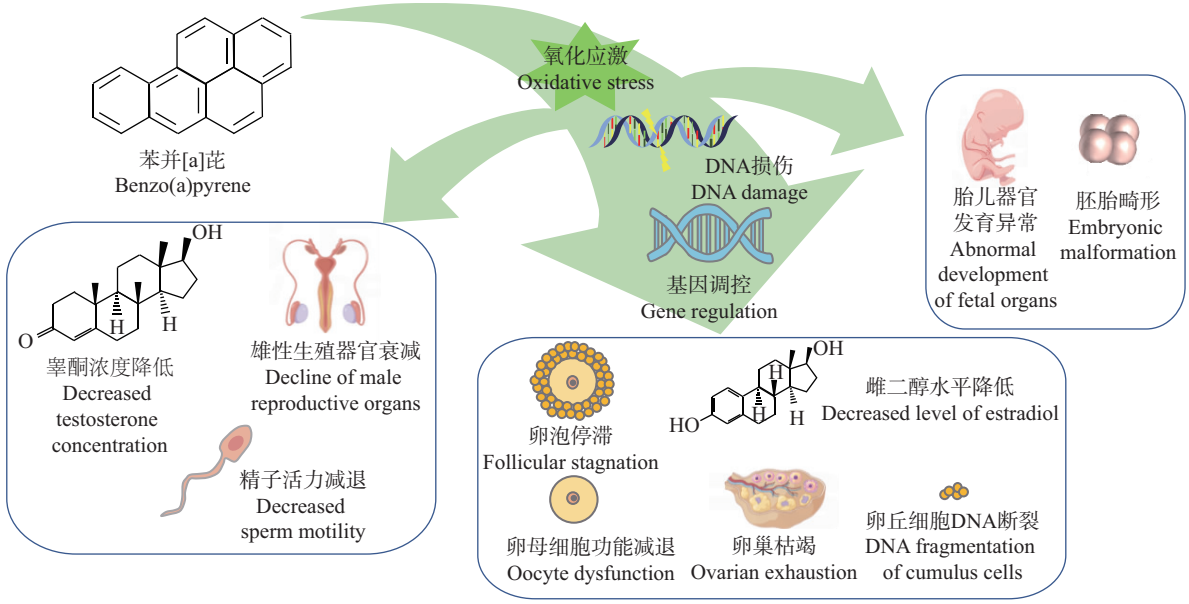


**图 3　BaP 的生殖毒性**

Fig. 3　Reproductive toxicity of BaP

**表 1 BaP 作用于不同样本引起的生殖毒性**

Table 1 Reproductive toxicity induced by BaP acting on different samples

| 样本类型 Sample type | | BaP 改变因素 BaP modifying factors | 最终结果 Final result | 参考文献 References |
|---|---|---|---|---|
| 雄性 Male | 鼠 Rat | IL-1$\beta$ ↑ | 睾酮 ↓ Testosterone ↓ | [46] |
| | | STAR、3$\beta$-HSD、CYP17A1、CYP Ⅱ A1、17$\beta$-HSD ↓, P450scc ↑ | 睾酮 ↓ Testosterone ↓ | [50-52] |
| | | CAT、SOD、GPX 活性 ↓, ROS ↑<br>CAT、SOD、GPX acticity ↓, ROS ↑ | 睾丸组织凋亡 Apoptosis of testicular tissue | [51,57] |
| | | P38MAPK 通路激活, Caspase-3、Caspase-9 ↑, 启动线粒体凋亡途径<br>P38MAPK pathway activation, Caspase-3, Caspase-9 ↑, initiates mitochondrial apoptosis pathway | 睾丸细胞损伤, 凋亡 Testicular cell damage, apoptosis | [52,59] |
| | | DNA 损伤 DNA damage | 精子数量 ↓ Sperm count ↓ | [60] |
| | | 端粒变短 Telomere shortening | 精子凋亡 Sperm apoptosis | [73] |
| | | MMP ↓, Caspase-3、Caspase-9 ↑ | 精原细胞凋亡 Spermatogonia apoptosis | [63] |
| | 栉孔扇贝 *Chlamys farreri* | 精巢氧化应激 3$\beta$-HSD、CYP17 和 17$\beta$-HSD ↓, 扰乱精子发生相关基因<br>Sperm nest oxidative stress 3$\beta$-HSD, CYP17 and 17$\beta$-HSD ↓, disrupt spermatogenesis-related genes | 精子数量 ↓ 睾酮 ↓, 精子生成减少<br>Sperm count ↓ Testosterone ↓, decreased spermatogenesis | [54,58] |
| | 底鳉 *Fundulus heteroclitus* | 精原细胞包囊增加 Increased spermatogonia encapsulation | 睾酮 ↓ Testosterone ↓ | [55] |
| | 斑马鱼 Zebrafish | 生殖细胞相关基因甲基化上调 Up-regulation of methylation of germ cell-related genes | 抑制精子生成 Inhibits spermatogenesis | [64] |
| 雌性 Female | 栉孔扇贝 *Chlamys farreri* | CYP17、3$\beta$-HSD、17$\beta$-HSD ↓, AHR、ARNT、*CYP1A1* ↓ | 雌孕激素 ↓ Estrogen and progesterone ↓ | [58] |
| | | Adcy-PKA 通路抑制, *VTG*、*CCND2* ↓<br>Adcy-PKA pathway inhibition, *VTG*, *CCND2* ↓ | 孕酮、E2 ↓, 卵巢病变 Progesterone, E2 ↓, ovarian lesions | [78] |
| | 三疣梭子蟹 *Portunus trituberculatus* | 干扰靶组织中的激素膜受体 Interferes with hormone membrane receptors in target tissues | E2 ↓ | [75] |
| | 斑马鱼 Zebrafish | *GnRH3* 甲基化 ↑<br>*GnRH3* methylation ↑ | E2 ↓ | [76] |
| | 海马 Hippocampus | *GnRH2*、*GnRH3* ↑ | E2 ↓ | [77] |

