综述

双酚AF毒性及其机制的研究进展

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摘 要：双酚AF（BPAF）是一种双酚A（BPA）类似物，随着欧盟颁布在多种场所中禁用或限用BPA的规定，大量BPA类似物随之出现，其中BPAF因其韧性优良等特点应用较广。本文将从生殖、发育、内分泌、免疫、神经等方面对BPAF的毒理学作用及机制研究进行梳理，并对存在的问题进行总结，为后续研究和管理提供思路和依据。

关键词：双酚AF；双酚A类似物；雌激素受体；BPAF毒性
中图分类号：R155 **文献标识码：**A **文章编号：**1004-8456（2024）08-0976-06
DOI：10.13590/j.cjfh.2024.08.013

Research progress on the toxicity and mechanism of BPAF

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Abstract: Bisphenol AF (BPAF) is a kind of bisphenol A analogue. With the promulgation of the EU to ban or restricting the use of BPA in a variety of places, a large number of BPA analogues have emerged. The production of BPAF is increasing due to its excellent toughness and other characteristics. Based on a large number of BPAF laboratory studies, this paper sorts out the toxicological data of BPAF from the aspects of reproductive toxicity, developmental toxicity, endocrine toxicity, immunotoxicity, and neurotoxicity, summarizes the toxic effects of BPAF, provides ideas for scientific research, and provides policy basis for scientific management.

Key words: BPAF; BPs; Estrogen receptor; BPAF toxicity

双酚AF（Bisphenol AF）是毒理学领域中最常被研究的双酚A（Bisphenol A，BPA）类似物之一[1]，BPAF与BPA结构相似，均由碳桥连接2个酚环而成，不同的是BPA的碳桥另外连有2个甲基，而BPAF的碳桥则连有2个三氟甲基，因此BPAF又称为六氟双酚A。与BPA相同，BPAF也属于内分泌干扰物。BPAF可经口、皮进入人体，日常生活中随处可见含有BPAF的产品，如塑料产品、罐头、医疗器械等。随着BPAF的毒性研究逐渐深入，近年来发现BPAF在一些研究中表现出比BPA更强的毒性。对中国20个饮用水处理厂的水源水和饮用水进行检测发现：水源水中，BPA的检出率为80%，检出范围为（nd~34.9 ng/L），而BPAF的检出率为50%，检出范围为（nd~10.8 ng/L）；饮用水中BPA的检出率为40%，检出范围为（nd~6.5 ng/L），BPAF的检出率为30%，检出范围为（nd~4.7 ng/L）[2]。与BPA相比，BPAF出现的时间较短，在人群中的检出率较低，在中国和沙特阿拉伯人群尿液样本中BPAF的检测结果范围从低于检测限到3.93 μg/L[3-4]。近些年来，有关BPAF的毒性研究越来越多，涉及的毒性领域也越来越广泛，本研究从以下几方面综述了BPAF的毒性文献，为科学管理BPAF提供方向。

1 内分泌毒性

内分泌毒性是BPA类似物主要毒性表现之一，BPAF亦不例外。与BPA相比，BPAF与雌激素的结合效力更强[5]，进一步研究发现BPAF对雌激素受体β（ERβ）的结合活性比雌激素受体α（ERα）的活性更高[1,6-7]。而ERα和ERβ在不同性别、年龄

收稿日期：2023-08-25
基金项目：上海市卫生健康委员会科研项目计划（20224Y0329）；上海市自然科学基金（23ZR1459600）
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的人体中表达量不同,在同一个体的不同组织、器官中的表达水平也不同,且不同雌激素与ERα和ERβ的结合能力也不同[8]。此外,BPAF还可通过雌激素受体影响趋化因子配体12(CXCL12)和Ca^{2+}流,进而改变细胞正常周期[9-10],也可直接通过GPR30激活ERK1/2和Akt磷酸化等信号通路诱导细胞增殖[11-12]。BPAF可诱导ER靶基因,包括TFF1、GREB、CTSD[13]。ZHAO等[14]研究发现,RTK信号的激活对BPAF介导的雌激素依赖性的细胞增殖至关重要,且AREG是BPAF诱导的ER-RTK串扰的关键物质。BPAF不仅可以影响雌激素受体,还可以改变激素水平。BPAF已显示出与BPA相似或更强的雌激素和/或抗雄激素活性[15-18]。研究指出BPAF可通过经典基因组通路和细胞外信号调节激酶(ERK1/2)依赖的非基因通路调控雌激素活性[13]。以雌性斑马鱼为模型的研究发现BPAF可导致体内雌二醇水平升高[19-20]。双酚A类似物的A-苯环和B-苯环的4-羟基是性激素活性所必需的,苯环3,5-位置的取代基和桥联烷基部分则显著影响性激素活性[21]。在化学结构上,双酚AF比双酚A多2个三氟甲基。有限的实验数据表明,不同卤化模式的BPA类似物影响过氧化物酶体增殖物激活受体γ(PPARγ)和ERα受体的活性能力明显不同[22]。FENG等[23]研究发现:BPAF可能通过抑制H295R细胞的类固醇生成,导致孕酮和睾酮下调,并观察到72 h半数致死浓度的细胞毒性排序为BPAF>BPA>BPS>BPF。大鼠垂体(GH3)细胞系研究发现:BPAF促进细胞增殖的能力最强,表明具有较强的甲状腺激素激动作用[24]。以斑马鱼为模型的糖代谢研究发现,BPAF可通过干扰糖代谢网络引起空腹高血糖[25]。暴露BPAF还可以改变斑马鱼幼虫的甲状腺激素含量,参与下丘脑-垂体-甲状腺轴中基因转录,触发甲状腺内分泌毒性[26]。

