

【专题报告】

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分化、体质量和胰岛素水平^[14]。作者最近也观察到环境相关剂量 BPA 暴露导致普通饲料和高脂饲料喂养大鼠出现糖代谢紊乱,并且可能与胰腺的自噬水平改变有关^[15]。近来,大量的人群研究也发现 BPA 水平与糖尿病前期和 2 型糖尿病相关^[16-19];但也有研究结果报道 BPA 水平与糖尿病不具有相关性^[20-22]。

目前“发育起源”假说已被广泛接受,该假说认为在子宫内或出生后早期子代受到刺激或损伤能导致机体组织和结构“程序化”改变,并成为个体生长后期易患病的因素^[23]。而成人 MS 则可能是早期发育对疾病易感性的影响和随后生活方式复杂作用的结果。Vom Saal 等^[24]对 BPA 与肥胖进行了综述。Ryan 等^[25]用 CD1 小鼠模型验证围生期暴露于生理相关剂量的 BPA (约 $0.25 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) 是否能增加成年 CD1 小鼠对高脂饮食导致的肥胖和胰岛素抵抗的易感性;结果显示 BPA 干预未影响成年子代小鼠体质量和血糖等指标,甚至断奶后给予高脂饮食也未发生明显变化。随后 Wei 等^[26]将怀孕 Wistar 大鼠在怀孕期和泌乳期暴露于不同浓度的 BPA (50 、 250 、 $1\,250 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) 环境中,测定断乳后给予普通饲料或高脂饲料喂养子代大鼠的体质量、糖脂代谢参数以及胰岛 β 细胞的形态和功能;结果发现普通饲料喂养的成年子代大鼠在 $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ BPA 暴露剂量下可致体质量增加、血浆胰岛素水平增高、葡萄糖耐量受损;并且高脂饲料喂养明显加重这些不利影响,导致严重的 MS;而其他 2 个 BPA 暴露剂量在 2 种饮食下均未引起明显的不良影响。这表明低剂量 BPA 有特异性的干扰作用。此外,该研究小组进一步观察到围生期 $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ BPA 暴露可加重高脂喂养子代大鼠的肝脏损害^[27]。除动物实验外,人体试验也对 BPA 导致 MS 的风险进行了评估。Teppala 等^[28]通过对美国国家健康和营养调查 2003 ~ 2008 年中 2 104 例具有代表性的美国成年志愿者的研究数据进行分析,结果显示尿 BPA 水平的升高与 MS 呈正相关,且这种现象独立于年龄、性别、种族、吸烟、乙醇摄入、体力活动和尿肌酐等因素。

2 邻苯二甲酸盐

邻苯二甲酸盐是一种人造的化学物质,是工业生产中广泛应用的成型剂。这类物质主要存在于工业涂料和溶剂,也存在于玩具、个人生活用品和医用材料(静脉输液管和血袋)。在这些产品中,邻苯二甲酸盐占产品总重量的 80% 以上。与 BPA 不同,它们不能以共价键与多聚体结合,所以更容易浸出而

造成食品污染,使人体通过应用相关的消费产品而广泛暴露于邻苯二甲酸盐^[29]。

目前邻苯二甲酸盐被认为是导致心血管疾病发生的可能原因^[30]。泌乳期暴露于邻苯二甲酸盐的雌性 F1 子代 Albino 大鼠的心肌胰岛素信号发生损害^[31]。最近,动物实验证明邻苯二甲酸盐和代谢性疾病相关;在啮齿类动物的短期和长期干预研究中,邻苯二甲酸盐能剂量依赖地降低血清胰岛素、肝糖原和皮质醇水平,增加血糖、血清 T_3 和 T_4 水平^[32-33]。Stahlhut^[34]、Trasande 等^[35-36]在 2003 ~ 2008 年全美营养与健康调查中发现,尿中邻苯二甲酸盐与儿童高血压和肥胖有关;对 766 例 12 ~ 19 岁青少年的调查发现,邻苯二甲酸盐可增加青少年对胰岛素的耐受^[37]。最近对 560 例老年志愿者的研究还发现,老年人群暴露于邻苯二甲酸盐增加了胰岛素耐受的发生,并且与氧化应激有关^[38]。

