



双酚 A 对畜禽的毒性研究进展

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摘 要: 双酚 A (bisphenol A, BPA) 是一种环境内分泌干扰化学物质, 广泛应用于塑料生产。由于 BPA 的大量生产和使用, 对人类和动物健康构成威胁。本文系统梳理了近些年国内外关于 BPA 毒性效应的研究成果, 全面综述了 BPA 的暴露来源和途径、在动物体内的代谢转化以及对畜禽健康的毒性作用进展, 有助于提高对 BPA 毒性的认识, 以期为深入研究 BPA 的动物毒性机理, 预防 BPA 在畜禽养殖中的危害提供有价值的参考资料。

关键词: 双酚 A; 畜禽; 毒性作用; 内分泌干扰; 氧化应激

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Research Progress on Toxicity of Bisphenol A to Livestock and Poultry

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Abstract: Bisphenol A (BPA) is an environmental endocrine disrupting chemical which widely used in plastic production. Due to the large-scale production and use of BPA, it poses a threat to human and animal health. This article systematically sorts out the research results on the toxic effects of BPA at home and abroad in recent years, and comprehensively reviews the sources and routes of BPA exposure, its metabolic transformation in animals, as well as the progress of its toxic effects on livestock and poultry health. It will help to improve the understanding of the toxicity of BPA, and is expected to provide valuable reference materials for in-depth studies on the animal toxicity mechanism of BPA and prevention of the hazards of BPA in livestock and poultry farming.

Keywords: bisphenol A; livestock and poultry; toxic effect; endocrine disruption; oxidative stress

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双酚 A (bisphenol A, BPA), 即 4,4'-二羟基-2,2'-二苯基丙烷 (CAS 编号: 80-05-7), 是一种人工合成的有机化合物, 也是一种环境内分泌干扰物^[1]。BPA 被广泛用于聚碳酸酯塑料和环氧树脂的合成, 这些材料应用于储物容器、饮用水瓶、食品罐内衬等包装材料以及医疗保健设备等产品的制造^[2]。BPA 在环境中普遍存在, 人类和动物群体可

能会长期接触到这种化合物。BPA 可以与雌激素受体、雄激素受体、过氧化物酶体增殖激活受体、甲状腺激素受体以及雌激素相关受体结合, 表现出内分泌干扰作用, 进而对生殖系统、神经系统、代谢功能、免疫功能以及后代的生长发育造成健康危害^[1]。在最新的风险评估中, 欧洲食品安全局将 BPA 的每日可耐受摄入量设定为 $0.2 \text{ ng} \cdot \text{kg}^{-1} \text{ 体重}$ ^[3] (除特殊

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说明外,以下提到每 kg 的 BPA 剂量均是以体重为基础)。美国环境保护署则认为,每日 $50 \mu\text{g}\cdot\text{kg}^{-1}$ BPA 暴露剂量对人类是安全的。然而,众多研究表明,在人类和啮齿动物模型中,妊娠期和哺乳期 BPA 暴露量在每日 $50 \mu\text{g}\cdot\text{kg}^{-1}$ 或以下时,会出现诸如出生缺陷,发育和生殖障碍,肝脏、肾脏和呼吸系统疾病等问题,对健康造成不良影响^[4]。许多研究也使用了广泛的剂量和动物模型来评估 BPA 的影响,然而,由于试验设计和剂量的不同以及不同物种的敏感性和环境等其他外在因素的差异,均干扰了对 BPA 不良健康效应的准确解读,是否能在不同的试验对象中获得类似的结果,还需加以验证。本文全面综述了 BPA 暴露的现状(来源和途径)、在动物体内的吸收和代谢转化,同时通过收集近五年的体内和体外试验数据,总结了 BPA 对畜禽健康的毒性作用及其相关机制,旨在为制定针对性的预防和保护措施提供依据,以降低动物因 BPA 暴露导致的健康风险,保障其健康与福利,同时提升公众对 BPA 暴露潜在风险的认知。

