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烟毒暴露的机体毒性研究进展

曾惠,李小清,吕晓东,冷嘉鹏
(辽宁中医药大学,辽宁 大连 116600)

摘要:目的 对烟草产品和烟气中的各毒性成分及其作用机制进行综述,以期更好地开展对烟毒所致疾病的研究。方法 对有关细胞培养、动物模型和人体暴露的烟毒研究文献进行查阅、比较与分析,并对其进行归纳整理与综述。结果 烟草烟雾中含有多种有毒成分,包括尼古丁、一氧化碳、胺类、酚类、烷烃、醛类、多环芳烃、氮氧化合物和重金属元素等,且对多种癌症,包括肺癌、胰腺癌、卵巢癌、膀胱癌、心脑血管疾病等都具有明显的促进作用。此外,烟毒所致疾病的作用机制具有多样性,主要涉及增加氧化应激水平、促进 DNA 加合物产生、诱导趋化因子生成、影响烟碱型乙酰胆碱受体(nicotinic acetylcholine receptor,nAChR)介导的各种通路等方面。结论 烟草流行是世界迄今面临的最大公共卫生威胁之一,每年导致许多人死亡。中医病因学研究中的烟毒,即人体吸入的烟草燃烧产生的烟气,是一种兼具燥热之性的毒邪。目前对烟毒中致癌物质的研究比较广泛,但是从人体多个系统入手研究烟毒暴露所致的疾病相对较少。因此明确烟毒的致癌成分,并探究其作用机制,以期扩大中医病因学研究范围。

关键词:病因学;作用机制;烟毒;人体九大系统
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Research Progress on Toxicity Induced by Cigarette Exposure

ZENG Hui, LI Xiaoqing, LYU Xiaodong, LENG Jiapeng
(Liaoning University of Traditional Chinese Medicine, Dalian 116600, Liaoning, China)

Abstract: *Objective* To review the toxic components and their mechanisms of action in tobacco products and smoke, in order to better carry out the research on the diseases caused by tobacco toxin. *Methods* The literature on cell culture, animal models and human exposure to tobacco toxicity was reviewed, compared and analyzed, and their literature was summarized and reviewed. *Results* Tobacco smoke contains a variety of toxic components, including nicotine, carbon monoxide, amines, phenols, alkanes, aldehydes, polycyclic aromatic hydrocarbons, nitrogen oxides and heavy metals, and has a significant promoting effect on a variety of cancers, including lung cancer, pancreatic cancer, ovarian cancer, bladder cancer, cardiovascular and cerebrovascular diseases. In addition, the mechanisms of action of diseases caused by tobacco toxicity are diverse, mainly involving increasing the level of oxidative stress, promoting the production of DNA adducts, inducing chemokines, and affecting various pathways mediated by nicotinic acetylcholine receptor(nAChR). *Conclusion* The tobacco epidemic is one of the greatest public health threats that the world is facing to date, killing many people each year. Tobacco toxicity in the etiology of traditional Chinese medicine, that is, the smoke produced by the combustion of tobacco inhaled by the human body, is a kind of toxin that has the characteristics of dry heat. At present, there is a wide range of research on carcinogens in tobacco toxin. However, there are relatively few studies on the diseases caused by exposure to tobacco toxins from multiple systems in the human body. Therefore, the carcinogenic components of tobacco toxicity should be clarified, and its mechanism of action should be explored, in order to expand the scope of etiological research in traditional Chinese medicine.

Keywords: etiology; mechanism of action; tobacco poisons; nine systems of human body

国家卫生健康委员会发布的《中国吸烟危害健康报告2020》[1]指出,我国是全球最大的卷烟生产国和消费国,烟民超过3亿,每年因吸烟死亡的人数超过100万,超过结核病、艾滋病和疟疾导致的死亡人数总和。

吸烟与中医的毒邪理论有着深厚的渊源[2-6]。《本草害利》对烟草的描述为"火气熏灼,最烁肺阴,耗血损年,卫生者宜远之"。经常吸烟者易生痰浊,伤神耗血,《本草纲目拾遗·烟草火》曰:"予乃悟向之痰咳,悉烟之害也,耗肺损血世多阴受其祸而不觉"。《诸病源候论》强调了毒气是重要的致病因素。烟雾性多火热燥烈。《调疾饮食辨》载:"论其味辛气烈,自非和平之物……此则燃之以火,熏其喉舌。"以火热为本,其性属阳。烟草以草木为体,草木皆能生火,故烟雾首先具有火热之性,属阳邪。其火热程度,既不同于外感六淫之暑、热,也不同于内伤之火热,烈于六淫与七情之火。香烟毒邪严重危害人类健康,其有别于传统的六淫之邪毒,是集火、

