

# 双酚 A 暴露致神经细胞凋亡和炎症性死亡的研究进展

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**摘要:**双酚 A(BPA)是生产聚碳酸酯和环氧树脂塑料的添加剂,具有内分泌干扰物效应。由于大量研究发现 BPA 具有神经毒性,其暴露对大脑神经功能及行为变化的影响受到越来越多的关注。研究发现,氧化应激常伴随着 BPA 诱导的神经细胞凋亡和炎症性死亡(焦亡)反应的发生,导致神经细胞形态和功能改变,是 BPA 暴露与神经系统疾病相关性的一个重要连接纽带。研究聚焦 BPA 暴露诱导神经细胞凋亡和炎症性死亡这一生理现象,对 BPA 暴露通过线粒体、内质网以及死亡受体通路信号上的细胞凋亡的分子作用机制的详细介绍,探讨了细胞凋亡、细胞焦亡之间的关系以及他们与神经系统疾病的潜在关系,指出 BPA 暴露诱导的神经细胞凋亡与炎症反应的分子机制尚需要大量的动物、靶向敲除实验以及人群实验加以验证。同时,应关注低剂量 BPA 暴露参与毒性通路与其他毒性通路相互作用而加重复合污染物暴露的健康效应,为深入研究 BPA 暴露的神经毒性机制及其毒性干预提供参考。

**关键词:**双酚 A;神经毒性;氧化应激;细胞凋亡;炎症性死亡

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双酚 A(BPA)是环境内分泌干扰化学品(EDCs)中的一种,具有类雌激素效应,被大量用于环氧树脂和聚碳酸酯食品包装材料、牙齿固封剂、婴儿奶瓶、输液袋等产品的添加剂,也常被用做热敏纸上的显色剂<sup>[1]</sup>。BPA 在生产中以及生活用品中的泄露导致其在环境中无处不在,人类通过饮食、呼吸以及皮肤接触等方式暴露于 BPA。其暴露具有剂量低、被动性、不可避免性和长期性等特点。研究显示,BPA 除了具有生殖毒性、心血管毒性、免疫毒性以及产生代谢综合征<sup>[2-4]</sup>,增加肥胖、高血压、糖尿病、乳腺癌和神经退行性疾病的发生外,大量的体内、体外试验研究证明 BPA 暴露也会对神经系统产生不利影响,导致抑郁、兴奋性下降、降低学习记忆能力、增加退行性疾病的发生率等<sup>[5-9]</sup>。迄今为止,关于 BPA 神经毒性的机制探究已有很多报道,主要有突触可塑性的降低、神经发生的抑制、氧化应激的产生以及自噬和凋亡的诱导等。其中,越来越多的研究表明线粒体凋亡参与了 BPA 的神经毒性进展。因此本文就 BPA 诱导的细胞凋亡及神经炎症性细胞死亡的作用机制进行综述,为进一步理解 BPA 神经毒性与风险评估提供参考。

## 1 双酚 A 神经毒性研究现状

2015 年,全球 BPA 产量已达 770 万 t,而且每年还以 4.8% 的速率增长,预计 2022 年可达 1 060 万 t<sup>[10]</sup>。BPA 在生产和使用过程被大量地释放到水体、土壤以及大气中。除了呼吸途径和皮肤接触,BPA 主要通过被污染的膳食途径进入体内<sup>[11]</sup>。皮肤接触是职业暴露人群(如超市收银员)的另外一种重要暴露途径<sup>[12]</sup>。世界各国的人群暴露监测显示,在血液、尿液、胎盘以及母乳等体液或组织中均可检测到 BPA 的存在,在尿液中的检出率高达 95%<sup>[13-14]</sup>。我国普通非职业暴露人群体内的 BPA 质量浓度与国外相比,处于同一水平。在幼儿、孕妇等敏感人群尿液均可检出 BPA,非职业暴露人群尿中以及血清中的 BPA 质量浓度水平几何均值为 0.87  $\mu\text{g/L}$  和 0.18  $\mu\text{g/L}$ <sup>[15]</sup>。

