持久性有机污染物与糖尿病发病相关分子机理

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摘要 持久性有机污染物(persistent organic pollutants, POPs)是一类理化性质稳定、难降解、高脂溶性、高蓄积性的环境污染物。越来越多的研究表明, POPs与糖尿病发病密切相关, 但涉及的分子机理较为复杂。该文综述了国内外近年关于POPs引起1型和2型糖尿病发病的分子机理, 旨在讨论POPs与两种糖尿病发病的内在联系。

关键词 持久性有机污染物; 糖尿病; 分子机理

Molecular Mechanisms Related to Persistent Organic Pollutants Induced Diabetes

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Abstract Persistent organic pollutants (POPs) belong to environmental chemicals with properties such as stabilization, degradation-resistant, high lipid solubility and high accumulation. More and more studies have shown that POPs were closely associated with diabetes and the related molecular mechanisms were complex. The present review discussed the molecular mechanism about type 1 and type 2 diabetes induced by POPs. The purpose of this review was to illuminate the internal relation of POPs and two types of diabetes.

Keywords persistent organic pollutants (POPs); diabetes; molecular mechanism

持久性有机污染物(persistent organic pollutants, POPs)是一类理化性质稳定、难降解、高脂溶性、高蓄积性的环境污染物, 包括重金属、有机氯农药、多氯联苯、二恶英等。POPs可以通过食物链对人类及其他生物造成多方面的健康危害, 其“三致”(致癌、致畸和致突变)作用已经得到公认。越来越多的研究表明, POPs也是代谢性疾病等其他疾病不容忽视的危险因素[1]。糖尿病(diabetes mellitus, DM)是一种因体内胰岛素绝对或者相对不足所导致的代谢性疾病, 其中1型糖尿病(type 1 diabetes mellitus, T1DM)和2型糖尿病(type 2 diabetes mellitus, T2DM)占绝大多数。T1DM患者自身免疫反应异常, 导致分泌胰岛素的β细胞损伤而无法生产胰岛素, 造成体内胰岛素缺乏[2], 患者通常在儿童或青少年时期发病。T2DM常出现于成年人, 是遗传因素和环境因素共同作用的结果。越来越多的研究表明, POPs与这两种糖尿病密切相关[3]。

1 POPs与T1DM

调查数据表明, 近年来全世界儿童T1DM发病率呈明显上升趋势。1989~2003年, 欧洲儿童T1DM平均年发病率上升3.4%[4]。T1DM发病率的快速上升与工业化发展引起的环境污染日益恶化进程一致, 提示环境化学污染物可能是导致T1DM发病率升高的原因之一[5]。国内外学者对各种环境因素与T1DM的关系进行了初步的研究探讨, 发现POPs在T1DM的发病中起着重要的作用[6-7]。大型横断面研究发现, 孕妇T1DM患者血液样本中多氯联苯浓度

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比对照组高30%[8]。另一项研究发现, 多氯联苯工厂工人体内谷氨酸脱羧酶抗体(一种T1DM标志物)滴度是对照组的4倍[9]。

T1DM的主要致病机理是自身免疫异常。免疫功能异常包括免疫抑制和免疫增强, 前者表现为机体免疫反应减弱, 后者表现为免疫易感性增加, 导致机体出现自身免疫反应。POPs对自身免疫损害方面的研究报道并不多见, 个别研究证据表明, 环境化学物质可导致自身免疫疾病的发生[10]。Alonso等[11]研究发现, 双酚A可以直接作用于β细胞引起损伤, 使β细胞更容易受到自身免疫的攻击。Zuo等[12]研究发现, 雄性小鼠长期(60 d)低剂量暴露于有机锡可引起胰岛细胞凋亡、胰岛素分泌不足, 导致葡萄糖代紊乱。重金属、有机溶剂和二恶英等POPs既具有免疫抑制作用, 也有免疫增强作用, 与作用浓度和作用途径有关[13-14]。有研究报道, 三丁基锡(tributyltin, TBT)通过激活芳烃受体(aryl-hydrocarbon receptor, AhR)导致自身免疫性疾病[15]。AhR是一种配体激活性转录因子, 可介导POPs, 如多环芳烃类化合物的毒性反应, 还参与一些重要的生物学过程。环境化学污染物除了暴露剂量外, 暴露时间对有害效应的影响也很大, 儿童期各系统和器官功能还没有发育成熟, 早期暴露于环境化学污染使免疫系统更易受到破坏[16]。