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作者简介:曾惠(1999-),女,江西赣州人,硕士在读,研究方向:生药学。
通讯作者:冷嘉鹏(1985-),男,辽宁丹东人,教授,博士研究生导师,博士,研究方向:中西医结合预防医学、药学。E-mail:jpleng@126.com。

热、燥、涩、浊、秽、毒于一气,汇集多种性质于一体的复合性致病因素。

目前,采取各种行政和立法手段难以完全控烟,在不能全面戒烟的情况下,吸烟对健康的威胁已经成为一个严峻的社会医学问题[7],建立针对香烟毒邪的中医研究体系迫在眉睫。本文就吸烟对人体各个系统的毒性进行综述,为研究烟草毒邪致病提供重要参考依据。

1 表现在呼吸系统的毒性

WANG G Z 等[8]用烟草致癌物亚硝胺酮(nicotine - derived nitrosamine ketone,NNK)处理正常人肺上皮细胞 60 d 后发现 NNK 可以诱导趋化因子 CCL20 的产生,而 CCL20 能促进肺癌细胞增殖和迁移。多环芳烃(polycyclic aromatic hydrocarbons,PAHs)作为烟草烟雾的主要致癌物。WANG G Z 等[9]发现苯并(a)芘[bezo(a)pyrene,BaP]诱导小鼠肺上皮细胞产生趋化因子 CXCL13,这表明 CXCL13 在 PAHs 诱导的肺癌发生中起着关键作用。白细胞介素 8(interleukin - 8,IL - 8)是诱导肺炎发生和发展的关键趋化因子。KO H K 等[10]发现 AMPK/MAPKs/NF - κB 信号通路对诱导 IL - 8 产生至关重要的作用。体外研究表明,C - C 趋化因子受体(C - C chemokine receptor,CCR1)通过调控 JAK/STAT3/NF - κB 信号通路在调节烟雾诱导的炎症反应中发挥重要作用[11]。IL - 22 通路通过增加经上皮阻力和上皮细胞再生和修复来保护肺功能。作为香烟的有毒和成瘾性成分,尼古丁会损害支气管上皮细胞的再生能力。NGUYEN H M 等[12]实验数据证明尼古丁对 IL - 22 - IL - 22R 轴有负面影响,这种损伤可能是尼古丁介导的对肺功能的不利影响。当暴露于尼古丁时,小鼠显示出明显的炎症反应和肺蛋白酶变化[13]。YEAGER R P 等[14]发现吸入香烟烟雾引起的丙烯醛暴露会导致氧化损伤、细胞坏死和慢性炎症循环,随着时间的推移会导致呼吸道组织重塑和破坏,最终表现为慢性阻塞性肺疾病(chronic obstructive pulmonary disease,COPD)。BODAS M 等[15]却认为 COPD 的潜在机制是尼古丁通过活性氧(reactive oxygen species,ROS)介导的自噬损伤诱导支气管上皮细胞凋亡和衰老而引起。然而 MANEVSKI M 等[16]最新的研究表明 LASI lncRNA 可能是控制气道反应失调和 COPD 恶化的新靶点。CHAYA S 等[17]发现产前和产后烟草暴露会损害学龄前儿童肺功能。NOËL A 等[18]将受孕小鼠暴露于二手烟雾(second - hand smoke,SHS)并监测子代小鼠成年后的肺功能状况,研究发现在子代为雄性的小鼠中,子宫内单独暴露 SHS 会改变成年后小鼠的肺功能和结构。PHAM A K 等[19]探究小鼠暴露于烟草烟雾(tobacco smoke,TS)12 周后是否能加剧 COPD 样细胞的病理生理过程,研究发现烟草烟雾暴露可导致持续性肺损伤和炎症反应。有研究表明暴露于环境烟草烟雾(environmental tobacco smoke,ETS)的儿童尿中可替宁(urinary cotinine,UC)水平较高。与不暴露于烟草烟雾的儿童相比,受烟草烟雾影响的儿童患呼吸系统疾病的风险很高;且 UC 水平越高,儿童患呼吸疾病的风险越大[20]。与儿童期未接触 ETS 的女性相比,儿童期暴露于 ETS 的女性患 COPD 的可能性是男性的两倍,而男性肺功能损害的风险略有增加[21]。