1 BPA 的暴露来源和途径

BPA 在环境和食品中无处不在^[5]。塑料包装是动物饲料受到 BPA 污染的一个来源,动物通过接触饲料中的双酚类物质(BPs)使其极易在动物和动物源性食品中发生生物积累^[6]。在中国两家畜牧场猪和牛尿液 BPs 的检测中发现,有 10 种 BPs 频繁被检出^[7]。BPA 在肉类及肉制品中常被检出,其污染可能贯穿“从农场到餐桌”生产链的不同环节^[8]。乳制品受 BPA 污染的一个途径是环境污染,如在挤奶和加工过程中接触含 BPA 的器具、设备的塑料部件或从包装材料迁移,另一个途径可能源于奶牛饲喂不当^[9-10]。因此,在畜牧生产中(如饲料包装、畜栏设备、食槽等)减少 BPA 的使用,可能会降低畜产品受污染的程度。

BPA 被用作合成聚碳酸酯塑料的单体,也用作增塑剂和稳定剂。由于聚合反应不完全,未反应的 BPA 会发生水解或扩散,从涂层和塑料材料中释放到食物和饮水中^[11]。酸碱度、温度和使用时间等因素会改变 BPA 释放的速率。释放的 BPA 通过呼吸系统、消化系统和皮肤接触进入体内,其中口服摄入受污染的食物和饮用水是 BPA 暴露的主要来源^[12]。然而,经皮肤接触 BPA 的危害比口服摄入更为严重^[13]。这是因为经皮肤接触的 BPA 可以绕过

肝脏首过代谢,阻止无毒的 BPA 结合物——BPA-葡萄糖醛酸苷的形成,导致 BPA 在生物体液中存在的时间延长,以及体内未结合的 BPA 浓度升高^[14]。而口服吸收的 BPA 会经历肝脏首过效应,形成 BPA-葡萄糖醛酸苷,使 BPA 浓度降低^[15]。

2 BPA 在体内的吸收、分布和代谢转化

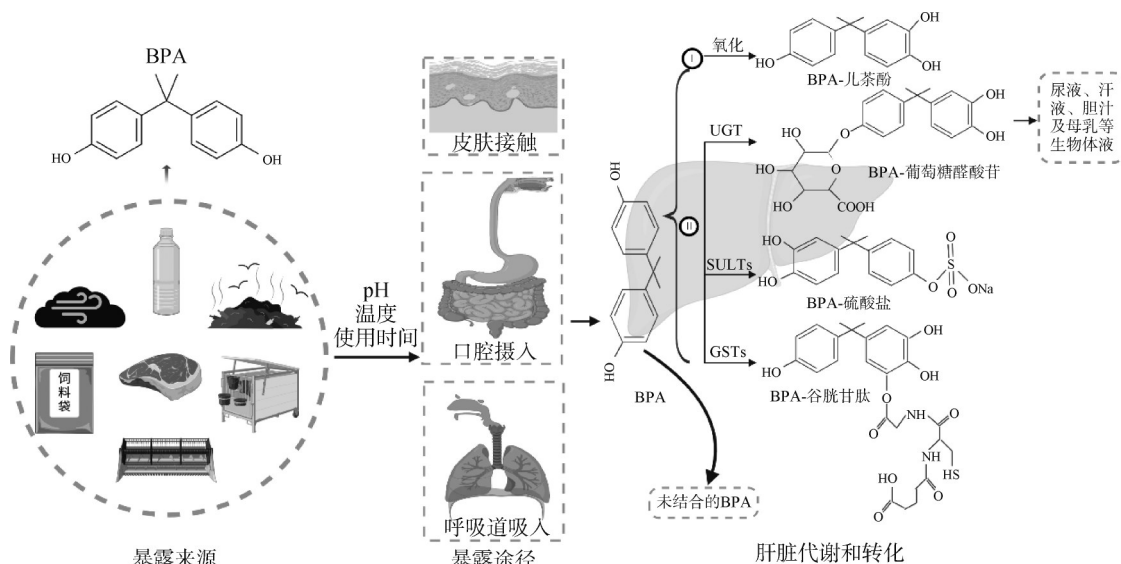
BPA 主要在肝脏中进行代谢^[16]。其代谢过程分为两个转化阶段,第一阶段代谢通常是非合成型的,主要包括氧化和水解过程,由细胞色素 P450 酶将 BPA 氧化为其羟基化形式——BPA-儿茶酚^[17]。第二阶段代谢涉及形成结合物和复合物,以使 BPA 失活并促进其排泄。尿苷二磷酸葡萄糖醛酸基转移酶、磺基转移酶和谷胱甘肽-S-转移酶是参与 BPA 第二阶段代谢的酶^[16]。药代动力学研究表明,BPA 经胃肠道迅速吸收、进入体循环之前,在肝脏和肠道中主要与尿苷二磷酸葡萄糖醛结合,由尿苷二磷酸葡萄糖醛酸基转移酶催化,代谢为 BPA-葡萄糖醛酸苷,随后排泄到尿液、汗液、胆汁及母乳等生物体液中^[15,18]。当葡萄糖醛酸化途径达到饱和时,还会形成其他少量代谢产物,如具有生物活性的未结合的 BPA、BPA-硫酸盐和 BPA-谷胱甘肽等^[16,19]。进入血液的 BPA 可与血浆蛋白结合,将其运输至包括生殖组织在内的各种组织中^[20]。在卵巢内部,磺化反应是 BPA 主要的代谢途径。研究表明,在奶牛卵巢卵泡颗粒细胞和卵泡膜外植体、绵羊胎儿和成年完整卵巢中 BPA 可转化为其磺酸化代谢产物 BPA-磺酸酯^[21-22]。BPA 在体内的暴露来源、途径和代谢转化示意图 1。

