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大气细颗粒物与糖尿病

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摘要: 随着我国社会经济和城市化的快速发展,大气颗粒物是影响我国城市空气质量的首要污染物,大气细颗粒物污染已严重威胁我国居民健康。本文简要综述了 $PM_{2.5}$ 诱导的氧化应激和炎症反应在糖尿病的发生和发展中的分子作用机制。
关键词: 细颗粒物; 氧化应激; 炎症反应; 胰岛 β 细胞; 糖尿病
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A Review: The Relationship between Fine Particulate Matter and Diabetes Mellitus

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Abstract: An increasing number of epidemiological and experimental studies demonstrate the adverse effect of air pollution as one of major risk factors with consequences on human health in both industrialized and developing countries. Ambient fine particulate matter ($PM_{2.5}$) is associated with a propensity to chronic diseases, including diabetes mellitus. The recent studies have provided a new link to $PM_{2.5}$-induced oxidative stress, inflammation and insulin resistance. In this review, we focused on the $PM_{2.5}$-induced oxidative stress and inflammation how these factors contribute to the progression and development of diabetes mellitus.
Keywords: fine particulate matter; oxidative stress; inflammation; diabetes mellitus

我国现已成为全球糖尿病人数最多的地区[1],成年人发病率达到了 9.7%[2]。其中 2 型糖尿病占到 90% 以上。目前,1 型糖尿病的发病与自身免疫紊乱、遗传因素、环境因素等其他因素相关。诱发 2 型糖尿病的原因主要有: 遗传因素、环境因素、肥胖、高糖和脂毒性、炎症反应和氧化应激等,导致 β 细胞功能紊乱和胰岛素抵抗[3]。

我国大气颗粒物污染对健康的影响已日益受到公众关注和政府重视。大量流行病学和临床研究表明,大气细颗粒物($PM_{2.5}$,空气动力学直径 < 2.5 μm

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的大气颗粒物)污染严重危害人体健康,导致呼吸、心血管、内分泌等系统的发病率上升。并且,细颗粒物的组成成分和浓度与疾病发生密切相关[4-8]。毒理学研究也显示,颗粒物中金属元素、脂多糖、多环芳烃、醌类化合物等组分诱导体内活性氧(ROS)生成[9]和炎症反应[10, 11],引起组织和细胞的氧化损伤[9, 12, 13]和内质网(ER)应激,激活细胞转录因子参与一系列信号通路,引起细胞凋亡和坏死等生物效应及疾病[9]。目前发现,大气颗粒物污染也与糖尿病并发症的发病率相关[14]。

1 细颗粒物与糖尿病

流行病学调查结果显示,长期 $PM_{2.5}$ 暴露可诱发糖尿病。Sun 等发现北京市 $PM_{2.5}$ 浓度升高与 2 型糖尿病发病率增加呈正相关[15]。Chen 等的研究结果也表明,$PM_{2.5}$ 年平均浓度每升高 10 $\mu g \cdot m^{-3}$,2 型糖尿病发病的危险度将增加 1.11[16]。空气污染与糖尿病急性并发症、昏迷和酮症酸中毒相关[14]。Pearson 等发现,$PM_{2.5}$ 日平均浓度每增加 10 $\mu g \cdot m^{-3}$,2 型糖尿病发病率增加 1%[17]。短期亚急性暴露低浓度 $PM_{2.5}$ 导致人体胰岛素抵抗[18]。

糖尿病、高血压患者和肥胖人群暴露于高浓度 $PM_{2.5}$ 后,机体的 C-反应蛋白(CRP)、白介素-6(IL-6)、白细胞数量等炎症水平明显高于正常人群[19]。2 型糖尿病患者外周血中血管内皮细胞粘附因子(VCAM-1)的浓度随着 PM 暴露水平增加而升高[20]。$PM_{2.5}$ 日平均浓度每增加 10 $\mu g \cdot m^{-3}$,2 型糖尿病患者血液中 IL-6、TNF-α 水平分别升高 20.2% 和 13.1%[19]。