2 表现在内分泌系统的毒性

内分泌系统由内分泌器官和内分泌组织组成,内分泌细胞通过分泌不同的激素维持身体稳态。REHAN M 等[22]研究发现尼古丁及其 3 种代谢物(可替宁、反式 - 3′ - 羟基可替宁、5′ - 羟基可替宁)可能会干扰睾酮、雌二醇、皮质醇、孕酮、甲状腺素和三碘甲腺原氨酸与其载体蛋白的结合,导致其在血液循环中的运输和稳态失衡。已有研究表明尼古丁通过下丘脑 - 垂体 - 终末器官轴而损害内分泌系统[23]。下丘脑 - 垂体 - 甲状腺轴由下丘脑分泌的促甲状腺激素释放激素(thyrotropin - releasing hormone,TRH)激活,然后刺激垂体前叶释放促甲状腺激素(thyroid stimulating hormone,TSH)。TSH 诱导甲状腺产生和释放三碘甲状腺素(triiodothyronine,T3)和甲状腺素(thyroxine,T4)。ABDELHAFEZ A M 等[24]通过定量测定血清中总 T3、总 T4 和总 TSH,使用组织学方法研究子宫内暴露于尼古丁对 1 月龄大鼠垂体 - 甲状腺轴的影响,结果表明尼古丁激活甲状腺滤泡和滤泡旁细胞,降低甲状旁腺细胞活性。而且吸烟会急剧激活下丘脑 - 垂体 - 肾上腺轴而导致皮质醇水平升高[25]。YUAN S 等[26]通过一项孟德尔随机研究提供遗传证据证明吸烟与 2 型糖尿病之间存在正向因果关系。然而,吸烟和 2 型糖尿病之间因果关系背后的机制尚不完全清楚。TONG X 等[27]研究结果表明 CS 会通过氧化应激和神经酰胺积累导致胰岛素生成、加工和分泌受损,β 细胞活力和增殖降低,从而破坏葡萄糖稳态。TOPSAKAL S 等[28]还发现香烟烟雾会对大鼠胰腺的内分泌和外分泌细胞造成损伤。ALAHMARI A A 等[29]实验数据表明,尼古丁代谢物 NNK 会导致胰蛋白酶原活化和细胞损伤,从而引发胰腺炎,而这些效应是通过非神经性 α7 - 烟碱型乙酰胆碱受体(nicotinic acetylcholine receptor,nAChR)通路介导。

3 表现在循环系统的毒性

ETS 不仅直接影响内皮细胞的活性,也会导致其功能改变,最终导致内皮细胞受伤。EL - MAHDY M A 等[30]利用小鼠吸烟暴露诱发心血管疾病的模型发现慢性 CSE 会通过白细胞介导的氧化应激的恶性循环引发血管内皮功能障碍(vascular endothelial dysfunction,VED)。除此之外,ETS 可以通过炎症反应影响脂质分布,增加动脉僵硬度和促进血栓形成加速动脉粥样硬化[31]。PAWEL G 等[32]综述了 ETS 暴露可能会导致心血管系统的形态和功能变化,如 ETS 暴露可能会通过诱导左心室轻度肥大和主动脉根部几何形状的变化而对心脏形态产生不利影响。LEONE A[33]却认为吸烟引起的改变始于功能性损害,功能性损伤会发生形态学改变,而形态学改变最初是可逆的,后来不可逆。研究表明在众多与心血管系统疾病相关的烟草成分中,尼古丁和一氧化碳(carbon monoxide,CO)起主要损害作用[33-34]。尼古丁是通过结合 nAChR 代替内源性激动剂 ACh 而影响心血管系统[35]。尼古丁可以通过刺激交感神经系统而作用于心血管系统,从而释放去甲肾上腺素,并增加肾上腺素的释放。此外,尼古丁还可以增加心率、血压、心肌收缩力和全身血管收缩而引起全身血流动力学变化[34]。CO 是由碳氢化合物不完全燃烧产生的,是吸烟的副产物,它改变了血红蛋白与氧气的结合。长期吸烟者的碳氧血红蛋白(carboxyhemoglobin,COHb)浓度通常高达 10%[36]。一氧化碳通过双重机制产生羧基血红蛋白除去氧气,组织缺氧和细胞内呼吸功能受损则进一步加剧对心血管系统的损伤程度[33]。即使每天只抽一根烟,也会增加患心血管疾病(cardiovascular disease,CAD)的风险。HACKSHAW A 等[37]研究清楚地表明,要想减少患心血管类疾病的风险,吸烟者应该以戒烟为目标,而不是减少吸烟。更严重的是,孕妇在怀孕期间暴露于烟草环境会导致胎儿在子宫内接触到烟草成分,这不仅会对母体造成损伤,一项中国西北地区的孕产妇二手烟暴露与婴儿患出生缺陷的横断面研究表明,母体暴露于 SHS 可能会增加后代出生缺陷(尤其是循环系统缺陷)的风险[38]。