邻苯二甲酸盐被认为是 PPARs 的配体。Desvergne 等^[39]对邻苯二甲酸盐与 PPARs 的关系做了分析,认为邻苯二甲酸盐能与 3 种 PPARs 相互作用,直接激活 PPAR α 和 PPAR β ,进而促进脂肪生成^[40];其代谢产物还是 PPAR γ 的选择性调节子,而 PPAR γ 与维甲类 X 受体(retinoid X receptor, RXR)形成功能转录因子复合物后促进了前脂肪细胞的分化、影响葡萄糖摄取和三酰甘油的沉积,并对肝脏和骨骼肌等多个器官组织中的多个关键脂肪形成基因具有调节作用,这些研究结果提示邻苯二甲酸盐暴露可能促进了肥胖的发生和流行。目前已知 PPAR γ 激活剂能改变对胰岛素的敏感性,并被应用于治疗 2 型糖尿病。为了调查邻苯二甲酸盐是否能预防 2 型糖尿病,Lind 等^[41]对 1 016 例 70 岁老年人进行了调查,结果表明邻苯二甲酸盐与 2 型糖尿病的发生和流行相关。

3 己烯雌酚(diethylstilbestrol, DES)

DES 是一种人工合成的有效雌激素和已知的围生期致癌物。与雌二醇相比,DES 与 ER α 有更强的亲和力,并且它与 ER β 的结合力与植物雌激素相似,此外,还能像 BPA 一样与膜结合受体结合^[42]。

目前关于 DES 和 MS 关系的研究较少。动物实验结果表明,DES 暴露小鼠体质量和体脂百分数增加^[42]。已经发现 DES 刺激的小鼠腹部脂肪过度增多,这可能与心血管疾病和糖尿病相关^[43]。研究还发现,DES 暴露的小鼠中有 25% 的血糖水平高于对照组,并且具有较慢的血糖清除率^[44]。此外,通过对出生前暴露于 DES 环境中的 5 590 例女性和 2 657 例男性志愿者的调查研究发现,出生前 DES

暴露与成年后疾病(心血管疾病、冠状动脉粥样硬化性心脏病、心肌梗死、高血压、高胆固醇和骨质疏松)显著相关^[45]。要确证 DES 与 MS 之间的联系可能需要进一步的动物实验和人群实验以提供更多的证据。

4 双对氯苯基三氯乙烷 (dichloro-diphenyl-trichloroethane, DDT)

DDT 是一种应用广泛的有机氯杀虫剂。尽管有机氯杀虫剂在大多数发达国家禁止使用,并且在 1975 年被有机磷酸盐和氨基甲酸酯类所代替,但包括 DDT 在内的有机氯杀虫剂的污染仍然存在。英国的 1 项研究显示 127 种杀虫剂具有内分泌干扰性,揭示了杀虫剂与健康危害的联系^[46]。

流行病学研究发现杀虫剂暴露与包括肥胖、糖尿病、胰岛素抵抗和 MS 等代谢紊乱疾病有关^[47-48]。最近,Skinner 等^[49]报道怀孕大鼠暴露 DDT 后,可通过表观遗传学改变代间传递和继承造成子代大鼠肥胖。他们将怀孕的大鼠短暂地暴露于 DDT,观察 DDT 对 F1 代至 F3 代的影响,结果发现,F1 代未发展为肥胖;F2 代发生了肾脏疾病、前列腺疾病、卵巢疾病及肿瘤;F3 代雌性和雄性大鼠中分别有超过 50% 的个体发展为肥胖,并且 F3 代的精子发生甲基化改变。围生期暴露于 DDT 能影响碳水化合物和脂代谢,这可能是 DDT 增加了成年雌性子代小鼠 MS 的易感性^[50]。此外,DDT 的分解产物二氯二苯二氯乙烯还能增加成年女性的体质指数^[51]。韩国 1 项小样本的人群调查结果显示,暴露低浓度的有机氯杀虫剂(包括 DDT)与韩国人 2 型糖尿病的发生具有很强的相关性,并认为亚洲人与其他种族相比对有机氯杀虫剂的有害作用更易感^[52]。对沙特阿拉伯成人的横断面研究也发现 DDT 及其代谢物与 2 型糖尿病风险的增加相关^[53]。

然而,也有研究报道 DDT 与 MS 及糖尿病的发生并不相关。例如,在 1 项研究中对 50 例 MS 患者和在年龄、性别与之相匹配的对照人群进行横断面调查,并未发现血清 DDT 水平与 MS 的发生有相关性^[54];并且另 1 项研究结果显示未观察到糖尿病的发生与血清 DDT 水平有相关性^[55]。

5 二噁英 (tetrachlorodibenzodioxin, TCDD)

二噁辛类是一组有机氯物质,其来源于自然界中火山喷发和森林火灾,但大部分来源于人类生产活动中有机氯化物生产的副产品,以及含氯物质(如聚氯乙烯)的焚烧和漂白纸的生产。目前认为