3 BPA 的动物毒性作用

近年来,BPA 对猪、鸡、牛、羊等畜禽的毒性效应引发广泛关注。本文系统梳理了 2020—2025 年发表的研究成果,总结了 BPA 对畜禽不同物种生殖、肝脏、肠道及肾脏等重要器官系统的潜在危害,以更好地了解不同物种对 BPA 的敏感性。然而,这种毒性背后的确切机制尚未完全探明,可能涉及多种途径。

3.1 BPA 对猪的毒性效应

3.1.1 BPA 诱导猪生殖毒性 多项研究探讨了 BPA 对体外培养猪卵母细胞的影响。高浓度(高于 $50 \mu\text{mol}\cdot\text{L}^{-1}$)BPA 暴露诱导氧化应激、损害细胞氧化还原状态,抑制卵母细胞成熟和早期胚胎发



UGT. 尿苷二磷酸葡萄糖醛酸基转移酶;SULTs. 磺基转移酶;GSTs. 谷胱甘肽 S-转移酶

UGT. Uridine diphosphate-glucuronosyltransferase; SULTs. Sulfotransferases; GST. Glutathione S-transferases

图1 BPA的暴露来源、吸收和代谢(绘自BioRender画图软件)

Fig. 1 Exposure sources, absorption and metabolism of BPA (Created with BioRender)