总的来说, 国内外学者对POPs与T1DM的关系研究较少, 并且在研究结论方面也存在争议。例如, 瑞典研究人员测量母体血清中两种POPs(多氯联苯和有机氯农药)水平, 并观察她们的子代T1DM发病情况, 结果发现, 母体血清中的这两种POPs与她们子代的T1DM发病率并无关联[17]。有学者认为, 造成这一现象并不表示这两种POPs与T1DM无关, 而可能是由于这两种POPs的剂量–反应关系的特殊性。

2 POPs与T2DM

有关POPs与T2DM的关系国内外研究很多。近年来, 许多流行病学资料证实, POPs暴露人群的胰岛素抵抗及T2DM发病率明显升高, 其中, 青少年T2DM发病增多现象尤为显著[18-20]。Pal等[21]研究比较了T2DM患者和非T2DM患者血液POPs的含量, 发现糖尿病人血液中多种POPs含量高于非糖尿病人2~7倍。Porta等[22]发现, 即使POPs的环境浓度很低, 但如果通过饮食慢性长期接触, POPs也会在体内积累而使T2DM发病危险性升高。Rylander等[23]调查了瑞典的一个渔村196名男性和184名女性血液样本中的POPs, 发现有机氯农药浓度与糖尿病有密切的关系。有关POPs与T2DM发病相关机理的研究较多, 主要有以下几方面。

2.1 对胰岛素及脂联素信号系统影响

T2DM的主要发病机理是胰岛素信号系统异常, 研究报道, POPs可直接影响胰岛素信号系统。Ruzzin等[24]用含有机氯农药残留的鲑鱼油喂大鼠, 发现脂质代谢的重要调控基因(*Insig-1*和*Lpin1*)下调, 动物出现胰岛素抵抗(insulin resistance, IR)时间较对照组明显缩短。据研究报道, 有些POPs通过激活AhR干扰胰岛素信号系统, 最终引起胰岛素抵抗及T2DM。研究证明, 二恶英, 如TCDD在胞质内与AhR结合后, 下调脂肪和肝脏等胰岛素敏感性组织的胰岛素受体及葡萄糖转运蛋白4(glucose transporter type 4, GLUT4)的表达与活性, 诱发胰岛素抵抗[25]。研究发现, POPs暴露会使人体内脂联素水平降低, 脂联素是一种由脂肪组织分泌、具有胰岛素增敏效应的激素[26], 脂联素通过与细胞膜上的脂联素受体相结合刺激磷酸酪氨酸衔接蛋白1(adaptor protein containing pleckstrin homology domain and phosphotyrosine binding domain and leucine zipper motif 1, APPL1)与脂联素受体结合[27], 从而介导腺苷酸活化蛋白激酶(adenosine 5′-monophosphate-activated protein kinase, AMPK)和p38有丝分裂原激活蛋白激酶(p38 mitogen activated protein kinase, p38 MAPK)激活。Mullerova等[28]发现, 人血液样本中脂联素含量与多氯联苯(PCB-153)含量呈负相关; 另有研究发现, 双酚A可以抑制脂联素释放[29]。研究证明, T2DM的发病与APPL1在脂联素–胰岛素信号通路之间的"阴阳调节"失衡有关[30]。

