

大气细颗粒物诱发血压升高的分子机制研究进展

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摘要:

高血压作为最常见的心血管疾病之一, 是我国慢病防治的重中之重。大气细颗粒物(PM_{2.5})是多种心血管疾病的危险因素。在PM_{2.5}影响血压的机制中, 氧化应激和炎症反应发挥着关键性作用。PM_{2.5}的理化成分包括炭黑、有机物、无机离子和金属等, 不同理化成分可以激发不同炎症通路, 从多个途径影响血压调控。本综述总结PM_{2.5}影响血压的分子机制, 并着重介绍PM_{2.5}中不同组分在调控血压中发挥的作用, 以期为空气污染诱发高血压的防治问题提供理论依据和研究思路。

关键词: 细颗粒物; 血压; 分子机制; 金属元素; 有机物; 炭黑

Advances on potential mechanisms of blood pressure increase induced by ambient fine particulate matters XU Jialin, XU Jiayu, JIA Guang (School of Public Health, Peking University, Beijing 100191, China)

Abstract:

As one of the most common cardiovascular diseases, hypertension is the top priority of chronic diseases prevention and control in China. Ambient fine particulate matter (PM_{2.5}) is a risk factor for multiple cardiovascular diseases. In reported mechanisms by which PM_{2.5} affects blood pressure, oxidative stress and inflammation play key roles. The components of PM_{2.5} include black carbon, organic matters, inorganic ions, and metals, and they can stimulate different inflammatory pathways and affect blood pressure regulation in varied ways. This review summarized the potential molecular mechanisms of PM_{2.5} affecting blood pressure, and focused on the roles of different components of PM_{2.5} in regulating blood pressure, aiming to provide a theoretical basis and research ideas for the prevention and treatment of hypertension induced by air pollution.

Keywords: fine particulate matter; blood pressure; molecular mechanism; metal element; organic matter; black carbon

1 PM_{2.5}与高血压的关联

高血压居全球可预防性死因之首, 每年全球因高血压及其并发症死亡者超过900万^[1]。高血压是以体循环动脉血压升高为主要特征, 可伴有心、脑、肾等器官功能损害的临床综合征, 是最常见的慢性病之一, 也是众多心脑血管疾病的危险因素^[2]。高血压发病机制复杂, 是遗传因素和环境因素共同作用的结果。大气细颗粒物(fine particulate matters, PM_{2.5})是多种心血管疾病的危险因素。PM_{2.5}是空气动力学直径小于或等于2.5 μm的颗粒物, 与雾霾形成有关, 对生态环境、社会发展和公众健康造成巨大威胁^[3-5]。一系列研究证实PM_{2.5}可诱发血压升高, 并对其机制进行了探讨。

1.1 PM_{2.5}与高血压关联的流行病学研究

流行病学研究证实PM_{2.5}可诱发血压升高, 且对心血管基础疾病的人群影响更为显著。PM_{2.5}浓度与健康人群高血压发病率呈正相关^[6], 短期和长期暴露于PM_{2.5}的健康人群血压均有不同程度的升高, 且该结果有统计学意义^[7-8]。

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Zanobetti 等^[9]以 62 名有心血管基础疾病的波士顿居民为对象,通过混合效应模型分析得出,PM_{2.5}质量浓度每上升 10.5 μg·m⁻³,心率大于等于 70 次·min⁻¹的患者收缩压和舒张压分别上升 2.8 mmHg 和 2.7 mmHg。该研究提示 PM_{2.5}可通过诱发血压升高加重人群心血管基础疾病。

由于样本人群和暴露条件的差异,部分研究并未得出有统计学意义的结论,但是多数流行病学研究支持 PM_{2.5}暴露与血压升高有正相关关系^[10]。本文对相关流行病学研究^[6, 8-14]的时间、地点、对象等条件进行归纳(表 1),比较造成结论不同的差异性因素。

表 1 PM_{2.5}与高血压关联的代表性流行病学研究
Table 1 Representative epidemiological studies on PM_{2.5} and hypertension