育^[23-24]。同时,褪黑素对BPA产生的抗氧化作用可改善卵母细胞的成熟过程^[25-26]。Elmetwally等^[27]研究表明,所有浓度的BPA处理均降低了猪滋养外胚层细胞的增殖和黏附能力。其中,较低浓度(低于 $0.1 \mu\text{mol}\cdot\text{L}^{-1}$)BPA促进细胞迁移,高浓度(10 、 $100 \mu\text{mol}\cdot\text{L}^{-1}$)则抑制细胞迁移,这些不利影响会妨碍猪受精卵在妊娠着床期的发育。此外,BPA能够干扰子宫功能,其对猪子宫平滑肌收缩活动的影响因猪的生理状态而异。在未成年猪中, $100 \mu\text{mol}\cdot\text{L}^{-1}\sim 100 \text{mmol}\cdot\text{L}^{-1}$ BPA可降低子宫平滑肌收缩幅度。动情期和早期妊娠猪则需 $10\sim 100 \text{mmol}\cdot\text{L}^{-1}$ 才能产生同样效果。在收缩频率方面,早期妊娠猪对 $0.01 \text{nmol}\cdot\text{L}^{-1}\sim 100 \text{mmol}\cdot\text{L}^{-1}$ 浓度的BPA敏感,未成年猪响应 $10 \text{nmol}\cdot\text{L}^{-1}\sim 100 \text{mmol}\cdot\text{L}^{-1}$ 浓度,而动情期猪仅在高浓度($100 \text{mmol}\cdot\text{L}^{-1}$)才出现子宫平滑肌收缩频率的下降^[28]。对猪子宫内膜类器官的研究表明, $0.5 \mu\text{mol}\cdot\text{L}^{-1}$ BPA可诱导类器官形态变化、氧化应激和细胞凋亡^[29]。

对猪睾丸细胞的研究证实,猪饲料中接触的BPA($9.7\sim 47.9 \mu\text{g}\cdot\text{kg}^{-1}$)会通过持续激活内质网应激和未折叠蛋白反应引发细胞凋亡和炎症反应^[30]。Chen等^[31]研究表明,BPA($125 \text{nmol}\cdot\text{L}^{-1}$)通过活性氧(ROS)介导的核因子红细胞2相关因子2(Nrf2)信号通路诱导猪睾丸细胞线粒体凋亡。胡婷等^[32]研究表明,BPA($50 \mu\text{mol}\cdot\text{L}^{-1}$)暴露初期猪睾丸

支持细胞表现出以肿瘤坏死因子(TNF)、p53和丝裂原活化蛋白激酶(MAPK)通路协同激活为特征的炎症反应,在暴露后期氨基酸及糖代谢通路显著激活。酪氨酸磷酸化和蛋白激酶A(PKA)活性在调节精子获能和顶体反应中起重要作用。高浓度($100 \mu\text{mol}\cdot\text{L}^{-1}$)BPA暴露会增强酪氨酸磷酸化^[33],降低p-PKA水平^[34-35],从而抑制公猪精子活力。

3.1.2 BPA诱导猪肝肾毒性 每日经 $0.5 \text{mg}\cdot\text{kg}^{-1}$ BPA处理的猪肝内交感神经纤维数量明显增加,提示了神经纤维失调^[36]。本课题组前期研究表明,高浓度BPA($200 \mu\text{mol}\cdot\text{L}^{-1}$)诱导猪肾细胞氧化应激,促进脂质积累、细胞凋亡以及炎症反应^[37-38]。张卓等^[39]研究表明,低浓度BPA($1 \mu\text{mol}\cdot\text{L}^{-1}$)也会诱导猪肾细胞DNA损伤和细胞凋亡。

3.1.3 BPA诱导猪胃肠道毒性 仔猪日粮每日添加 $500 \text{mg}\cdot\text{kg}^{-1}$ 的BPA会诱发肠道炎症并扰乱微生物群平衡^[40],影响仔猪生长、营养消化能力和肠道功能^[41]。Gonkowski^[42]研究表明,两种剂量的BPA(每日 0.05 和 $0.5 \text{mg}\cdot\text{kg}^{-1}$)均会增加猪小肠黏膜层5-羟色胺阳性细胞数量,促进胃肠道的病理过程。此外,即使是低剂量(每日 $0.05 \text{mg}\cdot\text{kg}^{-1}$)BPA也会引起猪肠神经元神经化学特征的变化^[43-46]。在以猪肠上皮细胞(IPEC-J2)为模型的研究中发现, $50 \mu\text{mol}\cdot\text{L}^{-1}$ BPA暴露会增加细胞死亡率和形态学损伤,诱导炎症反应和细胞凋亡^[47]。 $150 \mu\text{mol}\cdot\text{L}^{-1}$