2 神经毒性

神经系统是人体最重要的调节系统,主要对机体内外环境的变化进行感觉和分析,并通过其传出信息的变化调控整个机体予以应对[27]。BPAF会导致神经内分泌紊乱,这可能是雌激素受体依赖性的[28]。有研究比较双酚A类似物对斑马鱼的神经毒性发现BPAF>BPF≈BPA>BPS,其可能与神经递质的变化和神经元发育抑制有关[29]。BPAF对斑马鱼的神经毒性研究发现:50 μg/L和500 μg/L的BPAF显著增加了成年斑马鱼的焦虑样和攻击行为,并观察到大脑组织病理学改变和乙酰胆碱酯酶活性下降[30]。毒性机制研究发现,BPAF诱发的氧化应激和细胞凋亡可以转化为行为和神经发育异常[31]。神经毒性往往与发育毒性分不开,其他神经发育相关内容的机制研究见发育毒性。

3 免疫毒性

免疫系统行使功能时,往往与其他系统,特别是神经和内分泌系统发生互相作用[32]。有研究表明BPA在较高浓度下会降低细胞活力和ATP水平,但BPAF在0.3~3 μmol/L(0.1~1.0 μg/mL)的低浓度时即表现出对外周血单个核细胞(PBMC)强烈的细胞毒性[33]。BPAF还可以通过诱导人外周血单核细胞的坏死从而影响细胞寿命[34]。BPAF可对DNA嘧啶造成明显的氧化损伤及DNA单链断裂[35-36]。在10~350 μmol/L浓度条件下,BPAF即表现出较强地负向调节人单核细胞来源的树突状细胞(MDDC)的分化和成熟,BPAF还可负向调节核因子NF-κB和ERK1/2通路。BPAF暴露对MDDCs的内吞和同种异体刺激能力产生负面影响[37]。此外,BPAF诱导人体红细胞形成ROS和脂质过氧化的能力高于BPA[38]。在双酚A类似物BPAF、BPF、BPS对人红细胞影响的研究中,BPAF表现出最强的溶血能力,此外BPAF还可导致高铁血红蛋白的形成,并诱导棘状红细胞增多[39]。同样地,BPAF提高人红细胞胞质钙离子、钙蛋白酶和半胱天冬酶-3活性的能力最强[40]。

4 生殖毒性

BPAF具有雌激素样作用,对斑马鱼表现出生殖毒性[20],也有斑马鱼胚胎生殖毒性研究发现:与其他双酚A类似物相比,BPAF的生殖神经内分泌毒性与BPA更相似[41]。SHI等[19]、YANG等[20]发现:在发育过程中接触BPAF会导致雌性斑马鱼的雌二醇水平升高,而雄性斑马鱼则出现睾酮(T)水平下降且睾丸形态发生改变。此外,暴露于1 mg/L BPAF的斑马鱼中观察到睾丸卵母细胞发育延迟[20]。除了以斑马鱼为基础的研究外,还有以大鼠为动物模型的试验发现:BPAF诱导的睾丸毒性效应与BPA相似[42]。孕期和哺乳期大鼠暴露于BPAF会损害雄性后代的生殖功能[43]。有研究提示BPAF可能通过抑制睾酮生物合成相关基因和蛋白质,降低成年大鼠血清T水平[44]。也有研究表明母鼠孕前暴露于750 mg/kg BPAF不影响胎鼠体内T的正常水平[45]。另有大鼠一代繁殖研究发现,妊娠期暴露BPAF,可导致黄体、活胎或活产数等减少[46]。BPAF可通过GPER1途径,发挥雌激素作用从而促进子宫生长[47]。此外,BPAF还能通过NF-

κB影响前列腺细胞的增殖活动[48]。

在体外研究中，多参数高内涵分析发现，BPAF比BPA的精原细胞毒性更强，暴露于1 μmol/L的BPAF会改变核形态并诱导细胞周期停滞，10 μmol/L浓度的BPAF会导致细胞骨架扰动和细胞多核化，而25 μmol/L的BPAF会导致细胞出现DNA损伤[49]。NAKANO等[50]发现，暴露于50 μg/mL的BPAF可以影响卵母细胞成熟，并导致细胞周期延长。BPAF可显著降低人卵巢颗粒细胞瘤细胞的活力，并影响卵巢卵泡发育过程[51]。其他研究也发现BPAF对人卵巢颗粒细胞和猪卵巢细胞均有不同程度的影响[52-53]。