动物实验研究也发现,肥胖 ICR 小鼠暴露于 15 $\mu g \cdot m^{-3}$ $PM_{2.5}$ 10 周后,肥胖小鼠的血糖水平、脂肪组织炎症因子(TNF-α、Nos2、IL-6)均明显升高,抗炎症因子(IL-10、Mgl-1、PPARγ)的表达水平下调,并出现胰岛素抵抗和内脏脂肪增多症状[21]。近期研究表明,当用 $PM_{2.5}$ 暴露处理 C57BL/6 小鼠 10 周后,小鼠肝细胞的 c-jun 氨基末端激酶(JNK)、核因子 κB(NF-κB)、Toll 样受体 4(TLR4)等炎症信号通路激活,并出现非酒精性脂肪肝、肝脏葡萄糖代谢紊乱以及胰岛素抵抗等症状[8, 22, 23]。$PM_{2.5}$ 暴露明显引起高脂饲料(HFD)组小鼠胰岛素和葡萄糖代谢失衡和炎症反应[15],也引起糖尿病小鼠骨骼肌中 ROS 产物增加,并诱发胰岛素抵抗[24]。此外,$ApoE^{-/-}$ 小鼠长期暴露 $PM_{2.5}$ 和过渡金属元素 Ni 后,出现空腹血糖升高、线粒体损伤、炎症反应和胰岛素抵抗[25]。$PM_{2.5}$ 长期暴露导致小鼠白色脂肪组织内脂滴的生成和沉积[26],引起受体识别的低密度脂蛋白氧化和脂质受体功能紊乱[18, 27]。

2 致病作用机制

大气颗粒物导致的健康损害主要由细胞氧化损伤和炎症反应所引起的。大气颗粒物诱导的氧化应激,巨噬细胞分化[28]、DNA 和线粒体损伤[23, 29, 30],抑制肝脏糖代谢相关酶活性,促进炎症因子释放[31, 32],上调与炎症应答通路[33, 34]相关的 JNK、NF-κB 和 TLR4 表达水平。有研究发现,炎症应答通路与胰岛素抵抗之间密切相关[35]。此外,$PM_{2.5}$ 降低肝糖原合成水平,破坏血糖和胰岛素稳态,抑制胰岛素受体底物-1(IRS-1)介导信号通路的激活,下调肝脏 PPARγ 和 PPARα 蛋白的表达水平[22],并引起免疫功能紊乱或细胞毒性[22, 36-38]。大气颗粒物介导的炎症反应激活 JNK 通路,引起细胞功能紊乱或细胞凋亡。同时,炎症因子进一步引起 ROS 水平升高。大气颗粒物中的多环芳烃化合物(PAHs)可以持续激活 DNA 损伤的信号通路[39]。当用颗粒物中提取的含碳有机物处理 HepG2 细胞后,细胞 8-羟基脱氧鸟苷(8-OHdG)和 NF-κB p65 蛋白水平均升高,该结果与 ROS 诱导的 DNA 损伤相关[40]。下面主要从氧化应激、炎症因子、糖脂毒性和其他方面探讨大气颗粒物的致病机制。

2.1 氧化应激对胰岛 β 细胞功能的影响

胰岛 β 细胞是氧化应激介导氧化损伤的靶组织之一[41-44],$PM_{2.5}$ 经非酶糖化反应[45, 46],线粒体中的电子传递链[43, 47]和氨基己糖通路[41]诱导 ROS 的生成,导致氧化应激。$PM_{2.5}$ 诱导的 ROS 生成激活 JNK 信号通路,抑制胰岛素分泌相关基因的表达[48]。研究表明,细胞保护性转录因子—胰腺十二指肠同源异型盒 1(PDX-1)在 GLP-1/GLP-1R 信号通路和葡萄糖刺激的胰岛素合成中发挥着关键作用[49, 50]。当 ROS 激活 JNK 后,后者进一步抑制 PDX-1 的核定位水平和转录活性[49, 51]。此外,ROS 显著下调 pdx-1 mRNA 表达水平,降低 PDX-1 蛋白的表达水平[52, 53],并加重 β 细胞的氧化损伤。在氧化应激状态下,2 型糖尿病患者体内有大量 ROS(如 O_2^-、H_2O_2)生成,其血清、白细胞和胰岛细胞中氧化 DNA 碱基增多[54, 55],引起 β 细胞氧化损伤和功能紊乱[56, 57]。