BPA 暴露导致 BRD4/腺苷酸活化蛋白激酶 (AMPK)/mTOR 信号通路关键因子异常表达,进而诱导细胞凋亡和自噬^[48]。

3.1.4 BPA 诱导猪神经毒性 给猪每日口服含有 0.05 和 0.5 mg·kg⁻¹ 的 BPA 胶囊会影响主动脉分支管壁内神经的神经化学编码^[49]、改变膀胱内神经结构和各类神经元的神经化学特征^[50-51]、子宫交感神经支配的神经化学特征^[52]以及心脏壁神经^[53]的神经化学特征。

3.2 BPA 对家禽的毒性效应

以产蛋鸡为试验模型的研究表明,每日口服 0.05 mg·kg⁻¹ 的 BPA 会减少产蛋鸡排卵前卵泡数量,增加卵巢中淋巴细胞核浆细胞的浸润^[54]。每日 0.5 mg·kg⁻¹ 的 BPA 显著降低产蛋鸡生产性能,导致卵泡和间质细胞退化,同时通过调节雌激素受体 α (ER α)-Nrf2- Kelch 样 ECH 相关蛋白 1(Keap1)通路破坏卵巢的氧化还原稳态^[55]。在卵内给药的 BPA 会诱导睾丸雌性化。Mentor 等^[56]研究表明,鸡胚暴露于 210 nmol·L⁻¹/g 蛋的 BPA 会干扰生殖器官发育。在鸡胚早期发育阶段,蛋中 0.228 和 2.28 mg·枚⁻¹ 的 BPA 暴露延迟神经系统发育和中线闭合^[57]。经 50、100 和 250 μ g·枚⁻¹ 的 BPA 处理后,胚胎的法氏囊发育迟缓^[58],胫骨生长板的发育受到抑制^[59]。Harnett 等^[60]研究表明,鸡胚在蛋内暴露于浓度逐渐增加(0.03~30 μ mol·L⁻¹)的 BPA 显著损害胚胎发育、生长和存活。BPA 作为选择性雌激素受体调节剂,参与代谢综合征的发生和发展。研究表明,接触高剂量(5 mg·(kg·d)⁻¹)BPA 破坏脂质稳态、加剧胰岛素抵抗和炎症,并加重由高能量低蛋白日粮诱导的蛋鸡非酒精性脂肪肝病^[61]。Li 等^[62]研究表明,0.05 mg·(kg·d)⁻¹ 剂量的 BPA 能够调节 ER α ,其类似雌激素的作用可以缓解高脂饮食诱导的老龄母鸡肥胖,而 5 mg·(kg·d)⁻¹ 剂量的 BPA 会诱导氧化损伤,加速产蛋鸡腹部脂肪沉积。饲料中补充 50 mg·(kg·d)⁻¹ 的 BPA 抑制磷脂酰肌醇 3 激酶(PI3K)/丝氨酸/苏氨酸激酶(AKT)通路,诱导鸡法氏囊细胞凋亡和程序性坏死^[63]。

在畜禽养殖中,硒缺乏与 BPA 暴露常常同时发生,会加剧 BPA 对动物造成的危害。大量的研究已经证实了硒缺乏和 BPA 暴露对家禽的影响。在体内肉鸡模型和体外鸡淋巴瘤细胞模型的研究表明,硒缺乏和 BPA(体内 0.05 mg·(kg·d)⁻¹,体外 60 μ mol·L⁻¹)联合暴露对法氏囊和细胞均具有细胞

