

香烟烟雾暴露对孕妇及胎儿生长发育危害的研究进展

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摘要

香烟烟雾中含的有害物质,可能造成多种疾病的发生,尤其是对胎儿健康产生影响的机制还不完全清楚。本综述主要介绍香烟中的主要有害成分对健康的危害影响。孕妇吸入香烟烟雾产生的不良影响可能传递给胎儿,最后对孕妇吸入香烟烟雾对后代的脑、肺、肾、心脏、肝脏等器官造成的影响研究进展进行综述。期望未来人们对香烟烟雾的危害引起重视,为孕妇提供更健康的生活环境。

关键词

香烟烟雾, 健康影响, 孕妇, 后代影响

Research Progress on the Harm of Cigarette Smoke Exposure to the Growth and Development of Pregnant Women and Fetuses

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Abstract

The harmful substances contained in cigarette smoke may cause a variety of diseases; especially the mechanism of the impact on fetal health is not completely clear. This review mainly introduces

the harmful effects of the main harmful components in cigarettes on health. The adverse effects of cigarette smoke inhalation by pregnant women may be passed on to the fetus. Finally, the research progress on the effects of cigarette smoke inhalation by pregnant women on the brain, lung, kidney, heart, liver and other organs of offspring is reviewed. It is expected that people will pay attention to the harm of cigarette smoke in the future so as to provide a healthier living environment for pregnant women.

Keywords

Cigarette Smoke, Health Effects, Pregnant Women, Offspring Effects

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1. 引言

吸烟已知会危害人体健康, 且受到世界各国的重视[1]。全球有超过 10 亿吸烟者[2], 而中国吸烟人数超过 3 亿[3]。2021 年, 世界卫生组织估计, 每年有 800 万人因吸烟或咀嚼烟草导致的相关疾病死亡, 另外约有 130 万的非吸烟者死于与二手烟相关的疾病[4]。香烟烟雾包含的多种有害化合物几乎对身体的每个器官都有损伤作用[5], 可能增加人患肺癌[6]、肝癌[7]、肾病[8]、心脏疾病等相关疾病的风险[9]。如吸烟会增加慢性呼吸道疾病, 例如慢性阻塞性肺病(chronic obstructive pulmonary disease, COPD) [10]、哮喘[11]、尘肺病[12]、间质性肺病[13]和结节病[14]等疾病的发病率和死亡风险[15] [16]。2019 年慢性呼吸道疾病已成为全球第三大死因, 导致约 400 万人死亡[17]。所以吸烟对于疾病的发生是一个重要的危险因素之一, 了解其生理损伤机制十分重要。

孕妇接触二手烟比主动吸烟者更常见[18]。孕妇会因为家庭成员有吸烟者而长期暴露于二手烟环境[19]。在中国孕妇吸烟者的比例低, 但是孕妇暴露于二手烟的比率超过 50% [20]。孕妇在孕期吸烟会增加流产的机率[21]或者胎儿早产[22]。也会造成新生儿出生体重低[23], 还会增加新生儿畸形的概率[24] [25]。因此了解怀孕期间吸入香烟烟雾对胎儿发育产生影响的生理机制非常重要。本综述将介绍目前香烟烟雾中有害物质对机体产生危害影响, 并阐述目前孕妇吸入香烟烟雾对胎儿发育产生影响的研究进展

2. 烟草烟雾中的有害物质

烟草烟雾中已鉴定出有 7000 多种复杂的化学物质[26] [27]。主要有害物质包括, 尼古丁(nicotine), 多环芳烃类化合物(polycyclic aromatic hydrocarbons, PAHs), 焦油(Tar), 一氧化碳(Carbon monoxide)等。这些有害物质可直接伤害肺部功能[28], 也可经由肺部吸收进入血液循环传送而损害身体各个器官[29]。香烟中主要有害物质的影响简述如下。

2.1. 尼古丁

尼古丁(nicotine)是一种天然存在于许多植物中的生物碱, 以两种对映异构体(S)-nicotine 和(R)-nicotine 的形式存在[30]。烟草中含有大量(S)-nicotine, 尼古丁总含量中只有 0.1%~0.6%是(R)-nicotine [31]。尼古丁属于弱碱, 解离常数 pK_a 为 8.0, 它以 69%的电离和 31%的自由形式结合, 酸度会影响尼古丁的吸收, 在 pH 值为 5.5~6.0 的酸性下, 尼古丁呈电离形式, 不被组织吸收。因此, 从香烟烟雾中释放的尼古丁呈电离形式, 不会穿过膜, 从而阻止其口腔吸收, 而肺泡液的 pH 值为 7.4, 可将尼古丁转化为结合形式,