体内外研究均表明BPAF的生殖毒性与BPA相似或更强，可能由于BPAF与雌激素受体的结合能力较强有关，进而影响其他激素的分泌，最终造成生殖发育异常。

5 发育毒性

从早期胚胎到行为表现的全生命发育周期，BPAF均表现出不同程度的毒性，并显示出不同性别的生殖发育毒性。非洲爪蛙胚胎暴露于BPA或BPAF中96 h，结果显示：BPA和BPAF均可导致脊髓、头部和肠道的早期分裂，但BPAF的毒性效力是BPA的1 000倍[54]。一项以鸡胚为模型的试验研究发现，BPA可导致胚胎死亡率增加，且BPAF诱导鸡胚雌激素样作用的能力与BPA相似[55]。多代生殖发育毒性研究显示：围产期大鼠暴露BPAF可以导致胎儿畸形及子代体重下降，并影响子代阴道开放及包皮分离时间[46]。小鼠母体暴露BPAF诱导成年后代的神经发育缺陷以及行为异常，主要表现出焦虑和抑郁样行为，以及学习记忆、社交能力损伤等，这可能与BPAF导致母体免疫功能障碍有关[56]。围产期暴露BPAF对子代造成的影响在多项研究中表现出性别差异：在小鼠围产期暴露BPAF会破坏雄性后代海马体中的氧化和抗氧化平衡，并降低雄性后代海马ERα的表达和认知能力，且呈现剂量依赖性，而雌性后代没有相应变化[57]。GONG等[58]研究发现，小鼠母体暴露于BPAF显著影响后代青春期的情绪相关行为，其中雄性后代出现焦虑、抑郁、记忆障碍的可能性更高。进一步研究发现：BPAF可通过Aim2(黑色素瘤-2)-NF-κB-IFNs信号通路在成年雄性后代睾丸中引起先天性和适应性免疫反应[59]。以斑马鱼为模型的多代生殖毒性的研究发现，父系斑马鱼暴露于BPAF可降低F1代幼鱼的卵化率，增加死亡率，并缩短子代的体长，还影响亲代和F1代DNA、m6A RNA的甲基化表达水平[60-61]。而母系斑马鱼暴露同样可引起F1代死亡率增加，但只影响自身和F1代的DNA甲基化水平[60]。相关机制研究指出：环境相关浓度的BPAF暴露可通过调节MAPK信号通路影响斑马鱼幼鱼的早期发育和免疫系统[62]。

6 讨论

大量实验室结果表明，BPAF可能是毒性更强的双酚类似物[28,33-34,42-43,63-64]。目前已在环境中检测到BPAF，包括工业厂房附近的水源和土壤。BPAF在水、土壤和沉积物中的半衰期约是BPA的4.8倍，因此BPAF的环境生物累积越来越受到关注[65-66]。一项由350名青少年组成的前瞻性研究发现，人血清中BPAF的检出率为100%，且男性比女性更易暴露于BPAF[67]。现已有文献指出BPAF并不是BPA的安全替代品[55]。与BPA相同，BPAF的毒性机制错综复杂，且雌激素受体在其中发挥关键作用，BPAF在较低浓度下即可激活ERα，与ERβ的亲和力更强[6-7,68]。在众多双酚A类似物中，BPAF展现出的类雌激素作用最强[69]。这可能与BPAF分子结构中的卤化作用有关，其对配体与ERα结合过程中的互相作用和氢键的产生有较大影响[22]，因此BPAF的内分泌毒性值得重点关注。未来可从分子结构上继续深入研究BPAF的特殊结构—三氟甲烷对雌激素受体的影响机制。此外，基于低剂量BPA即可促进小鼠体内的炎症反应，欧洲食品安全局建议进一步降低BPA的接触限制[70]，而BPAF亦表现出较强的免疫细胞毒性，有必要研究BPAF对免疫反应能力的影响，完善BPAF的毒理学资料。BPAF发挥毒效应的机制通路可能与G蛋白偶联受体、细胞外信号调节激酶和磷脂酰肌肽3激酶(FI3K)/蛋白激酶B(Akt)、钙离子、ROS稳态等有关[9-12,14-13]。至今尚无文献完整梳理BPAF涉及的毒性通路及作用机制。本文广泛阅读了相关资料发现BPAF在内分泌毒性、生殖发育毒性等领域表现出的毒性比BPA更为强烈，提示需要慎重考虑是否用BPAF替代BPA。此外，现有文献的研究基础较为单一，研究结论分散不连贯，且缺少流行病学相关调查，未来可从细胞到动物再到人群的综合研究，探讨BPAF的毒性表现，进一步关注双酚A类似物的生产及使用管理规范。

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