研究时间	研究地区	研究类型	研究人群	研究结果
1996—2010	加拿大安大略	队列研究	35 303 名健康成人, 年龄≥35 岁	PM _{2.5} 可增加突发性高血压发生风险, PM _{2.5} 每增加 10 μg·m ⁻³ , HR=1.13 (95% CI : 1.05~1.22) ^[6]
2000—2002	美国巴尔的摩、福赛斯、纽约、芝加哥、洛杉矶、圣保罗	队列研究	5 112 名健康成人, 年龄(62.3±10.0)岁	脉压、收缩压与 PM _{2.5} 浓度呈正相关; PM _{2.5} 每增加 10 μg·m ⁻³ , 脉压升高 1.12 (95% CI : 0.28~1.97) mmHg, 收缩压升高 0.99 (95% CI : -0.15~2.13) mmHg ^[8]
1999—2001	美国波士顿	重复测量研究	62 名心血管基础疾病患者	PM _{2.5} 浓度每上升 10.5 μg·m ⁻³ , 心率大于等于 70 次·min ⁻¹ 的患者收缩压和舒张压分别上升 2.8 (95% CI : 0.1~5.5) mmHg 和 2.7 (95% CI : 1.2~4.3) mmHg ^[9]
2007—2010	中国上海、广东、湖北、吉林、陕西、山东、云南、浙江	队列研究	12 665 名健康成人, 年龄≥50 岁	PM _{2.5} 可增加高血压发生风险, PM _{2.5} 每增加 10 μg·m ⁻³ , OR=1.14 (95% CI : 1.07~1.22) ^[10]
2007.1—2007.12	中国北京	病例交叉研究	北京市居民	PM _{2.5} 与高血压急诊人数增加有关, PM _{2.5} 每增加 10 μg·m ⁻³ , OR=1.084 (95% CI : 1.028~1.139) ^[11]
1998—1999	芬兰、德国、荷兰	多中心研究	131 名冠心病成人患者, 年龄≥50 岁	PM _{2.5} 浓度与舒张压呈负相关; PM _{2.5} 每增加 10 μg·m ⁻³ , 舒张压下降 0.39 (95% CI : 0.75~0.03) mmHg ^[12]
2000—2001	挪威	队列研究	16 756 名健康成人, 年龄(74.9±5.2)岁	未发现血压与空气污染之间的关联 ^[13]
2017.4—2017.12	中国广州	定组研究	37 名健康大学生	PM _{2.5} 浓度与血压呈负相关; PM _{2.5} 每增加 10 μg·m ⁻³ 时, 收缩压和舒张压分别降低 0.54 (95% CI : -1.03~-0.05) mmHg 和 0.22 (95% CI : -0.59~0.15) mmHg ^[14]

1.2 PM_{2.5}与高血压关联的毒理学研究

在 PM_{2.5}诱发血压升高的分子机制中,公认的是氧化应激、炎症反应和自主神经调节紊乱学说,而氧化应激、炎症反应是后者的使动因素^[15]。PM_{2.5}促使血管内皮细胞产生过量的活性氧(reactive oxygen species, ROS)^[16]。ROS引起机体氧化应激,损伤血管内皮,引起心肌纤维化,并可损伤肾脏,引起水钠潴留,通过多重效应最终导致血压升高^[17]。PM_{2.5}短时间内即可引起脐静脉内皮细胞释放过量 ROS^[18],抑制一氧化氮合酶(nitric oxide synthase, NOS)。一氧化氮(nitric oxide, NO)在生理条件下介导血管舒张,抑制血小板聚集活化,调控炎症细胞释放炎症因子^[19-20],通过多种途径控制血压。除了影响 NO 介导的血压调节,ROS 还可通过损伤线粒体,间接升高血压。研究表明,暴露于 PM_{2.5}的大鼠心肌线粒体功能受损,影响心脏舒缩功能^[21],导致心血管系统功能紊乱,血压调控失常。

更为重要的是,ROS 可以激活一系列炎症通路,引起全身炎症反应。虽然吸入的 PM_{2.5}先在肺内诱发局部炎症反应,但是继发的全身炎症反应和血管功能障碍在诱发血压升高上更为关键^[22]。PM_{2.5}与核因子 κB(nuclear factor-κB, NF-κB)的持续活化有关^[23]。