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BPA 本身的毒性不大,动物实验未发现有明显的“致癌、致畸和致突变”效应.美国环境保护署(EPA)经过系列动物实验,根据其暴露剂量产生的毒副效应,将其安全剂量设置为  $50 \mu\text{g}/(\text{kg} \cdot \text{d})$ <sup>[16]</sup>.众多科学家就对此提出了质疑:(1)越来越多的动物以及敏感人群(婴幼儿及孕妇)实验发现,即使是低于环境安全剂量的 BPA 暴露,简称为低剂量 BPA 暴露,也会产生明显的不良健康效.如每天 2 或  $20 \mu\text{g}/\text{kg}$  的 BPA 暴露会对 F344 大鼠子宫生长和血清催乳素水平产生影响,但每天  $50 \mu\text{g}/\text{kg}$  BPA 暴露剂量则对 Sprague-Dawley(SD)大鼠的子宫发育和血清催乳素水平无影响<sup>[17]</sup>.普通儿童经常暴露于 BPA 后(尿中 BPA 的均值  $3.44 \mu\text{g}/\text{L}$ ),增加患儿童注意力缺陷多动症,且男童比女童更敏感<sup>[18]</sup>.这些研究均说明 BPA 所谓的“安全暴露剂量”可能并不安全.(2)也有科学家认为目前 BPA 的监测方法有问题.目前我们普遍使用葡糖酸苷/硫酸酯酶对尿中 BAP 的结合代谢物进行水解后,通过液相色谱串联质谱仪间接测定水解得到的 BPA 来定量人体的 BPA 暴露量.由于 BPA 代谢途径的多样性,导致这种间接测定法使得人体 BPA 的暴露量被严重低估<sup>[19]</sup>.因此 2015 年欧洲食品安全局(European Food Safety Authority,EFSA)将 BPA 的日可耐受摄入量(Tolerable Daily Intake,TDI)调整为  $4 \mu\text{g}/(\text{kg} \cdot \text{d})$ <sup>[20]</sup>,但即使这样仍有科学家不断对此质疑.EPA 和美国国家毒理学计划(National Toxicology Program,NTP)一项基于 BPA 的本身毒性以及其与多种信号通路相互作用能力的研究,将 BPA 列为 309 种化学品中第 3 高的毒理学优先指数(Toxicological Priority Index,ToxPi)<sup>[21]</sup>.

BPA 是一种具有内分泌干扰作用的外源性环境污染物,进入机体后,通过与雌激素受体(Estrogen Receptor,ER)的竞争性作用,产生类雌激素效应或拮抗雄激素效应,从而对下游的生理功能产生影响.最初的研究主要集中在其产生的生殖毒性和发育毒性上.如长期高质量浓度 BPA 暴露抑制生精和卵巢功能,增加女性罹患乳腺癌的风险,降低男子精子活力,诱发前列腺增生等<sup>[22-25]</sup>.但随着研究的深入,人们发现 BPA 暴露的健康效应不仅限于生殖毒性,BPA 还会造成代谢综合征,增加肥胖和糖尿病的发病风险<sup>[26-29]</sup>.同时,大量的动物实验显示,即使是低剂量的 BPA(环境暴露剂量为  $0.5 \mu\text{g}/(\text{kg} \cdot \text{d})$  以及  $5 \mu\text{g}/(\text{kg} \cdot \text{d})$ )也具有明显的神经毒性,并逐渐成为 BPA 的研究热点之一.如动物实验显示 BPA 暴露导致 DNA 损伤脑细胞,减少神经元数量<sup>[30]</sup>.YIN 等<sup>[31]</sup>的研究发现 BPA 使幼龄 SD 大鼠的海马长时程增强功能受损,树突棘密度下降,并对其空间记忆能力产生明显的干扰和影响作用;进一步的突触前研究结果显示,BPA 明显抑制了电生理过程中突触可塑性的配对脉冲易化.在一定程度上,BPA 暴露导致下丘脑内质网  $\beta$  表达的改变,进而可能促进了小鼠空间记忆缺陷和焦虑行为<sup>[32]</sup>.BPA 也可导致斑马鱼下丘脑在发育过程中过度活跃,造成下丘脑神经早熟<sup>[33]</sup>.BPA 暴露不仅引起树突重塑、空间记忆、焦虑行为障碍、神经早熟等神经毒性,而且会增加海马神经元过氧化物酶的释放,诱导生成活性氧(reactive oxygen species,ROS),造成线粒体损伤和自噬,最终降低海马神经元的存活率<sup>[34]</sup>.此外,短暂的  $\text{Ca}^{2+}$  通量会导致钙稳态的致命变化和 ROS 的增加,最终导致细胞死亡.反过来,BPA 诱导生成的 ROS 含量也受细胞内  $\text{Ca}^{2+}$  的调控<sup>[35]</sup>.体外实验显示,低质量浓度的 BPA 急性处理可以触发胞质  $\text{Ca}^{2+}$  超载,并激活下游蛋白激酶,引起细胞凋亡<sup>[36]</sup>.不同化学物质诱导的多种形式的细胞凋亡都有线粒体的参与,线粒体功能受损可能导致 ATP 消耗和细胞坏死,并在调节细胞凋亡中发挥重要作用<sup>[37]</sup>.研究发现 BPA 可以诱导不同神经细胞凋亡,继而诱发炎症性细胞死亡<sup>[38-40]</sup>.综上所述,BPA 导致认知障碍等神经毒性可能主要是由于 BPA 诱导线粒体和多种蛋白功能障碍,导致细胞内钙稳态失调,继而引起细胞凋亡以及炎症性细胞死亡,最终导致神经系统损伤.