促进快速吸收[32]。人吸一口烟后, 高水平的尼古丁在 10~20 秒内到达大脑, 比静脉注射更快[33]。尼古丁被吸收后, 进入血液, 可广泛分布于身体组织, 根据对吸烟者的尸体样本检测发现, 尼古丁在肝脏、肾脏、脾脏和肺中的浓度最高, 在脂肪组织中的浓度最低[34]。尼古丁是烟草中的主要精神活性物质, 它能够和位于整个大脑和周围神经系统中的烟碱乙酰胆碱受体(nicotinic acetylcholine receptors, nAChRs)结合[35]。烟碱乙酰胆碱受体几乎在大脑的每个区域表达[36], 包括突触前和突触后[37], 并且可以在轴突末梢、轴突、树突[36] [38]和体细胞[39]上表达。当尼古丁与烟碱乙酰胆碱受体结合后, 尼古丁刺激会使大脑伏隔核(nucleus accumbens, NAcc)中的多巴胺分泌升高[40], 这会刺激“奖励通路(reward pathway)”, 使得对尼古丁摄入的欲望增加[41] [42], 促使人不断的吸烟来得到满足, 长期发展下去则会对香烟成瘾[43]。此外尼古丁和肺部烟碱乙酰胆碱受体结合可以刺激包括 RAS 通路在内的多种信号通路, 导致细胞增殖增加, 通过激活细胞生长途径促进肺癌的发展[44] [45]。而急性尼古丁中毒的症状表现为恶心、呕吐、头痛、腹部绞痛、呼吸困难、体温异常、面色苍白、腹泻、发冷、血压和心率波动、出汗和流涎增加[46] [47]。

对于怀孕妇女, 尼古丁被母体吸收后不仅直接对身体产生作用, 还有可能通过母体如胎盘[48]和母乳[49]传递到胎儿体内产生作用。尼古丁很容易穿过胎盘屏障, 有证据表明尼古丁在胎儿血清和羊水中的积累浓度略高于母体血清[48]。但目前对于尼古丁对胎儿造成的生理影响及可能机制目前仍不清楚。

2.2. 多环芳烃类化合物

香烟烟雾中含有多种多环芳烃类化合物(polycyclic aromatic hydrocarbons, PAHs), 尤其包含致癌的多环芳烃[50], 主要包括苯并芘(Benzo[a]pyrenes, BaP)、萘(naphthalene)、屈烯(chrysene)等[50]。吸烟经滤嘴吸入的烟雾称为主流烟雾, 而香烟燃烧时释放到空气中烟雾称为侧流烟雾, 抽一支香烟摄入约 20~40 ng 的苯并芘[51], 研究发现在侧流烟雾含有的苯并芘(BaP)约为 103 ng/支, 是主流烟雾(10.9 ng/支)的 10 倍[52], 因此推测侧流烟雾对身体的危害风险可能更大。苯并芘(BaP)进入体内后, 除了小部分以原始形式在粪便中排泄外, 大部分会积聚在胃肠道、附睾脂肪、肺、肝、脑和肾中, 而且它具有高度亲脂性, 可以很容易地通过质膜被吸收到细胞中[53]。大多数多环芳烃本身没有基因毒性, 它们需要代谢成与 DNA 反应的环氧化物, 从而诱导基因毒性损伤[54]。

多环芳烃化合物(包含 BaP)在生物体内的代谢过程可概括为, 首先经胞色素 P450 (cytochrome P450) 中的 CYP1 家族(CYP1A1, CYP1A2, CYP1B1 等)和微粒体环氧化物水解酶的作用下将多环芳烃转化为一些酚类、苯酚二醇、二氢二醇、醌类和反应性二醇环氧化物对映异构体[55], 而苯并芘(BaP)在这一过程中可能会形成环氧化物 B[a]P-7,8-epoxide, 然后经过环氧化物水解酶产生二醇 B[a]P-7,8-diol, 这一产物在经 CYP450 酶的再次催化作用下产生具有反应活性的二醇环氧化物(BPDE), 它能够和 DNA 的鸟嘌呤反应结合, 形成 DNA 加合物(DNA adducts), 大量持续的产生 DNA 加合物可能会在 DNA 复制时引起核苷酸的不匹配[56], 从而这些 DNA 损伤的作用可能造成基因的突变和异常基因表达, 可能造成细胞癌变的发生[57]。