毒性,通过调节 ROS/AKT/叉头盒 O1(FOXO1)通路,加剧细胞凋亡和自噬^[64]。硒缺乏和 BPA(体内 50 mg·(kg·d)⁻¹,体外 100 μ mol·L⁻¹)联合暴露通过多种机制诱导鸡脾脏损伤。一方面,通过硝化应激上调肿瘤坏死因子- α (TNF- α)/Fas 相关死亡结构域蛋白(FADD)信号通路^[65],诱导程序性坏死和细胞凋亡。另一方面,通过诱导氧化损伤激活 ROS/核苷酸结合寡聚化结构域样受体蛋白 3(NLRP3)信号通路^[66],从而诱导鸡的脾组织发生细胞焦亡。Wang 等^[67]研究表明,BPA 暴露(体内 0.05 mg·(kg·d)⁻¹,体外 50 μ mol·L⁻¹)和硒缺乏共同作用,通过氧化应激/内质网应激诱导鸡胸腺细胞焦亡和铁死亡。BPA 能够穿透血脑屏障,对大脑构成威胁。研究表明,BPA(体内 20 mg·(kg·d)⁻¹,体外 75 μ mol·L⁻¹)暴露和硒缺乏通过诱导线粒体自噬和细胞凋亡之间的串扰失衡,对鸡脑造成损伤^[68]。BPA(20 mg·(kg·d)⁻¹)暴露和硒缺乏激活诱导型一氧化氮合酶(iNOS)/一氧化氮(NO)/Janus 激酶(JAK)/信号转导和转录激活因子 3(STAT3)信号通路,引发细胞焦亡和鸡肌胃分化紊乱,最终导致肌胃组织结构损伤和炎症^[69]。在 BPA 和硒缺乏的鸡肝脏体内外模型中,BPA 暴露(体内 20 mg·(kg·d)⁻¹,体外 8 μ g·mL⁻¹)和硒缺乏通过增加氧化应激,诱导细胞焦亡和 M1 型极化,加剧肝脏炎症^[70]。Yin 等^[71]研究表明,BPA(50 mg·(kg·d)⁻¹)通过 NF- κ B/NLRP3/半胱天冬酶 1(Caspase-1)通路,加剧硒缺乏诱导的鸡气管细胞焦亡。Peng 等^[72]研究表明,BPA(体内 50 mg·(kg·d)⁻¹,体外 150 μ mol·L⁻¹)暴露通过调节 miR-155/肿瘤坏死因子受体作用因子 3(TRAF3)/ROS/NF- κ B 轴,加重硒缺乏鸡的气道炎症损伤。Fan 等^[73]研究表明,BPA(体内 50 mg·(kg·d)⁻¹,体外 300 nmol·L⁻¹)暴露调节 miR-26a-5p/ADAM17 表达,诱导 ROS 生成并激活肿瘤坏死因子受体 1(TNFR1)通路,加剧了硒缺乏诱导的鸡血管组织程序性坏死和炎症。Luo 等^[74]研究表明,硒缺乏通过 ROS/P53 途径诱导线粒体功能障碍、细胞凋亡和细胞周期停滞,加剧 BPA(体内 50 mg·(kg·d)⁻¹,体外 300 nmol·L⁻¹)诱导的鸡肠道损伤。BPA(50 mg·(kg·d)⁻¹)和低硒联合暴露诱导的 NO 依赖性内质网应激,通过促进程序性坏死途径的激活,对肉仔鸡的心肌组织造成严重损伤^[75]。PI3K/AKT 通路器与器官和组织的细胞凋亡损伤相关。Sun 等^[76]研究表明,BPA(0.05 mg·(kg·d)⁻¹)暴露

和低硒通过激活磷酸酶与张力蛋白同源物 (PTEN)/PI3K/AKT/哺乳动物雷帕霉素靶蛋白 (mTOR) 通路, 加剧线粒体损伤、细胞凋亡和自噬, 对鸡胰腺组织造成损伤。Chen 等^[77]研究表明, BPA (体内 $50 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$, 体外 $150 \text{ nmol} \cdot \text{L}^{-1}$) 暴露和硒缺乏激活氧化应激和 PI3K/AKT 信号通路, 加剧鸡肾细胞凋亡和程序性坏死。Li 等^[78]研究表明, BPA (体内 $50 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$, 体外 $200 \text{ nmol} \cdot \text{L}^{-1}$) 暴露和硒缺乏激活 ROS/PI3K/AKT 信号通路, 加剧鸡动脉内皮细胞的凋亡。