二噁辛类是一种 EDCs,其中 TCDD 和多氯联苯 (polychlorinated biphenyls, PCBs) 是二噁辛类的典型代表。TCDD 和 PCBs 具有很好的脂溶性,容易通过脂肪组织生物蓄积进入食物链。

较早的研究发现血中高 TCDD 水平可能导致胰岛素耐受^[56],并且可能通过芳烃受体影响能量和脂代谢^[57]。全美营养与健康调查数据库的调查结果表明,TCDD 和多氯二苯并呋喃与代谢疾病具有很弱的关联性,但 PCBs 和 2 型糖尿病具有明显的相关性^[58],该现象得到一些横断面调查研究结果的支持^[59]。为了确定 TCDD 与 MS 的联系,Chang 等^[60]对居住接近 TCDD 高污染地区的 1 490 例非糖尿病台湾居民进行了调查。研究发现舒张压、血糖和腰围随着血清 TCDD 水平的增加明显增高,提示高浓度的 TCDD 暴露是高血压发生的相关因素,可增加 MS 的风险;并且女性年轻时暴露于 TCDD 也会增加未来 MS 的发生^[61]。

但是也有与上述研究结果相反的报道。Sugai 等^[62]报道了子宫内和泌乳期暴露于 $3.0\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ TCDD 的子代 C57Bl/6J 小鼠在其成年后并未发生严重的肥胖相关疾病(如成年后开始的糖尿病);低剂量 TCDD 暴露反而减轻了小鼠高热量饮食引起的脂代谢紊乱。TCDD 对糖尿病模型动物和健康动物的糖代谢可能具有相反的生物学效应。TCDD 能有效对抗高脂饮食和链佐星诱导的 2 型糖尿病大鼠模型的高糖血症;然而与观察到的降血糖影响相比,TCDD 在不同的剂量范围内能诱导健康大鼠 PPAR γ 的转录活性^[63]。

6 重金属

重金属能干扰机体的激素合成、分泌、活性及代谢^[64],目前认为重金属也是一种 EDCs。重金属(如铅、汞和镉)在环境中广泛存在,除了职业暴露人群外,一般人群在生命过程中广泛地暴露于低剂量的重金属环境中。由于它们有较长的半衰期,往往在体内蓄积不易排出。

重金属能增加氧化应激和诱导线粒体功能紊乱^[65-66];这种对机体的氧化损伤提示它可能是导致高血压和糖尿病等代谢疾病的机制之一。有研究表明,血中高浓度的铅和镉是长期暴露重金属的受试者动脉高血压发生的独立危险因素^[67]。重金属干扰胰岛素分泌报道最早可追溯到 19 世纪 70 年代,显示镉能抑制胰腺 β 细胞的分泌活性^[68]。之后的研究结果陆续发现,低浓度的镉能刺激胰岛素分泌,而高浓度的镉将导致胰岛素分泌率明显降低^[69]。此外,胰腺也是汞的靶点,汞能通过改变胰腺 β 细

胞内的钙离子平衡降低羞蟾鱼胰岛的胰岛素分泌^[70]。此外,体内外研究也已经证明汞和镉的暴露可增加胰岛素耐受和诱发 β 细胞功能紊乱^[71]。最近对生活在沿海的韩国老年人的调查研究发现,2型糖尿病受试者的生物样本中铅和镉的浓度明显增加^[72]。对2 114例韩国健康成年人血清汞水平与MS的研究中观察到,血汞水平与MS相关,并且汞暴露可能是心血管疾病的危险因素^[73]。但Moon^[74]的研究得出了不一致的结论。他对参加2009~2010年韩国营养和健康调查中年龄在30岁以上的1 588例男性和1 596例女性志愿者的调查分析显示,韩国人血铅、汞和镉水平与糖尿病无明显关系;对240例台湾本地居民的调查也未发现尿铅水平与高血压的发生具有相关性^[75]。最近研究人员对第4、5次韩国国家健康与营养调查数据中20岁以上人体血中铅、镉和汞与MS发病的关系进行研究,发现血中的重金属与血压和三酰甘油水平升高显著相关;血铅浓度与MS的流行率显著相关;并且铅、镉和汞对MS的流行率具有累积和协同影响^[76]。

综上所述,EDCs可能通过多种分子机制和信号通路对机体的胰腺、肝脏、脂肪等组织产生有害作用,但也存在一些不一致的结果。因此,进一步研究EDCs对机体产生不同生物学效应的机制及EDCs的累积或协同效应具有重要意义。这有助于预防和减轻EDCs的有害效应,降低MS、糖尿病等慢性疾病的发病率。

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