4 表现在生殖系统的毒性

香烟中的毒性物质能通过吸烟者的血液循环进入体内生殖系统,影响生殖细胞并造成遗传物质损伤,对后代产生不利影响。OZ M 等[39]探讨了 α7nAChR 与 G 蛋白相互作用在 MCF-7 乳腺癌细胞增殖、运动和钙信号传导中的作用。Mir-7a 是卵母细胞和卵巢中最丰富的 miRNA 之一,通过调节减数分裂活性来干预卵母细胞发育[40]。研究表明,长时间的烟雾暴露会诱导卵母细胞中的 miRNAs 改变,这可能不利于胚胎着床和发育,且香烟烟雾对 miRNAs 的影响与暴露时间有关[41]。LIU H G 等[42]首次采用动物模型研究 1-(N-甲基-N-亚硝基氨基)1-(3-吡啶基)-4-丁醛[1-(N-methyl-N-nitrosamino)1-(3-pyridinyl)-4-butanal,NNA]对小鼠卵巢卵泡和子代发育的毒性作用,结果显示 NNA 会减少卵巢卵泡数量和卵母细胞存活率,并影响断奶前子代发育。CHENG S F 等[43]用尼古丁体外培养人胚胎卵巢生殖细胞的实验证明了卵巢细胞凋亡可能是由 ROS 水平增加和 DNA 损伤造成。GANNON A M 等[44]研究结果却表明,CS 暴露不会诱导细胞凋亡,而是激活 Atg 途径,最终导致卵巢卵泡丢失。PACCOLA C C 等[45]最近的研究发现,在孕期和母乳喂养期间将大鼠暴露于尼古丁(相当于适度的人类吸烟剂量)不会减少每个周期释放的卵母细胞数量。但是,它会引起卵母细胞质量的轻微改变,如片段化、细胞大小的变化和卵黄周围空间变化。不仅如此,CS 会诱导子宫和卵巢异常发育。KIM S M 等[46]实验结果显示 CS 暴露后,子宫内雌激素受体(estrogen receptor,ER),C-X-C 趋化因子受体 4 型(C-X-C chemokine receptor type4,CXCR4)和基质金属肽酶 9(matrix metallopeptidase 9,MMP9)的表达上调,卵巢内黄体、囊性卵泡、ERα 和 CXCR4 的增加,MMP9 蛋白的产生,均会对雌性大鼠生殖器官正常功能产生不良影响。除了损害雌性鼠的生殖系统健康,吸烟也会对雄性鼠产生危害。MOHAMED M 等[47]证明了 CS 暴露显著增加大鼠附睾和腹侧前列腺的相对重量。OYEYIPO I P 等[48]用不同浓度的尼古丁处理精子并与仅悬浮在营养液中的精子进行比较后发现,高浓度尼古丁暴露可能会通过影响精子运动能力,顶体反应而造成人类受精能力受损。而且孕期母亲吸烟,那么其子宫里的男婴出生后睾丸更小,精液质量受损,该研究证明产前吸烟与子代男性的生殖健康受损有关[49]。总之,吸烟通过降低精液的重要参数而影响男性生育能力,但 LINGAPPA H A 等[50]认为烟毒暴露对精子活力的影响大于对精子数量的影响。