2.3. 一氧化碳和其他有害物质

烟草燃烧, 产生的一氧化碳是潜在的有害物质暴露来源, 对身体损害严重时会造成缺氧反应[58]。人类血红蛋白结合一氧化碳的亲合力比氧气高 200 到 250 倍[59], 当吸入大量一氧化碳时会降低血红蛋白的携氧能力并导致组织细胞缺氧[60]。一氧化碳和血红蛋白结合产生的碳氧血红蛋白(carboxy-hemoglobin, COHb)浓度在吸烟者中可能高达 10%, 而在正常人中则为 1%至 3% [59], 当 COHb 浓度超过 10%可能会出现头痛, 呼吸困难的状况[61]。

烟草燃烧产生的烟雾中的金属和重金属通常被认为以离子形式存在,但也可能以气态元素形式存在,如汞[62]。如果土地受到的污染严重可能会增加植物体内重金属的含量,有研究发现中国卷烟烟草中的砷、镉和铅浓度比加拿大卷烟中的含量高出两到三倍[63]。据报道,患有慢性阻塞性肺疾病的研究患者呼出气冷凝物中的铅浓度明显高于不吸烟的健康对照受试者。当慢性阻塞性肺病患者被细分为吸烟者与戒烟者和非吸烟者时,吸烟者呼出的呼气冷凝物中铝的浓度明显更高[64]。因此香烟烟雾中的重金属也是对身体造成损害的一个原因之一。

3. 香烟烟雾暴露对孕妇和胎儿的危害作用

3.1. 流行病学的研究

近年来,香烟中的有害物质对胎儿健康的影响也被广泛关注[25]。孕妇主动吸烟或者被动吸烟可能都会对自身和胎儿的健康产生影响[65]。孕妇在孕期吸烟会增加流产的机率[21]或者胎儿早产[22]。也会造成新生儿出生体重低[23],还会增加新生儿畸形的概率[24][25]。包含面部缺陷[66],如唇裂和腭裂[67]。肌肉和骨骼缺陷[68]和颅缝早闭[69],并增加新生儿出现先天性心脏缺陷的风险[70],以及新生儿猝死[71]。然而研究表明孕妇在孕期接触香烟对胎儿产生的不良影响,目前并没有可行的治疗方法,这种影响可能会伴随其终身[72]。

3.2. 孕妇暴露香烟烟雾对胎盘的影响

胎盘在妊娠期间作为胎儿和母体环境之间物质交换的桥梁[73]。孕妇孕期接触二手烟可能会引发胎盘发育不良[74],引起诸多并发症,例如前置胎盘、胎盘早剥、产前出血、流产、异位妊娠、宫内生长受限[75]。孕妇妊娠晚期吸烟与足月胎盘基地膜扩张,绒毛胶原蛋白含量增加,血管形成减少有关[76]。这些对胎盘造成的不良影响也会间接影响胎儿的发育。且产前暴露于环境烟草烟雾的影响与孕妇主动吸烟的影响相似[65]。

4. 香烟烟雾对胎儿的影响

香烟烟雾对发育的生物体如婴儿和发育中的胎儿的危害更大,孕妇接触香烟烟雾后所生的婴儿出生体重较低[22][77][78],头围较小[79],体长较短[80][81]。孕妇香烟烟雾暴露会影响胎儿的发育,然而其原因仍不明确,下面将阐述目前的研究进展。

4.1. 脑

孕妇产前吸烟与胎儿神经发育障碍的风险增加有关[82]。此外孕期吸入二手烟会增加婴儿神经管缺陷,无脑畸形、脊柱裂和脑膨出的风险[83][84]。孕妇吸入二手烟雾对胎儿产生的影响不仅体现在出生后,而且可能还会增加子代在成年后患脑部疾病的风险,一项针对子代成年者的调查研究发现其感觉皮层有长期负面影响[85]。

烟草烟雾中的一氧化碳和尼古丁被认为是主要影响胎儿发育的毒害物质,一氧化碳可以扩散穿过胎盘屏障并进入胎儿循环。它与胎儿血红蛋白结合,减少氧气释放到胎儿组织中[86]。香烟中的尼古丁被认为是一种能够干扰胚胎发育的致畸物质[87],可以经母体吸入通过胎盘传递给胎儿并在胎儿体内积累对胎儿产生不良影响,研究发现孕妇吸烟在胎儿循环中产生比孕妇更高的尼古丁浓度[88]。