续表1

| 样本类型 Sample type | | BaP 改变因素 BaP modifying factors | 最终结果 Final result | 参考文献 References |
|---|---|---|---|---|
| 雌性 Female | 鼠 Rat | Bax ↑ | 卵巢细胞凋亡 Ovarian cell apoptosis | [82] |
| | | Caspase-3 ↑ | 卵巢功能受损 Impaired ovarian function | [81] |
| | | 干扰 AHR 途径,ROS ↑ Interference with AHR pathway, ROS ↑ | 卵泡形成障碍,精卵融合障碍 Follicle formation disorder and sperm egg fusion disorder | [24] |
| | | BPDE-DNA 加合物形成 BPDE-DNA adducts formation | 卵母细胞和卵丘细胞受损 Damage to oocytes and oval cells | [34] |
| | | 破坏线粒体,卵母细胞基因组高甲基化,阻滞减数分裂 Disruption of mitochondria, oocyte genome hypermethylation, blockage of meiosis | 卵母细胞功能受损、凋亡 Impaired oocyte function, apoptosis | [98] |
| | | AMH ↓ ,CYP1A1、CYP1B1、Bax、*Hsp90aB1* ↑ | 卵泡发育延迟 Delayed follicular development | [93,96] |
| | D4 小鼠 D4 mice | ANT1 ↓ | 卵巢功能受损 Impaired ovarian function | [85] |
| | 猪 Pig | 干扰纺锤体形态和染色体排列,降低乙酰化 α-微管蛋白,ROS ↑ Interferes with spindle morphology and chromosome alignment, reduces acetylated α-microtubulin, ROS ↑ | 卵母细胞减数分裂停滞,卵母细胞凋亡 Oocytes meiotic arrest, oocytes apoptosis | [36] |
| | | AdipoR1、AdipoR2 ↓ | 卵巢功能受损 Impaired ovarian function | [84] |
| 胚胎/胎儿 Embryo/fetus | 鼠 Rat | ROS ↑ ,Nanog 或 Oct4 阳性内细胞团比率 ↓ ROS ↑, ratio of Nanog- or Oct4-positive ICM cells ↓ | 受精卵和胚胎干细胞凋亡 Apoptosis in zygotes and embryonic stem cells | [35] |
| | | FOXO1、HoxA10、BMP2、CD34 ↓ | 抑制蜕膜血管生成 Inhibition of decidual angiogenesis | [115] |
| | | ROS ↑ | 肾脏受损 Kidney damage | [114] |
| | | 血管紧张素Ⅱ、血管紧张素原和内皮型一氧化氮合酶 ↑ Angiotensin II, angiotensinogen and endothelial-type nitric oxide synthase ↑ | 心血管异常 Cardiovascular anomaly | [121] |
| | | IBA1、SNCA ↑ | 神经发育异常 Neurodevelopmental abnormalities | [126] |
| | 牡蛎 Oyster | DNA 断裂 DNA damage | 牡蛎存活率 ↓ Oyster survival rate ↓ | [103] |
| | 类胚体 Embryoid bodies | Bax、APAF-1 ↑ ,EMT 相关基因 ↓ ,Akt/GSK-3β 通路异常,Vimentin、E-cadherin ↓ Bax, APAF-1 ↑, EMT-related genes ↓, Akt/GSK-3β pathway abnormalities, Vimentin, E-cadherin ↓ | 类胚体凋亡 Embryoid body apoptosis | [15] |