## 2 双酚 A 诱导神经细胞凋亡的分子机制

### 2.1 双酚 A 诱导的细胞凋亡

#### 2.1.1 线粒体凋亡

线粒体凋亡是细胞凋亡的主要途径之一,在细胞凋亡中扮演着至关重要的作用.在细胞正常状态下,促凋亡蛋白与各种凋亡抑制蛋白共同作用来调节细胞的凋亡,使细胞的增殖和细胞死亡处于动态平衡.当细胞凋亡时,这些蛋白被释放并靠近它们的凋亡作用位点.例如,细胞色素 c(Cytochrome c,Cyt c)通常位于线粒体膜间隙内,在细胞凋亡过程中被释放到细胞质中.Cyt c 是第一个被鉴定为在细胞凋亡时从线粒体释放的水溶性蛋白质,位于线粒体内膜外侧,参与线粒体能量代谢的调控<sup>[41]</sup>.Cyt c 与凋亡蛋白酶激活因子-1

(APAF-1), ATP 或 dATP 和 Caspase 9 相互作用形成凋亡小体.在 Cyt c 和 ATP/dATP 的存在下,APAF-1 发生构象变化,允许自聚集,并暴露其 CARD(Caspase 招募域),从而招募 pro-Caspase 9 通过蛋白裂解激活 Caspase 9.Caspase 9 可以反过来激活其他 Caspase,如 Caspase 3 和 Caspase 7,通过蛋白裂解各种下游靶点导致细胞死亡<sup>[42]</sup>.BPA 通过损害人皮层神经元(hCNs)线粒体功能,触发内质网应激,增加 Cyt c 的释放.最终,BPA 通过调控 Caspase 依赖的信号通路触发细胞凋亡<sup>[43]</sup>.也有研究显示 BPA 诱导大鼠海马区 Caspase-3 的表达增加<sup>[44]</sup>.执行 Caspases 的下游靶点可以被激活.通过 Caspase 介导的裂解,激活的底物不仅包括 Caspase 本身,还包括参与基因和细胞周期调控的各种激酶.包括抗凋亡蛋白 Bcl-xL 和 Bcl-2,ICAD,Caspase 激活的 DNase 抑制剂,细胞骨架蛋白(如肌动蛋白),结构核蛋白,DNA 修复蛋白(如 DNA 依赖蛋白激酶)和多聚 ADP-核糖聚合酶<sup>[45]</sup>.