4.2. 肺

有流行病学研究报告称,孕期香烟烟雾暴露会增加后代上呼吸道和下呼吸道感染、哮喘[89]、喘息[90]、肺动脉高压和后代肺功能受损的风险[90][91]。肺部发育缺陷通常与肺功能受损和呼吸系统疾病的

发病率增加有关[92]。母鼠孕期内接触香烟烟雾会显著影响幼崽的肺部的发育和生长, 表现为幼崽肺容积低, 造成幼崽具有较高的基线气道阻力、组织阻尼和组织弹性, 并且幼鼠的整体尺寸较小, 因此肺部较小, 这可能会使肺功能受到损害[93]。并且发现孕鼠孕期暴露于香烟烟雾中会增加子代在以后的生活中患肺部疾病的易感性[94]。妊娠期暴露于香烟烟雾中的有害物质尼古丁可能会受到不利影响, 尼古丁可能会破坏肺部的发育过程[95]。如促使动物胚胎干细胞分化为成纤维细胞, 而影响胚胎干细胞分化[96]。且使成纤维细胞层胶原蛋白表达增加和气道壁厚度增加, 可能会造成气道的口径和柔韧性的降低[97] [98], 肺泡发育不全[99], 增加呼吸时的肺阻力。

4.3. 肾

孕妇吸烟可能导致胎儿肾脏变小[100], 肾单位数量减少[100], 也发现新生儿肾小球未成熟[101] [102], 且使个体易发生肾损伤, 进而出现高血压、肾功能受损[103]和成年后易患肾脏疾病[100] [104]。对怀孕大鼠进行香烟烟雾冷凝物处理, 分娩 12 周的后代会出现平均肾小球体积、足细胞、系膜细胞和内皮细胞数量较低[105]。

4.4. 心脏

孕妇吸烟会增加胎儿患先天性心脏缺陷和冠心病的风险[25] [106] [107] [108]。相似的是, 当孕妇在怀孕早期暴露于二手烟可能也会增加后代冠心病的风险[109] [110]。孕期配偶吸烟也会增加胎儿孤立性圆锥形心脏缺(isolated conotruncal heart defects)、间隔缺损和左心室流出道梗阻的风险[111]。

尼古丁产前暴露对胚胎心脏发育的影响机制尚不清楚, 而氧化应激是胎儿冠心病和冠状动脉畸形发病机制的原因之一[112]。孕期尼古丁暴露, 在小鼠胚胎心脏中检测到较高的活性氧物质(reactive oxygen species, ROS)和脂质过氧化物[113], 而这些活性氧物质, 会破坏细胞内源性抗氧化能力, 从而降低细胞增殖[114]。

4.5. 肝脏

在早期妊娠终止形态正常胎儿的肝脏组织中蛋白质组学研究发现, 孕妇吸烟会影响胎儿肝脏组织内参与翻译后蛋白质加工和分泌的蛋白以及参与应激反应和解毒的蛋白质都发生了变化[115], 此外研究发现, 四种肝脂肪酸摄取转运蛋白(SLC27A3、SLC27A4、SLC27A6、GOT2)的 mRNA 水平也有所下降[116]。

孕鼠妊娠期香烟烟雾暴露也会导致胎鼠肝脏组织中 DNA 加合物的形成, 并且上调了肝脏中 116 个基因的表达, 这些基因参与代谢、氧化应激反应、DNA 和蛋白质修复以及信号转导, 并且刺激促凋亡基因的表达和下调细胞周期的基因[117]。这些基因表达的改变, 是否会对胎鼠的健康产生严重影响, 还有待进一步研究。

5. 总结与展望

目前研究发现孕妇暴露香烟烟雾, 会对胎儿的许多组织和器官如脑、肺、心脏、肾、肝脏等造成不同程度的影响, 然而造成这些影响的主导分子和机制尚不明确。这些影响对胎儿发育及生理功能产生的长期作用也不清楚。借由动物模型可进一步了解这些科学问题相关生理病理机制。这些研究可以帮助预防胎儿受到香烟烟雾中有害物质产生的不良影响。并且可倡导社会为孕妇提供一个无烟害的环境, 改善孕妇和胎儿的健康状况。

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