3.3 BPA 对羊的毒性效应

绵羊作为一种大型动物模型, 在解剖学和生理学上与人类相似, 其妊娠期较长 (相较于小型啮齿类动物模型), 且胎儿的发育轨迹更接近人类, 这使其成为一种理想的人类生物医学模型^[79]。产前接触 BPA 与成年期的代谢缺陷相关, 非单调剂量-反应关系是 BPA 毒性的一个常见特征。研究表明, 产前暴露于环境水平 BPA ($0.5 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$) 导致雌性后代在成年后出现外周胰岛素抵抗和脂肪组织紊乱、肝脏和肌肉氧化应激以及脂毒性^[80-81]、内分泌腺功能障碍^[82]。Motta 等^[83]研究表明, 产前 BPA 暴露 ($0.5 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$) 诱导的成年雌性后代脂肪肝表型, 与肝脏过早衰老以及昼夜节律基因的紊乱有关。妊娠期接触低剂量 BPA ($5 \text{ } \mu\text{g} \cdot (\text{kg} \cdot \text{d})^{-1}$) 会显著影响特定胎儿脑区的代谢组学特征, 这些影响大多与神经氨基酸通路和能量稳态有关, 且大多数变化具有区域特异性^[84]。一些体外研究表明, BPA ($10 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) 干扰绵羊颗粒细胞孕酮分泌, 通过改变参与细胞代谢过程的基因表达, 影响细胞凋亡、增殖和存活^[85]。BPA ($100 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) 降低了绵羊脐带间充质干细胞活力、细胞迁移能力以及成肌标记基因的表达, 抑制成肌分化^[86]。体外分离培养胎羊原代前脂肪细胞发现, 妊娠期暴露于 BPA ($0.5 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$) 可增强雌性胎儿前脂肪细胞的成脂分化能力, 并且与细胞外基质重塑信号的调节有关, 但对雄性胎儿前脂肪细胞没有影响^[87]。BPA 对绵羊红细胞具有氧化作用, 并且较高浓度 ($200 \sim 300 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) BPA 能够改变红细胞的形状^[88]。

BPA 能够穿过胎盘屏障, 干扰胎盘的发育和正常功能, 引发多种妊娠并发症。研究表明, BPA 暴露 (体内 $5 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$, 体外 300 和 $400 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) 会在绵羊胎盘和滋养层细胞中引发自噬、细胞凋亡、内质网应激、线粒体功能障碍以及肠道微生物失

调, 进而诱导胎盘功能障碍和胎儿生长受限^[89-91]。Song 等^[92]研究指出, 妊娠期 BPA ($0.5 \text{ mg} \cdot (\text{kg} \cdot \text{d})^{-1}$) 暴露导致胎盘效率和胎儿体重降低, 这是由 BPA 诱导的炎症、氧化应激、脂毒性、血管生成、类固醇相关和纤维化改变所导致的。在胎羊卵巢外植体系统的研究证明, BPA ($300 \text{ nmol} \cdot \text{L}^{-1}$ 和 $30 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) 暴露会干扰胎羊卵巢的减数分裂过程, 减少卵巢储备, 增加染色体异常卵母细胞 (非整倍体) 的出现频率, 造成成年雌性亚不育或不孕^[93]。