2.2 引起炎症反应

近年来, "炎症学说"在糖尿病发病机理研究中引起了广泛关注。研究证明, 长期低剂量POPs暴露可使机体出现慢性炎症, 而机体慢性炎症与胰岛素抵抗及T2DM发病密切相关[31]。许多炎性因子, 如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白细胞介素-6(interleukin-6, IL-6)、C-反应蛋白(C-reaction protein, CRP)、纤溶酶原激活抑制物-1(plasminogen activator inhibitor-1, PAI-1)等, 不但直接参与IR, 而且在T2DM的发生发展进程中起着重要的作用[32]。T2DM患者体内TNF-α和IL-6水平往往较正常人高[33];

炎性因子可以由POPs激活AhR而产生[34], 许多POPs可激活AhR产生TNF-α和IL-6[35]。炎性反应信号转导受一系列重要核转录因子和关键信号调控, 如Toll样受体(Toll-like receptor, TLR)、核转录因子kappa B(nuclear factor-kappa B, NF-κB)等, TLR相关信号通路在胰岛素抵抗中起重要作用[36]。流行病学调查显示, T2DM患者体内TLR4/2及其通路显著激活[37]; 肥胖儿童血清TNFα浓度升高与TLR4炎症通路调控具有相关性[38]。

2.3 导致氧化应激及线粒体损伤

大量研究表明, 活性氧(reactive oxygen species, ROS)可以激活细胞内多种信号通路。ROS的一个主要作用目标是线粒体, 线粒体在内源性途径中扮演了重要的角色, 它不仅是细胞呼吸链和氧化磷酸化的中心, 也是细胞凋亡调控中心和细胞生命活动控制中心。多种POPs, 如有机锡、二恶英、农药等均可诱导ROS产生, 导致线粒体功能障碍。有研究报道, TBT诱导小鼠体内ROS显著升高, 造成明显的氧化损伤和DNA损伤[39]; 研究发现, 低剂量二恶英暴露引起线粒体出现去极化现象, 胰岛细胞对血糖刺激的敏感性显著降低, 胰岛素分泌减少; 随着二恶英剂量加大, 线粒体嵴出现肿胀, 表现出明显的细胞毒性[40]; 除草剂阿特拉津可抑制多种氧化酶(如Na^+K^+ATP酶、Mg^{2+}ATP酶、Ca^{2+}ATP酶)活性, 长期暴露于阿特拉津可以抑制线粒体复合物活性和氧耗量, 诱发线粒体功能异常和胰岛素抵抗[41]。大量研究表明, POPs诱导的氧化应激还可导致多种信号通路激活, 如NF-κB、有丝分裂原激活蛋白激酶(mitogen activated protein kinases, MAPKs)等, 胰岛素抵抗状态下氧化应激的水平增加, ROS作为功能性信号分子激活细胞内多种应激敏感性信号通路, 而这些信号通路与胰岛素抵抗密切相关。POPs致胰岛素抵抗与氧化损伤和线粒体功能障碍有关, 氧化应激及线粒体损伤、NF-κB激活会影响胰岛素刺激的葡萄糖转运[42]。