线粒体凋亡的核心 Bcl-2 蛋白家族是内源性凋亡通路的关键调控因子,主要分布在线粒体外膜上,调节线粒体膜通道开放以及凋亡物质流动<sup>[46]</sup>.Bcl-2 蛋白家族包括促凋亡和抗凋亡蛋白,共同维持细胞生与死之间的平衡.促凋亡蛋白可以分为具有 BH1-3,BH3 结构域的蛋白,Bak 和 Bax,抗凋亡蛋白成员包括位于线粒体膜上的 Bcl-2 和 Bcl-xL 等,及存在于胞质中的 Bid 和 Bad 等.在一般情况下,Bax 和 Bak 的活性被抗凋亡蛋白所抑制,当细胞接收到凋亡信号时,激酶蛋白与抗凋亡蛋白相结合释放出激活蛋白,激活蛋白直接激活 Bax 和 Bak 的活性.Bax 或者 Bak 重新定位于线粒体表面,诱导蛋白结构构象变化,并在线粒体表面构成跨线粒体膜的孔,导致线粒体膜电位下降(MMP)下降,膜通透性增加,从而释放凋亡因子<sup>[47]</sup>(见图 1).

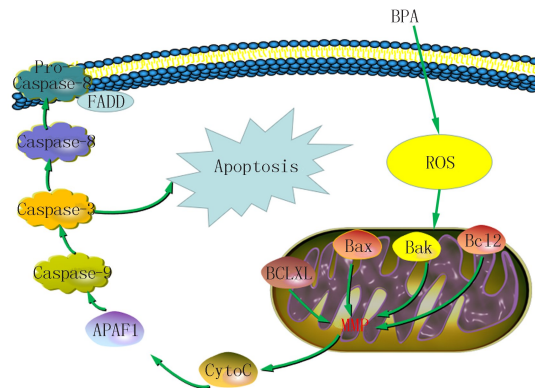


图1 线粒体凋亡通路图

Fig.1 Mitochondrial apoptosis pathway

人卵巢颗粒细胞(KGN)暴露于高质量浓度双酚 AF(BPAF,5 或 50  $\mu\text{mol/L}$ )后,胞内 ROS 水平显著升高,促凋亡蛋白 Bax,Bid,Bak 的表达显著上升,而抗凋亡蛋白 Bcl-2,Bcl-xL,Mcl-1 的表达则显著降低<sup>[48]</sup>.10  $\mu\text{mol/L}$ 和 20  $\mu\text{mol/L}$  BPA 处理胚胎 96 h 后,Bax/Bcl-2 mRNA 表达率显著上调,并导致胚胎细胞凋亡<sup>[49]</sup>.Caspase-8/9 的增加通常导致 caspase-3 的激活.有数据显示,BPA 暴露生精细胞显著增加了 Cyt c,Caspase-3/9 和 Bax 的转录和翻译水平<sup>[50]</sup>.另外一项研究发现,不仅 BPA 暴露导致 Caspase-3 的激活线粒体凋亡,其类似物双酚 F(BPF)、双酚 S(BPS)和 BPAF 暴露引起外周血单核细胞胞内  $\text{Ca}^{2+}$  水平上升、MMP 显著下降、Caspase-8,-9,-3 活性显著上升,继而导致细胞凋亡<sup>[51]</sup>.研究显示,不同质量浓度 BPA 处理神经母细胞瘤细胞 24 h 后,BPA 诱导 Caspase-3,Bak1,Bax 和 Cyt c 的蛋白非单调性增加,Bcl-2 蛋白非单调性下降,而添加抗氧化剂-表没食子儿茶素没食子酸酯(EGCG)进行共培养后,均使上述改变得到明显缓解<sup>[38]</sup>.

### 2.1.2 死亡受体通路

死亡受体途径指胞外的死亡信号通过死亡受体转入胞内诱发细胞凋亡.细胞表面死亡受体主要属于肿瘤坏死因子受体(Tumor necrosis factor receptor,TNFR)家族.TNFR 成员如 Fas 通过结合其死亡配体 FasL(Fas ligand)传递凋亡信号<sup>[52]</sup>.TNFR 的其他成员包括死亡受体(death receptor,DR),DR4,DR5 和 DR6 等<sup>[53-55]</sup>.Fas 基因编码的 Fas 蛋白是分布于细胞膜的膜蛋白,在死亡受体介导的凋亡通路中,特定的配体 FasL 参与后,死亡受体 Fas 的胞质结构域三聚体激活了与之相适应的 Fas 分子相关的死亡结构域(Fas-associated death domin,FADD).FADD 进而招募 pro-Caspase-8 形成诱导死亡的信号复合物,最终导致细胞