NF-κB 通路可调控肿瘤坏死因子 α(tumor necrosis factor-α, TNF-α)、白介素-1β(interleukin-1β, IL-1β)、白介素-6(interleukin-6, IL-6)等多种炎症相关细胞因子的表达^[24]。PM_{2.5}还能激活肺内 RhoA/Rho 激酶(RhoA/Rho-kinase, RhoA/ROCK)通路,一方面激活烟酰胺腺嘌呤二核苷酸磷酸氧化酶从而促进氧化应激,另一方面上调钙离子,使血管内皮对钙离子增敏,导致肺血管的收缩,最终升高血压^[25-26]。此外,PM_{2.5}与丝裂原活化蛋白激酶/激活蛋白-1(mitogen-activated protein kinase/activator protein-1, MAPK/AP-1)通路、肾素-血管紧张素系统的激活均有关系,引起全身多器官内炎症相关基因的过表达^[16, 27-29],共同影响心血管功能,导致血压的升高。

2 PM_{2.5}中不同组分诱发血压升高的机制

PM_{2.5}的组分包括碳质、无机离子和金属等,其中金属、部分有机物和炭黑被认为是引起血压升高的主要成分^[30]。

2.1 金属元素

PM_{2.5}中的金属种类多,形态复杂,时空分布差异较大。结合不同地区采样结果分析,铜、铬、镍、锰、钒、砷、铅等在各地样本中普遍存在^[31-32]。其中,重

金属如砷、铅存在致癌风险^[31], 而促氧化过渡金属如镍与激活胞内氧化应激有关^[32]。

PM_{2.5}中的金属可诱发哮喘、过敏和心血管疾病, 这些疾病均与炎症免疫反应密切相关^[33]。过渡金属是PM_{2.5}中引起血压升高的重要成分^[30]。PM_{2.5}中的镍是血压升高的独立风险因素, 尤其是舒张压^[34]。Li等^[35]发现PM_{2.5}中的铜和钒可诱发大鼠肺部血管收缩及人肺动脉内皮细胞中细胞外信号调节激酶1/2 (extracellular signal-regulated kinase1/2, ERK1/2) 和p38丝裂原活化蛋白激酶 (p38 mitogen-activated protein kinase, p38 MAPK) 的磷酸化。ERK和p38是MAPK家族成员, 可以激活下游信号分子AP-1和核因子E2相关因子2 (nuclear factor E2-related factor 2, Nrf2), 上调一系列炎症因子表达^[36]。

除了过渡金属, PM_{2.5}中的重金属如铅也可以通过炎症损伤血管内皮, 造成心血管功能紊乱, 间接诱发血压升高。Pb²⁺可以抑制人支气管上皮细胞长链非编码RNA-磷酸烯醇式丙酮羧基酶1-2:1 (long non-coding-phosphoenolpyruvate carboxykinase 1-2:1, lnc-PCK1-2:1) 的表达, 而该非编码RNA在炎症抑制中发挥作用^[37]。Pb²⁺也可以直接激活炎症通路, 上调IL-6和白介素-8 (interleukin-8, IL-8)^[32]。此外, PM_{2.5}中的金属成分还能促进组织细胞产生ROS如羟自由基 (hydroxyl radical, HO·), 引发氧化应激损伤^[38], 从多种途径损伤血管内皮, 诱发血压升高。

综上所述, PM_{2.5}中促氧化过渡金属如镍、钒、铜等以及重金属如铅, 可通过引发ROS产生, 激活炎症通路, 上调促炎细胞因子, 抑制抗炎基因等方式, 增强机体的氧化应激和炎症反应, 损伤血管内皮, 导致心血管系统调节紊乱, 诱发血压升高。

2.2 有机物

PM_{2.5}中的有机物组成复杂, 包括脂肪酸类、葡聚糖类、烷烃类等, 来源于汽车尾气排放、化石燃料燃烧、自然界植物排放等多种途径^[39-42]。部分有机物可以通过影响机体的氧化应激和炎症反应, 最终诱发血压升高。

多环芳烃 (polycyclic aromatic hydrocarbons, PAHs) 是含两个及以上苯环的芳烃, PM_{2.5}中的PAHs以有四个及以上苯环的高分子量PAHs为主^[43]。PAHs及其衍生物可以激发氧化应激和炎症反应, 造成心血管系统功能紊乱。PAHs可以升高机体脂质过氧化水平, 同时使部分抗氧化酶, 如对氧磷酶和芳基酯酶的活性下

降^[44], 而这两种抗氧化酶可以阻止众多心血管病的发生发展^[45]。在直接促炎方面, 通过基于时空质谱的组学方法发现, 暴露于PAHs及其衍生物的巨噬细胞释放过量IL-6、IL-1β、TNF-α等促炎细胞因子^[46]。此外, 以北京175名老人为对象建立的PM_{2.5}成分联合线性混合效应模型表明, PAHs与血浆补体C3呈正相关, 且在高血压群体中这一关联尤为显著^[47]。