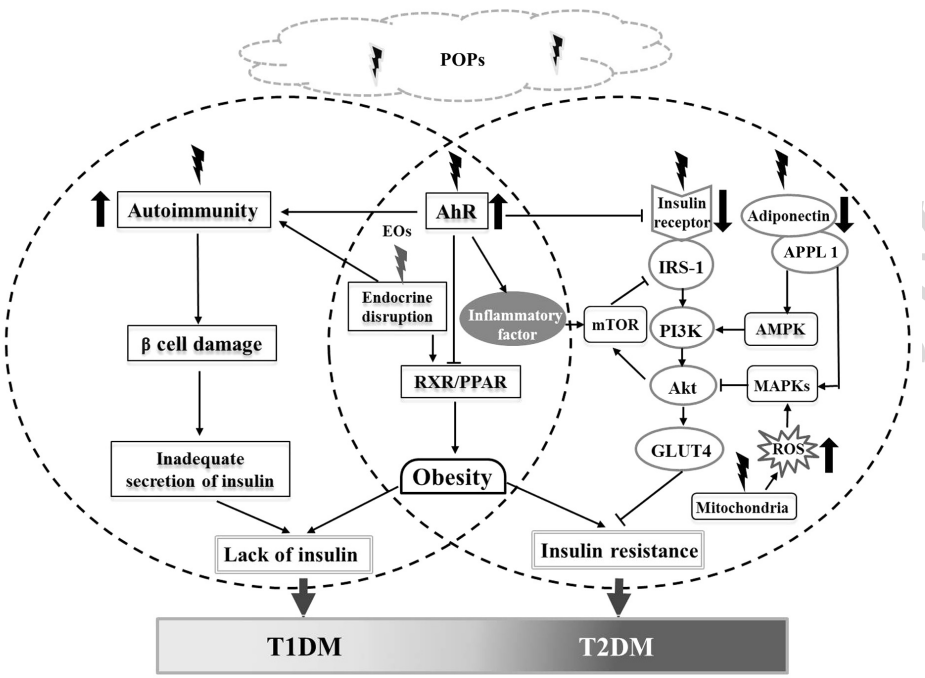
在POPs与T2DM的关系中, 胰岛素信号通路异常、炎症反应以及氧化应激的作用不是彼此独立, 而是相互作用和影响。例如, 胰岛素抵抗既与炎症反应相关, 也与氧化应激相关, 而炎症反应与氧化应激也关系密切。也有研究证实, POPs引起的细胞内应答是一种集成式细胞内信号应答反应, 各个“模块”之间关系密切, 相互影响[47]。

3 POPs的环境内分泌干扰作用与T1DM及T2DM

一些POPs在环境中含量虽然极低, 但是它们干扰机体正常内分泌功能, 被称为环境内分泌干扰物(environmental endocrine disruptors, EEDs)。EEDs与人类生殖障碍、发育异常、代谢紊乱及某些癌症等密切相关。EEDs既能直接损伤β细胞, 引起胰岛素分泌不足, 又能引起机体肥胖, 与糖尿病发病关系比较复杂, 可能与T1DM和T2DM都有关。长期以来, 肥胖的主要原因被认为是过量饮食和运动不足, 然而越来越多的研究表明, 环境污染对肥胖也有直接的影响[43]。流行病研究发现, 暴露于低剂量POPs的人群胰岛素抵抗和肥胖发病率明显高于对照组[17]; 许多研究证实, POPs暴露引起脂肪代谢异常, 导致肥胖[44], 学者们将这些能够促进机体肥胖的EEDs称为环境肥胖激素(environmental obesogens, EOs)[45]。

有机锡化合物是POPs中的重要成员, 也是研究报道较多的EEDs。TBT主要用于海洋防污涂料、木材防腐剂、增塑剂以及供水系统除黏菌剂和杀菌剂等。人类对TBT的接触主要是通过食物链, 包括被TBT污染的海产品、农产品、饮用水等。TBT具有多种毒性, 包括免疫毒性、生殖毒性、神经毒性等[46-48]。研究证明, TBT低剂量时表现为EOs效应, 诱导脂肪合成和刺激脂肪细胞分化; 高剂量时则表现为环境雌激素样作用, 激活雌激素受体引起肥胖[49]; 研究还发现, TBT可以激活AMPK, 通过促进交感神经兴奋而增加食欲, 从而导致肥胖[50]。