凋亡.其中 Fas 信号系统被认为是发育期间和睾丸损伤后生殖细胞凋亡的关键调控因子<sup>[56]</sup>.研究发现, BPA 诱导大鼠睾丸支持细胞 Fas, FasL 和 Caspase-3 的表达均升高, 激活了 JNKs/p38, MPAK 和 NF- $\kappa$ B 的转录表达, 诱导细胞凋亡, 说明 Fas/FasL 和 JNKs/p38, MPAK 信号通路在细胞凋亡中扮演了重要的作用<sup>[57]</sup>. 另有研究发现 BPA 诱导后, 神经母细胞瘤细胞(SH-SY5Y)内 TNF- $\alpha$  水平下降, 而 Caspase-8 水平显著升高, 凋亡细胞数量也相应增加<sup>[58]</sup>.

### 2.1.3 内质网通路

内质网(endoplasmic reticulum, ER)稳态的紊乱影响蛋白质折叠, 导致内质网应激.内质网应激也被认为与许多神经疾病的发生或发展有关.如 BPA 暴露后在哺乳动物肝脏中产生的主要活性代谢物 4-甲基-2,4-双(4-羟基苯基)戊-1 烯(MBP)通过 ERK 激活和 Akt 失活调控的线粒体依赖和内质网应激触发的凋亡通路相互作用, 从而产生神经元细胞毒性, 最终导致神经元细胞死亡<sup>[59]</sup>.内质网钙离子( $\text{Ca}^{2+}$ )与未折叠蛋白和其他伴侣蛋白的有效相互作用是维持正常内质网功能的必要条件<sup>[60]</sup>.细胞内  $\text{Ca}^{2+}$  水平的变化表明  $\text{Ca}^{2+}$  稳态的改变, 是内质网应激的明显信号<sup>[61]</sup>.YIN 等人观察到 BPA 引发了细胞内  $\text{Ca}^{2+}$  超载, 导致线粒体和内质网损伤, 表明  $\text{Ca}^{2+}$  稳态的改变参与了 BPA 诱导的细胞凋亡<sup>[62]</sup>.OGURO 等<sup>[63]</sup>的研究发现, BPA 刺激了 Hep3B 细胞中  $\text{Ca}^{2+}$  从内质网流出到细胞质, 而不是从细胞外通过质膜流出, 进而激活 IP3(内质网通道蛋白).

## 2.2 双酚 A 诱导的神经细胞炎症性死亡及与凋亡的关联

细胞炎症性死亡是另一种形式的程序性细胞坏死, 又称为细胞焦亡, 在脊椎动物中作为重要的先天性免疫防御机制而出现, 具体表现为细胞不断胀大直至细胞膜破裂.在细胞破裂之前, 细胞上形成凸出物, 形成孔隙, 细胞膜被破坏, 释放胞内物<sup>[64]</sup>, 如乳酸脱氢酶(LDH)和炎性细胞因子释放.经典的细胞焦亡是由 Caspase-1/4/5/11 介导 GSDMD 蛋白活化, 通过活化的 GSDMD 蛋白来促进质膜的打孔作用引起的<sup>[65]</sup>.其中 GSDMD 是细胞焦亡的执行蛋白, 被炎性相关蛋白 Caspase-1 或-11 切割, 释放 Gasdmin-N 端结构域.此结构域与质膜的内部小叶寡聚化, 造成细胞膜上 1~2 nm 的孔隙<sup>[66]</sup>, 从而增大了细胞膜的通透性, 钾离子外流, 钠离子和水内流, 细胞的离子梯度失衡, 胞内渗透压升高, 细胞膜受损, 急剧膨胀, 最终导致细胞膜溶解, 细胞发生渗透性崩解.另外受到外界条件的刺激, Caspase-1 前体与模式识别受体 NLRP1, NLRP3 等通过接头蛋白 ASC 变为一个高分子复合物, 即炎症小体, 也称依赖 Caspase-1 的炎症小体.细胞在 Caspase-1 激活同时会释放出炎性因子白细胞介素-1 $\beta$ (IL-1 $\beta$ )和白细胞介素-18(IL-18), 进而吸引更多的炎性细胞, 加重炎症反应.