研究表明,氧化应激激活 Iκ 激酶 β(IKKβ)后引起 NF-κB 水平升高[58, 59],诱导 β 细胞凋亡。此外,氧化应激还激活胰岛 β 细胞的 JNK、p38 丝裂原活化蛋白激酶(p38 MAPK)和蛋白激酶 C(PKC)[48]。P38 MPAK 通过蛋白激酶 D(PKD)抑制 PKD1 磷酸化,降低胰岛素的分泌水平,进一步调控 β 细胞的存活率和胰岛素的分泌。研究表明,P38δ 敲除小鼠的葡萄糖耐量和胰岛 β 细胞分泌胰岛素水平升高,高脂饲料诱导的胰岛素抵抗明显改善,氧化应激诱导的 β 细胞凋亡水平降低[60]。以上也表明,P38δ 是调控葡萄糖稳态平衡的重要调节因素之一。

核因子 E2 相关因子 2(Nrf2)与抗氧化反应元件(antioxidant responsive element, ARE)结合后,调节抗氧化蛋白的表达[61, 62]。Nrf2/ARE 信号通路已作为重要的抗氧化应激信号通路,在调节细胞氧化还原平衡中起到重要作用。此外,Nrf2 参与过氧化物酶体增殖物激活受体 γ(PPARγ)和 PI3K/Akt 调节的抗氧化酶活性[63]。动物实验也发现,Nrf2 对 Nrf2-KO 小鼠的肥胖、胰岛素抵抗和葡萄糖耐量方面具有一定的保护作用[64]

FoxO1 是 β 细胞中表达的 FoxO 家族主要的转录因子,也是生长因子信号的主要介导物,调控 β 细胞增殖和氧化应激应答[65, 66]、胰岛素分泌水平,抑制由游离脂肪酸(FFAs)激活的葡萄糖代谢[67-69]。此外,激活 β 细胞 PI3K/Akt 信号可以抑制 FoxO 活性[70, 71],引起胰高血糖素样肽(GLP-1)介导的细胞增殖和抗氧化水平升高。

2.2　炎症因子对胰岛 β 细胞功能的影响

炎症反应是诱导胰岛素抵抗的原因之一[35]。$PM_{2.5}$暴露降低与高密度脂蛋白(HDL-c)相关的抗炎能力[72],导致炎症反应增强。在细颗粒物长期暴露下,在各时间点暴露组小鼠的血糖浓度均明显升高,葡萄糖耐量受损,肝脏、肌肉和脂肪组织胰岛素抵抗,以及系统性炎症和肺组织中招募巨噬细胞[73]。巨噬细胞通过分泌的细胞因子(如 IL-1、IFN-γ 和 TNF-α 等)激活 NF-κB 和 STAT-1,尤其是 IL-1β 激活 NF-κB 可诱导胰岛 β 细胞凋亡[74]、NO 和趋化因子产生,造成内质网损伤[75]。IL-1β 持续激活 JNK 后,损伤胰岛 β 细胞[76, 77],抑制 JNK 通路可降低 β 细胞的氧化损伤[78, 79]。此外,游离脂肪酸(FFA)也可通过氧化/内质网应激或 PKC[80, 81]直接激活 IKKβ 和 JNK; 氧化应激也可能激活 PKC,且 PKC 也能通过 NADPH 氧化酶诱导氧化应激[82]。另有研究显示,TLR2 缺陷性可以保护高脂食物诱导的 β 细胞功能紊乱[83]; 炎症激酶和 PKC 激活诱导 β 细胞的功能紊乱和凋亡,影响 β 细胞的胰岛素信号通路[84],而且 $PM_{2.5}$暴露引起 Akt 磷酸化的表达下降[21],最终引起胰岛素抵抗。