续表1

| 样本类型 Sample type | | BaP 改变因素 BaP modifying factors | 最终结果 Final result | 参考文献 References |
|---|---|---|---|---|
| 胚胎/胎儿 Embryo/fetus | 青鳉 *Oryzias latipes* | 雄激素受体表达↑,Erα、CYP19a、VTG↓,*CYP2J*↑ Androgen receptor expression↑, Erα, CYP19a, VTG↓, *CYP2J*↑ | 性别比例异常,心脏畸形,心血管异常 Abnormal sex ratio, cardiac malformations, cardiovascular anomalies | [106,111] |
| | 斑马鱼 Zebrafish | 氧化应激 Oxidative stress | 心脏畸形 Heart malformations | [119] |
| | | 氧化应激 Oxidative stress | 神经行为缺陷 Neurobehavioral deficits | [120] |
| | | 心脏发育相关基因异常,$Na^+/K^+$-ATP 酶活性↓,T 盒转录因子 5、ATP2A2↑ Abnormalities in heart development-related genes, $Na^+/K^+$-ATPase activity ↓, T box transcription factor 5, ATP2A2 ↑ | 心脏发育异常,心包水肿 Abnormal heart development, pericardial edema | [122−124] |
| | | 激活 AHR2、PXR 异生和代谢途径 Activation of AHR2, PXR xenobiotic and metabolic pathways | 骨骼发育异常 Skeletal developmental abnormalities | [125] |
| | 褐菖鲉 *Sebastiscus marmoratus* | $Na^+/K^+$-ATP 酶和 $Ca^{2+}$-ATP 酶活性↓ $Na^+/K^+$-ATPase and $Ca^{2+}$-ATPase activity ↓ | 心脏发育异常 Abnormal heart development | [124] |

注:IL-1β 表示白介素 1β,CYP17A1 表示细胞色素 P450 17A1,STAR 表示类固醇生成急性调节蛋白,3β-HSD 表示 3β-羟基类固醇脱氢酶,17β-HSD 表示 17β-羟基类固醇脱氢酶,P450scc 代表细胞色素 P450 胆固醇侧链裂解酶,CAT 代表过氧化氢酶,GPX 代表谷胱甘肽过氧化物酶,SOD 代表超氧化物歧化酶,ROS 代表活性氧,Caspase-3 表示半胱氨酸蛋白酶-3,Caspase-9 表示半胱氨酸蛋白酶-9,MMP 代表基质金属蛋白酶,AHR 表示芳香族化合物受体,ARNT 表示芳香族化合物受体核转运蛋白,Adcy-PKA 代表上游腺苷环化酶-蛋白激酶,*VTG* 代表卵黄蛋白原,*CCND2* 代表细胞周期蛋白 D2,CYP1A1 代表细胞色素 P450 1A1,*GnRH2* 表示促性腺激素释放激素,*GnRH3* 表示促性腺激素释放激素,Bax 表示 Bcl-2 相关 X 蛋白,*Hsp90aB1* 代表 90kDa 热休克蛋白 aB1,CD34 代表分化簇 34,AMH 代表抗缪勒管激素,FOXO1 代表叉头框蛋白 O1,HoxA10 代表同源盒基因 A10,BMP2 代表骨形态发生蛋白-2,IBA1 代表离子钙结合衔接分子 1,SNCA 代表重组人 α-突触核蛋白,CYP19a 代表细胞色素 P450 家族 19 亚家族 a,*ATP2A2* 代表钙离子转运 ATP 酶 A2。