细胞凋亡和焦亡都是 Caspase 依赖的程序性细胞死亡途径, 细胞焦亡是细胞凋亡后的继发性坏死, 是凋亡细胞质膜完整性逐渐丧失的结果<sup>[67]</sup>.有趣的是, Caspase-3 是细胞凋亡的执行者, 线粒体凋亡可诱导 NLRP3 炎性小体介导的 Caspase-1 活性<sup>[68]</sup>.内源性和外源性凋亡中激活的 Caspase-8 或 Caspase-9 能激活 Caspase-3 和 Caspase-7 切割泛连接蛋白 pannexin-1 C 的末端, 促进膜通透性增加, 导致 ATP 释放和钾外排, 诱导 NLRP3 炎性小体组装, 最终造成 GSDMD 裂解<sup>[69]</sup>.受体相互蛋白激酶 1(receptor interacting protein kinase 1, RIPK1)具有促发凋亡作用, 最近发现其在某些细胞程序性坏死过程中也起重要作用<sup>[70]</sup>.新的研究发现 RIPK1-Caspase-8 被溶酶体卵泡素(FLCN)-卵泡素相互作用蛋白 2(FNIP2)-Rag-Ragulator 超级复合物招募至溶酶体上, 促进 RIPK1 的磷酸化及 Caspase-8 的活化;活化的 Caspase-8 能够介导 GSDMD 的切割, 从而触发细胞焦亡<sup>[71]</sup>.当 GSDMD 表达较低时, Caspase-1 的激活倾向于凋亡而不是焦亡.如前所述, 氨基末端 GSDMD 的裂解片段可定位到线粒体, 引起线粒体外膜通透化, 促进 Caspase-3 的激活<sup>[72]</sup>.另有研究表明, 凋亡标志物 Caspase-3 也可以通过切割 GSDME 诱导细胞焦亡, GSDME 可作为细胞凋亡和焦亡转化的开关分子<sup>[73-74]</sup>.简而言之, GSDME 被 Caspase-3 激活生成 GSDME-N 后, 一方面可引起细胞膜成孔作用, 介导焦亡;另一方面, GSDME-N 也可引起线粒体膜通透性的改变, 进而导致 Cyt c 从线粒体向细胞质转移, 而 Cyt c 可以继续激活凋亡小体, 诱导凋亡, 因此焦亡与凋亡之间的相互作用是一种反馈调节.此外, 钾外排和 Cyt c 在线粒体吞噬和焦亡的调控中也发挥了重要作用, 但更多的细节仍有待澄清.总之, 线粒体凋亡与细胞焦亡之间存在着许多交叉, 不能单纯地只强调某一种类型的细胞死亡.

细胞焦亡这种程序性细胞死亡方式正在逐渐被人们所了解.虽然人们对于细胞凋亡和焦亡在肿瘤生长



侧索硬化症(ALS)<sup>[96]</sup>、多发性硬化(MS)<sup>[97]</sup>;也会导致自闭症状的加重<sup>[98]</sup>;引起多动症的增加和行为的改变<sup>[99]</sup>。另有数据证明 BPA 暴露也易造成学习记忆障碍和焦虑抑郁<sup>[100]</sup>。这些 BPA 诱导的神经性疾病或多或少与神经性炎症或细胞的凋亡相关联。