2.3　糖脂毒性

$PM_{2.5}$暴露引起机体血糖水平升高和脂质堆积[21, 73],高血糖和高脂进一步诱导氧化应激,导致细胞内 ROS 水平升高[85]。而且,脂质也可引起血液循环系统相关氧化应激因子水平的增加[86]。长期高脂和高糖减少胰岛素分泌量,导致胰岛细胞功能紊乱[87]。研究发现,用高糖(11.1 mmol·L^{-1})培养仓鼠胰岛瘤 HIT-T15 细胞 6 个月后,细胞的胰岛素 mRNA 表达水平下降,胰岛素分泌量降低。相反,在低糖(0.8 mmol·L^{-1})条件下,细胞的胰岛素 mRNA 表达和胰岛素分泌量胰岛素均维持于正常状态[88]。另有研究发现,2 型糖尿病患者的胰岛 β 细胞凋亡水平明显升高[89]。在糖毒性中,MafA 是 Maf bZIP(basic region leucine zipper)家族的转录因子之一,长期高糖(11.1 mmol·L^{-1})培养的 HIT-T15 细胞的 MafA 结合和转录功能降低,导致胰岛素基因表达、MafA 和 PDX-1 蛋白水平降低[90]。重组 HIT-T15 细胞内 PDX-1 的 cDNA 可部分增加高糖培养细胞的胰岛素启动子活性[91]。而且,抗氧化剂 NAC 升高高糖培养 HIT-T15 细胞中 MafA 蛋白的表达水平[90]。

在高脂高糖条件下,β 细胞易发生凋亡,该作用可能与 Bax、caspase-2、NO 和 UCP-2(Uncoupling protein 2)水平升高相关[92, 93]。游离脂肪酸通过 JNK 激活和 IRS-1 丝氨酸磷酸化,影响 ER 的钙离子调控[94],抑制胰岛素信号通路,调节氧化调控蛋白 150(ORP150,保护细胞免受 ER 应激损伤)的水平。高浓度 FFAs 引起胰岛素敏感性降低[95]。大鼠注射葡萄糖和脂肪乳剂后,其胰岛素基因的表达水平降低[96]。当 FFAs 水平下降时,胰岛素的分泌水平升高[97, 98]。

2.4　其 他

成人发病型糖尿病(MODY)由 pdx-1 基因变异所引起[99, 100],PDX-1 在胰岛 β 细胞发育和功能中起到重要作用[49, 101]。PDX-1 下调严重影响胰岛素生成,导致 β 细胞功能紊乱和糖尿病[102]。MafA 在葡萄糖调节胰岛素基因表达和介导其他基因(如 PDX-1)表达中具有重要作用[49, 103, 104]。FoxO1 和 PDX-1 与 MafA 启动子结合后,介导 MafA 转录[49],β 细胞中,脂质和前炎症因子下调 MafA 和胰岛素基因的表

达[101, 105-107],用腺病毒转染 PDX-1 和 MafA 可明显增加内源性胰岛素 mRNA 水平约 93%[108]。因此,MafA 可能是治疗 β 细胞紊乱的潜在靶点[101]。