TBT的EOs作用主要是通过类视黄醇X受体(retinoid X receptor, RXR)/过氧化物酶体增殖物激活受体(peroxisome proliferator activated receptors, PPARs)途径影响内分泌和脂肪体内平衡。TBT可以同时激活这两种受体并具有双向调节作用, TBT通过这种机制, 激活脂肪存储转录基因的表达, 同时抑制脂肪分解基因的表达, 从而增加肥胖和T2DM患病危险性[51]。研究表明, TBT可以促进小鼠脂肪细胞的分化, 并调节肝脏、脂肪组织和骨髓中RXR-PPARγ依赖基因的表达, 促进脂肪合成[52]。无论雄性还是雌性小鼠胚胎期暴露于TBT, 出生后均会造成不可逆的病理变化, 并导致体重增加[53]; 有报道指出, 小鼠胚胎期暴露于TBT是通过激活PPARc使多能干细胞转化为脂肪细胞而增加体重的[54]。这些研究表明, 早期或胚胎期暴露于TBT对脂肪合成的影响尤为明



POPs与T1DM和T2DM的关系错综复杂: 不同种类的POPs可能诱导相同和(或)不同类型的糖尿病; 反之亦然, 不同类型的糖尿病也可能由相同和(或)不同的POPs引起。

The relationship between POPs and T1DM/T2DM is complex. Different kinds of POPs may induce same and/or different types of diabetes mellitus. And vice versa, different types of diabetes mellitus may also be caused by same and/or different kinds of POPs.

图1 POPs与1型糖尿病及2型糖尿病相关分子机理

Fig.1 Molecular mechanisms related to POPs induced T1DM and T2DM

表1 糖尿病相关的POPs

Table 1 DM related POPs

糖尿病类型 Type of diabetes mellitus	相关POPs Related POPs	中文名 Chinese name
T1DM, T2DM	polychlorinated biphenyls (PCBs)	多氯联苯
T1DM, T2DM	polycarbonate (PAB)	双酚A
T1DM, T2DM	tributyltin (TBT)	三丁基锡
T1DM, T2DM	Dioxins	二恶英
T1DM, T2DM	polycyclic aromatic hydrocarbons (PAHs)	多环芳烃
T2DM	organochlorine pesticides (OCPs)	有机氯农药
T2DM	Atrazine	阿特拉津

显。儿童肥胖是T1DM的重要诱因之一, 以上研究提示, EOs不仅是T2DM的重要诱因之一, 也可能是儿童T1DM发病率升高的重要原因, 因此可以推测, 许多POPs可能是T1DM和T2DM的共同致病因素。

4 结语

综上所述, 糖尿病发病率的升高与环境污染密切相关, 但大部分研究是关于T2DM的, 相比之下, 关于T1DM的较少。通常认为, T1DM和T2DM是两种不同的疾病, 以自身免疫损伤作为特征的T1DM主要发生在儿童时期, 而以糖代谢障碍为特征的T2DM主要发生于成年人。但这两种疾病联系密切, 有许多共同之处, 或者说这两种疾病就象一个连续的“疾病谱”[55]。研究发现, 大部分糖尿病患者可能既有自身免疫损伤, 又有糖代谢障碍[56], 成人T1DM患者往往也伴有代谢综合征[57]。POPs与T1DM和T2DM的关系也是错综复杂, 不同的POPs由于其不同的毒性特点, 可能诱导不同类型的糖尿病, 即使是同一种POPs, 在其作用时间、作用剂量不同时, 就会产生不同的有害效应, 这些有害效应有的与

T1DM致病机理相关, 有的与T2DM致病机理相关, 有的与两者都相关(图1和表1)。因此, 在研究POPs与糖尿病发病机理时, 也应该把T1DM和T2DM综合分析考虑, 尤其是一些具有环境内分泌干扰作用的POPs,它们可能与T1DM和T2DM都相关, 值得重点研究。

总之, POPs引起糖尿病的机制在很多方面还不清楚, 如介导POPs作用的其他调节因子, 以及POPs如何通过调节脂肪代谢引起肥胖、导致胰岛素抵抗和糖尿病等方面都存在空白。因此, 在今后的研究中, 应该着重考虑建立合理有效的动物模型, 在此基础上进行广泛深入的研究探讨。

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