## 4 讨论与展望

BPA 对神经系统的作用可能涉及不同的凋亡通路和炎症相关途径,每一种途径都可能在特定的易感性窗口期以多种方式激活,因此其潜在有害作用是多种且极其复杂的,由此产生的变化可能导致神经和非神经行为的改变。应当注意的是,BPA 本身毒性不大,但当 BPA 与其他环境污染物共存时,即使是非常低的环境剂量也可以通过参与毒性通路或与其他毒性通路相互作用,诱导或增强其毒性效应<sup>[101]</sup>。如体外实验显示,若使用的单个双酚化合物(bisphenols, BPs),包括 BPA 及其类似物,如 BPS, BPAF 和 BPF 预处理 HepG2 细胞,那么即使是纳摩尔级别(10 纳摩尔级)的 BPs 也通过增加相关受体或 CYP 酶的 mRNA 转录和蛋白质水平,加重人类细胞中几种有影响的一级致癌物(包括苯并[a]芘、4-(甲基亚硝胺)-1-(3-吡啶基)-1-丁酮、黄曲霉毒素 B1 和苯)对微核的诱导作用,从而导致更严重的染色体损伤<sup>[79]</sup>。人群研究只显示了 BPA 暴露与二型糖尿病的发病有关<sup>[102]</sup>。进一步的动物实验则显示,青春期 OLETF 大鼠暴露于低剂量 BPA (1 和 10  $\mu\text{g}/(\text{kg} \cdot \text{d})$ )可加速青年期糖尿病的发生<sup>[103]</sup>。因此通过研究 BPA 的毒性通路,抑制其相关途径,并进行体内的毒性干预对于减小复合环境污染物暴露下的健康风险具有重要的科学和社会意义。

多个体内及体外实验均显示,氧化应激是一种伴随着 BPA 毒性发生的常见现象,参与了 BPA 诱导的凋亡及炎症相关反应<sup>[104]</sup>,因此相应的抗氧化措施成为抑制或减小 BPA 诱导的毒性效应的一种手段。目前研究发现食物中存在的多种天然活性成分能够通过干预 BPA 诱导的氧化应激反应来实现对 BPA 神经毒性的保护作用,已经报道的包括番茄红素、槲皮素、褪黑素、柚皮苷等在内的天然抗氧化成分,均在干预 BPA 的神经毒性方面表现出显著的效果<sup>[105-108]</sup>。研究发现利用 EGCG,雌激素受体(ER)抑制剂和 Caspase-1 抑制剂进行干预,表现出同样显著的神经保护作用<sup>[79]</sup>。

综上所述,氧化应激、细胞凋亡和炎症性细胞死亡作为一种常见的环境毒素诱导的毒性反应,其在 BPA 毒性机制中的作用也将为其他毒物的毒性机制研究提供借鉴。细胞实验显示,通过抗氧化物质或者细胞凋亡和炎症性细胞死亡通路抑制剂能够显著干预 BPA 引起的神经毒性作用,这为以氧化应激、ER 和 Caspase-1 为靶标来预防及治疗 BPA 神经毒性提供了理论参考。但仍需要动物实验或靶向敲除基因加以证实。同时目前也缺乏人群实验佐证 BPA 诱导的细胞凋亡或炎症反应在 BPA 神经毒性作用通路中的贡献或作用。由于 BPA 在人类现代生活的作用和地位,短时间内无法找到比 BPA 更合适、更安全的替代物,因此持续研究低剂量的 BPA 通过参与毒性通路或与其他毒性通路相互作用而加重的其他污染物的健康效应十分必要。

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## Research progress of bisphenol A-induced neuronal apoptosis and inflammatory death

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**Abstract:** Bisphenol A(BPA) is an additive in the plastic production of polycarbonate and epoxy resin with the effects of endocrine disrupting. The effects of BPA exposure on brain neural function and behavior have attracted more and more attention because a large number of studies have shown that BPA has neurotoxicity. Studies have shown that oxidative stress is often accompanied by the BPA-induced nerve cell apoptosis and inflammatory death(pyroptosis), which often leads to the morphological and functional changes of nerve cells. Hence, it is an important link between BPA exposure and nervous system diseases. Therefore, this study focused on the physiological phenomenon of nerve cell apoptosis and inflammatory death induced by BPA exposure, comprehensively reviewing the molecular mechanism of apoptosis through mitochondria, endoplasmic reticulum and death receptor pathway signaling pathway. Their potential relationship with nervous system diseases were also discussed. The molecular mechanism of neuronal apoptosis and inflammatory response induced by BPA exposure still needs to be verified by a large number of targeted knockout animal experiments and population experiments. Besides, attention should be paid to the health effects of low-dose BPA exposure by the involvement in toxic signaling pathways or interaction with other toxic pathways. This review provides a viewpoint for further study on the neurotoxic mechanism and toxic intervention of BPA exposure.

**Keywords:** Bisphenol A; neurotoxicity; oxidative stress; apoptosis; inflammatory death

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