3.4 BPA 对牛的毒性效应

BPA 通过改变氧化应激通路影响生育能力。BPA ($50 \text{ } \mu\text{g} \cdot \text{mL}^{-1}$) 能够增加牛卵丘-卵母细胞复合体中 ROS 含量, 降低精子的运动能力^[94]。在体外牛颗粒细胞中添加低剂量 ($0.5 \text{ } \mu\text{g} \cdot \text{mL}^{-1}$) 和高剂量 ($50 \text{ } \mu\text{g} \cdot \text{mL}^{-1}$) BPA, 通过诱导氧化应激和线粒体功能障碍, 激活内源性线粒体途径, 诱导细胞凋亡, 降低细胞活力, 并且 BPA 诱导的凋亡与 miR-21 无关^[95-98]。BPA ($50 \text{ } \mu\text{g} \cdot \text{mL}^{-1}$) 暴露对牛卵母细胞和囊胚发育的影响与囊胚阶段抗苗勒管激素及其受体 II 水平的升高有关, 还与胚胎停滞和细胞凋亡的增加相关^[99-100]。在体外培养的牛黄体细胞中, BPA ($3 \sim 30 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) 通过干扰类固醇生成过程, 降低黄体孕酮水平^[101]。在基础培养条件和促黄体生成素刺激条件下, 高浓度 BPA ($100 \text{ } \mu\text{mol} \cdot \text{L}^{-1}$) 显著降低了牛膜细胞活力、孕酮和雄烯二酮生成量^[102]。此外, 暴露于 $50 \text{ } \mu\text{g} \cdot \text{mL}^{-1}$ 的 BPA 显著降低新鲜和冷冻保存牛精子的活力、获能、存活率和线粒体膜电位水平^[103]。

4 小 结

作为一种内分泌干扰物, 即使在极低的接触水平下, BPA 也可能有毒性, 并对动物机体健康构成威胁。在低暴露水平和高暴露水平下对 BPA 进行的研究都得出了令人担忧的结果。低暴露水平的研究旨在评估长期、低水平的 BPA 暴露, 这更符合动物和人类通常的暴露情况。高暴露水平的研究侧重于急性毒性以及在较高浓度下可能产生的不良影响。基于体外试验和动物试验研究证明, 无论是低暴露水平还是高暴露水平的 BPA, 对包括猪、鸡、羊和牛在内的各个物种都有生殖毒性、神经毒性、免疫毒性以及代谢毒性, 并且大部分的研究聚焦在 BPA 对生殖功能所造成的不良作用, 包括对卵母细胞和精子质量、类固醇生成, 卵巢、子宫和睾丸

功能的影响,以及通过胎盘或脐带对后代发育的影响。BPA 产生毒性作用的潜在机制包括:BPA 可以刺激受体介导的效应,干扰酶的功能,引发氧化应激、细胞凋亡和炎症反应,引起胞内细胞器和细胞成分的异常结构和功能改变,以及表观遗传变化,其涉及到的机制是多方面的。

BPA 对多器官系统的效应是复杂的,其作用并非与剂量呈依赖关系。BPA 的毒性效应取决于所研究的系统和终点,其对不同物种的影响差异取决于剂量、暴露时期和持续时间、性别和年龄等因素。同时,细胞、组织、物种和品系在观察到的毒理学终点方面的敏感性存在差异。从人类健康的角度来看,猪和人类相似,绵羊的子宫内发育时间线与人类相似,因此 BPA 对猪和羊的不良影响可能也适用于人类。然而需要注意的是,大量的试验研究是在高剂量下进行的,而这些剂量水平在实际生活中并不会出现,或者是在体外条件下进行的,这可能导致与人类和动物实际接触 BPA 的风险不相符。

近年来,对 BPA 的监管已得到加强,但因为 BPA 的产量急剧增加,且目前尚无相关限制或禁令,确定安全的接触限制是一项真正的挑战,因为对某个特定系统可能无害的剂量,对另一个系统而言可能并非如此。生物体会同时接触到 BPA 以及内源性和外源性物质,研究 BPA 接触所产生的影响及其与不良健康后果之间关系的相关研究,往往忽略了与环境中其他化学物质之间的相互作用。此外,尽管已有一些具有对抗 BPA 效果的天然产物被报道,但对其潜在靶点的研究却很少。因此,未来的研究是必要的,需要制定措施来防止环境和食品受到污染,加强对 BPA 使用的必要限制,持续开展接触情况的监测,关注 BPA 与其他环境化学物质共同作用的危害。与此同时,寻找安全的替代品来取代 BPA 的使用,以及利用各种成分(尤其是天然成分)来消除或减轻 BPs 对生物体健康所产生的不良影响,并深入探讨 BPA 调节靶点的信号网络。

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