PM_{2.5}中的二次有机气溶胶 (secondary organic aerosols, SOA) 也与炎症通路诱发的心血管风险关系密切。SOA可以通过影响表观遗传调控炎症和氧化应激过程。SOA可以影响人正常肺上皮细胞 (BEAS-2B) 内与炎症/氧化应激相关的微小RNA (microRNA, miRNA) 的表达量^[48]。SOA还可上调Nrf-2^[49], Nrf-2与AU富含元件结合, 启动下游抗氧化酶转录, 调节氧化/抗氧化平衡^[50]。与PM_{2.5}中的金属类似, SOA同样与IL-6、IL-8等炎症因子^[51], 以及ROS和有机过氧化物的产生有关^[52]。

水溶性有机物对血压升高具有作用。Almeida等^[53]将Raw264.7巨噬细胞暴露于水溶性有机物后, 促炎基因*IL-1β*和*Nos2*转录增加, 细胞处于中等程度的促炎状态, 同时对促炎刺激的反应能力减弱而血红素加氧酶 (heme oxygenase-1, HO-1) 表达量反馈性增加。HO-1可以通过HO-1/NO、Nrf2/HO-1、HO-1-胆红素-CO内源性保护系统广泛参与机体的抗炎抗氧化损伤过程^[54], 与心血管疾病的发生发展关系密切。

综上所述, PM_{2.5}中的有机物, 尤其是PAHs和SOA, 可以通过抑制抗氧化酶, 促进炎症分子表达, 促进炎症相关表观遗传修饰等, 加强机体氧化应激和炎症反应, 引起心血管功能紊乱, 诱发血压升高。

2.3 炭黑

炭黑 (black carbon, BC) 又称元素碳, 与有机碳一同构成PM_{2.5}的碳质组分, 与雾霾形成紧密相关^[55-56]。BC与金属、部分有机物一起, 在激活体内氧化应激和炎症通路方面发挥关键性的作用, 是PM_{2.5}中导致血压升高的主要组分^[30]。

流行病学研究表明, BC诱发血压升高, 特别是对于血压敏感的特殊群体, 如老年人和有基础疾病的人群, 其影响更为显著。一项关于代谢综合征病人的研究发现, BC暴露量每增加一个单位, 收缩压和舒张压分别升高0.53 (95%CI: 0.17~0.89) mmHg和0.37 (95%CI: 0.10~0.65) mmHg^[57]。中国纵向寿命健康调查队列研究^[58]表明, 使用生物质燃料烹饪的老年人比使用清

洁燃料者更易患高血压,且生物质燃烧物通量与血压呈正相关。厨房生物质燃料的排放物中,BC占有相当大比重,该研究从侧面证实了BC与血压升高相关。毒理学研究中,Liu等^[59]通过C57BL/6小鼠气管滴注证实BC致炎的一种机制:BC首先激活肺内巨噬细胞,导致外周血趋化因子配体2(C-C motif chemokine ligand 2, CCL2)升高,单核细胞募集,NF- κ B通路活化,进而上调外周血中TNF- α 和IL-1 β 的表达量,最终引起炎症反应,造成心血管系统功能紊乱,血压控制异常。在升高血压方面,BC比PM_{2.5}中的其他组分效果更强。使自发性高血压大鼠暴露于不同组分配比下的PM_{2.5},发现BC在导致高血压大鼠血压升高和心率加快中发挥的作用远大于有机碳等PM_{2.5}中其他组分^[60]。此外,纯BC颗粒致炎效果强于同条件下的PM_{2.5}。这是由于BC结构的高聚集状态使颗粒对细胞造成持续损伤,而PM_{2.5}引入了氧元素,提高了颗粒分散度,降低了聚集态,从而促进颗粒的生物相容性,一定程度上减轻了致炎损伤^[61]。

2.4 水溶性组分

PM_{2.5}诱发血压升高不是金属、有机物或炭黑的单一作用,而是多种组分相互叠加、共同作用的结果。有研究指出,PM_{2.5}中的水溶性组分(water-soluble PM_{2.5}, WS-PM_{2.5})比非水溶性组分(water-insoluble PM_{2.5}, WIS-PM_{2.5})在升高血压方面有更显著的作用^[36]。