Note: IL-1β represents interleukin-1β, CYP17A1 represents cytochrome P450 family 17 subfamily A member 1, STAR represents steroidogenic acute regulatory protein, 3β-HSD represents 3β-hydroxysteroid dehydrogenase, 17β-HSD represents 17β-hydroxysteroid dehydrogenase, P450scc represents P450 cholesterol side-chain lyase, CAT represents catalase, GPX represents glutathione peroxidase, SOD represents superoxide dismutase, ROS represents reactive oxygen species, MMP represents matrix metalloproteinase, AHR represents aryl hydrocarbon receptor, ARNT represents aryl hydrocarbon receptor nuclear transporter, Adcy-PKA represents adenylate cyclase-protein kinase, *VTG* represents vitellogenin, *CCND2* represents cyclin-D2, CYP1A1 represents cytochrome P450 family 1 subfamily A member 1, *GnRH2* represents gonadotropin-releasing hormone 2, *GnRH3* represents gonadotropin-releasing hormone 3, Bax represents Bcl-2 associated X protein, *Hsp90aB1* represents recombinant heat shock protein 90 kDa alpha B1, CD34 represents cluster designation 34, AMH represents anti-Müllerian hormone, FOXO1 represents forkhead box O1, HoxA10 represents homeobox A10, BMP2 represents bone morphogenetic protein-2, IBA1 represents ionized calcium-binding adapter molecule 1, SNCA represents recombinant human alpha-synuclein, and CYP19a represents cytochrome P450 family 19 subfamily a, *ATP2A2* represents ATPase sarcoplasmic/endoplasmic reticulum $Ca^{2+}$ transporting 2.

不利影响。对雌性生殖毒性主要为:BaP 可以通过基因表达调控降低雌性体内 E2 和孕酮水平并且诱导促凋亡基因高表达,导致卵巢细胞以及雌性生殖细胞凋亡,影响其正常功能。对胚胎或胎儿:BaP 导致卵母细胞和卵丘细胞氧化应激以及 DNA 损伤,抑制后期的精卵结合;BaP 抑制卵泡的发生和发育通过基因调控以及氧化应激。此外,胚胎及胎儿的发育是一个复杂且敏感的过程,接触到危险物如 BaP 都可能会导致胎儿发育畸形或流产。

生殖毒性主要研究及评定药物或毒物对生殖细

胞发生、卵母细胞受精、胚胎形成、妊娠、分娩和哺乳过程的损害作用,评定方法即为生殖毒性试验。而生殖毒性试验最常使用的实验动物为哺乳动物,以大鼠和小鼠为主,但由于毒理学机制广泛而复杂,实验者未必能在大鼠或小鼠中观察到相同或相似的结果。BaP 是常见的生殖毒物,大量试验发现其可以促进生殖细胞或器官凋亡,Rahmani 等[81]证实 BaP 通过提高 Caspase-3 表达进一步促进卵巢和输卵管的凋亡,而 Yi 等[127]研究发现 BaP 可以上调抗凋亡蛋白 Bcl-2 表达,并降低下调了凋亡蛋白 Bax 与 Caspase-3 表达进而抑制子宫内膜细胞的凋亡。这与 Rahmani 等[81]结果形成鲜明对比,这种矛盾可能与不同研究中使用的不同暴露剂量、不同的实验对象和组织特异性有关。Liu 等[128]发现稽留流产女性与正常妊娠女性相比,其宫内 BPDE-DNA 加合物水平显著高于正常妊娠女性,这为 BaP 与稽留流产风险之间的关联提供了证据。当今随着工业化的不断发展,越来越多的毒物随之出现,无论是人还是动物长期暴露于这种环境,对生殖系统产生有害影响,因此,关注生殖毒性,了解其毒理学机制刻不容缓。

BaP 作为多环芳烃最具有代表性的污染物,其广泛存在于生态环境中,不仅危害大气环境、水环境、土壤环境等多个方面,还可以对生态环境中的生物产生不利影响,除了损害动物的身体健康,还可以造成其生殖系统发育异常,最终影响生物的后代繁衍。对于这一现象,不仅需要更加重视 BaP 对陆地环境和水生环境及其生物的毒害效应,还要减少 BaP 的生成与排放,从根源上解决问题。对于环境中已经存在的 BaP,需要建立和完善 BaP 进入生物体内发挥其毒性的机制,进而迅速、准确地缓解其毒性作用,为 BaP 的治疗提供强有力的依据。如今随着科技的进步,科学家们聚焦于污染物与生物体之间分子水平的相互作用,而 BaP 是最常见的污染物,其对生物体的毒性作用非常值得研究。本文总结了 BaP 的致毒途径,并聚焦于生殖方面,除了总结常见的致毒途径,还在分子水平阐述了 BaP 对雄性、雌性以及胚胎或胎儿的毒性,为进一步了解 BaP 的致毒机制提供理论依据,通过科学手段阐明 BaP 的生殖毒性,找到 BaP 主要作用靶点及通路,并以此为基础探索治疗方案,合理预防和缓解因接触 BaP 等环境毒物而带来的健康影响。

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