总体而言,$PM_{2.5}$ 诱导的氧化应激和炎症反应在糖尿病的发生发展中具有一定的生物学作用(图 1)。

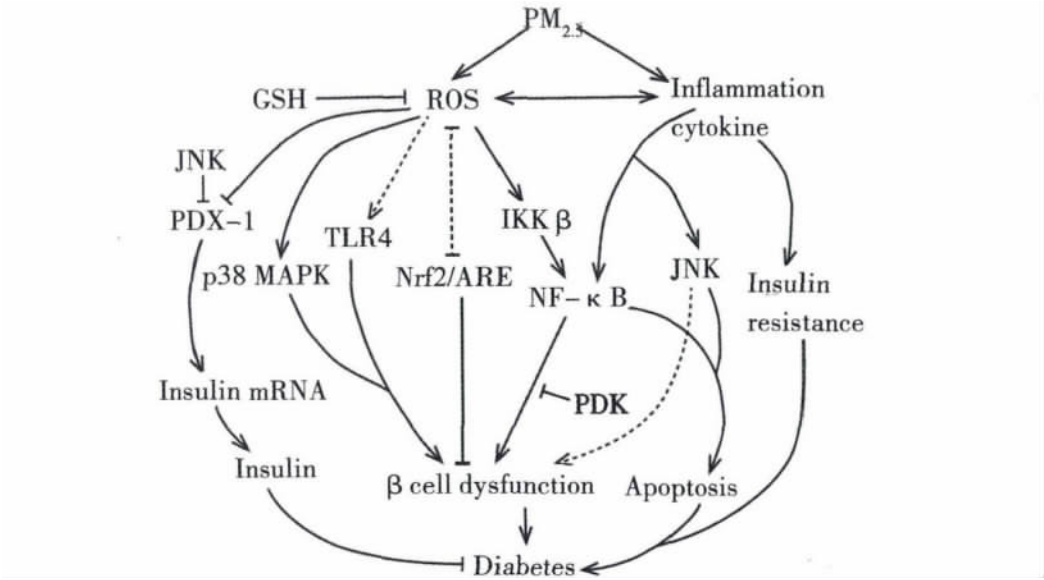

图 1 $PM_{2.5}$ 诱导的氧化应激在糖尿病发生发展的作用机制

ARE: 抗氧化反应元件,GSH: 谷胱甘肽,IKK-β: Iκ 激酶 β,JNK: 氨基末端激酶,NF-κB: 核因子 κB,Nrf2: 核因子 E2 相关因子 2,p38 MAPK: p38 丝裂原活化蛋白激酶,PDX-1: 胰腺十二指肠同源异型盒 1,PKD: 蛋白激酶 D,$PM_{2.5}$: 细颗粒物,ROS: 活性氧,TLR4: Toll 样受体 4

Fig. 1 The mechanesim of $PM_{2.5}$-induced oxidative stress on development of diabetes mellitus

ntioxidant responsive element, GSH: Glutathione, IKK-β: Inhibitor of nuclear factor kappa-B kinase, JNK: c-Jun N-terminal kinases, Nuclear factor kappa B, Nrf2: Nuclea factor erythroid-2-related factor 2, p38 MAPK: P38 Mitogen-activated protein kinases, PDX-1: Pancreatic and duodenal homeobox 1(Insulin promoter factor 1), PKD: Protein kinase D, $PM_{2.5}$: Fine particulate matter, ROS: Reactive oxygen species, TLR4: Toll-like receptor 4

3 研究展望

目前,有关大气细颗粒物组成成分(金属元素、离子和有机化合物等)引起胰腺 β 细胞损伤的研究报道甚少,其生物学作用机制有待于深入研究。

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中国《高风险污染物削减行动计划》出台

2014 年 5 月 1 日 来源: 中国化工报

4 月 28 日,工信部和财政部联合发出通知,为加快实施汞削减、铅削减和高毒农药替代清洁生产重点工程,从源头减少汞、铅和高毒农药等高风险污染物产生和排放,降低对人体健康和生态环境安全的影响,组织编制了《高风险污染物削减行动计划》,要求全国各地及中央企业遵照执行。中央财政清洁生产专项资金对实施效果显著的项目予以奖励。

据悉,我国已经成为世界上最大的汞、铅和农药生产和消费国,加强对涉汞、铅行业和农药行业的污染防治迫在眉睫。工业领域汞污染主要集中在汞使用量较大的电石法聚氯乙烯、荧光灯、干电池、体温计等领域,占汞总使用量的 95% 以上。铅污染主要集中在铅冶炼、再生铅行业,以及铅使用量达 80% 的铅酸蓄电池行业。农药行业主要问题是高毒农药品种仍有杀扑磷等 12 个品种,产量占农药总产量的 2.5% 左右; 此外,还有约 30 万吨的有害有机溶剂在农药制剂中应用。

通知要求有关企业抓紧实施清洁生产技术改造项目,制定清洁生产技术改造项目计划,实施清洁生产技术改造项目,并提出实施效果评估申请。

引自《化学品安全信息周报》2014 年第 19 期总第 283 期(中国检验检疫科学研究院化学品安全研究所编译)

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