WS-PM_{2.5}主要通过促进ROS形成、线粒体倍增和多层体形成,参与早期的氧化应激反应^[62-63],而WIS-PM_{2.5}通过细胞-颗粒相互作用直接破坏细胞膜^[15]。纵观前述氧化应激与炎症对血压升高的影响,WS-PM_{2.5}对于血压升高有更关键和直接的作用。WS-PM_{2.5}还可以作用于脂代谢间接影响血压。WS-PM_{2.5}在低密度脂蛋白apoA-I的聚集和低密度脂蛋白apo-B的降解中均发挥作用,还可促使氧化型低密度脂蛋白进入巨噬细胞,以剂量依赖方式促进氧化型低密度脂蛋白的吸收^[64]。血清脂蛋白参与机体抗氧化过程,WS-PM_{2.5}通过影响脂蛋白的聚集和降解干扰正常脂代谢,间接助长氧化应激,成为心血管风险的先发因素。动物实验也得到了相似结论。Zhao等^[65]发现长期暴露于WS-PM_{2.5}的BALB/c小鼠体内脂代谢异常,并伴有呼吸道炎症反应。Zhang等^[66]发现WS-PM_{2.5}干扰BALB/c小鼠脂代谢和糖代谢,WIS-PM_{2.5}主要影响氨基酸和能量的代谢,而前者所干扰的脂代谢与诱发血压升高的炎症氧化应激有更为直接的关系。

此外,WS-PM_{2.5}还可以引起肺动脉环的收缩,直接升高血压,并且与血管紧张素1型受体、血管紧张素II等血压调控相关分子以及p38 MAPK、ERK1/2等炎症分子激活有关^[36],可以通过多种途径促进血压升高。

3 结论

综合以往研究发现,金属如镍、钒、铜、铅,部分有机物如PAHs、SOA,以及BC,是PM_{2.5}中诱发血压升高的主要成分,且他们诱发血压升高的途径均与炎症和氧化应激相关。另外,PM_{2.5}升高血压不是一种或几种组分单独作用的结果,而是多组分的联合效应。相较于WIS-PM_{2.5},WS-PM_{2.5}与血压升高的关系更为密切(图1)。

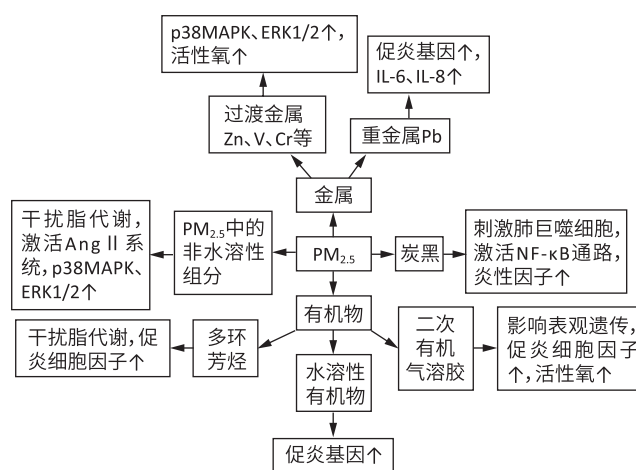


图1 PM_{2.5}中不同组分影响血压的分子机制

Figure 1 Proposed molecular mechanisms of PM_{2.5} components inducing hypertension

目前针对PM_{2.5}心血管毒性的综述较多,亦普遍探讨了炎症和氧化应激在疾病发生发展中的作用。然而,不同心血管疾病的发生机制不尽相同,无法一概而论。在现有综述中,Brook等^[16]总结了相关流行病学研究、动物实验和细胞实验,指出炎症和氧化应激对于急性暴露、慢性暴露引发的血压升高均有一定程度的作用。在国内,舒志浩等^[67]总结了PM_{2.5}诱发血压升高过程中部分炎症通路和信号分子。然而,类似综述多关注PM_{2.5}整体的毒理学效应,未详细探讨PM_{2.5}不同组分对于血压升高的贡献。随着相关研究不断涌现,不同组分截然不同的毒理学效应备受关注。因此,系统总结针对PM_{2.5}不同组分与血压升高关联的研究,探讨PM_{2.5}诱发血压升高的主导组分及其对应的分子机制,对于后续更有针对性的防控治疗具

有重要意义。

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