5 表现在运动系统的毒性

吸烟会造成骨骼肌功能障碍,并导致患有多种全身性疾病的患者预后恶化。据报道,许多 COPD 患者患有肌肉萎缩和肌无力等症状。已有研究表明吸烟会导致肌肉萎缩[51],肌肉氧化能力降低[52]和神经肌肉接头变性[53]。AN X 等[54]研究被动吸烟对女性患者接受全膝关节置换术(total knee arthroplasty,TKA)后的影响,发现被动吸烟引起疼痛和功能不良,加重抑郁和焦虑,恶化生活质量。THOME T 等[55]研究发现烟雾冷凝物激活了 AHR,引起线粒体损伤,并诱导 AHR 依赖性肌管萎缩。p38MAPKs 在肌生成的调节中起着核心作用[56]。BAO Z 等[57]研究认为 BaP 暴露诱导 C2C12 成肌细胞中的 MK2/Hsp70/p38MAPK 复合物降解,并通过蛋白酶体依赖性机制损害肌源性分化。GALITOVSKIY V 等[58]用高剂量尼古丁处理易受烟草诱导易患肺癌的 A/J 小鼠后发现长期尼古丁暴露可诱导肌肉肉瘤发展。然而,烟草烟雾暴露导致线粒体功能受损的潜在生化机制尚不清楚。KHATTRI R B 等[59]基于核磁共振的方法鉴别了香烟烟雾冷凝物(cigarette smoke condensate,CSC)中损害骨骼肌线粒体功能的化学物质。该实验鉴定了 CSC 中含量高的 49 种水溶性物质和 12 种脂溶性化学物质,结果表明尼古丁、邻甲酚、苯乙酸和癸酸,会严重抑制小鼠肌肉线粒体分离株中 ADP 刺激的呼吸。TORIGIAN D A 等[60]利用 18 氟脱氧葡萄糖-正电子发射断层扫描/计算机断层扫描(18F-fluorodeoxyglucose-positron emission tomography/computed tomography,FDG-PET/CT)检测长期暴露于烟草烟雾对全身器官的不良影响,结果显示长期吸烟与骨髓代谢活性降低显著相关。这表明吸烟会对骨髓产生毒性作用。除此之外,SCOLARO J A 等[61]证明吸烟明显增加骨折不愈合、胫骨骨折和开放性骨折的风险。

6 表现在消化系统的毒性

口腔是吸烟过程中第一个暴露于烟气溶胶的组织,当烟草烟雾中的有害化学物质经过口腔时,经过长时间的接触,这些化学物质会使口腔龋坏部位发生变化。NISHIOKA T 等[62]发现尼古丁通过表皮生长因子(epidermal growth factor,EGF)信号传导促进细胞生长和迁移,在口腔癌进展中发挥重要作用。而 JIANG X G 等[63]通过研究发现烟草可引起口腔上皮细胞的表观遗传改变,抑制宿主的多种全身免疫功能,并通过其有毒代谢产物对组织造成氧化应激,从而诱发口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)。口腔微生物组是仅次于肠道微生物组的第二大组织,对人体的健康状况有很大影响。SUZUKI N 等[64]发现在健康的日本成年人中,吸烟者和不吸烟者的唾液和舌头上的微生物在属种水平上存在差异,这表明吸烟者可能面临口腔异味和未来牙周炎的风险。SEO Y G 等[65]调查了韩国成年人中使用不同类型烟草产品与呼吸道疾病和过敏性疾病的患病率,研究发现使用加热烟草制品(heated tobacco products,HTPs)与过敏性鼻炎有关。ETEMADI A 等[66]测量了尿液中尼古丁、多环芳烃、挥发性有机化合物和烟草特异性亚硝胺等 33 种烟草暴露生物标志物的浓度,发现在使用烟草制品的人群中,苯乙烯、二甲苯和 2 种烟草特异性亚硝胺与食管鳞状细胞癌有关。越来越多的证据表明,吸烟与肝脏疾病的进展有关,尤其是肝纤维化和肝癌。BUDANI M C 等[67]总结了吸烟对肝病的影响,发现吸烟可以通过组织缺氧,铁积累,胰岛素抵抗,肝细胞损伤,全身、组织炎症,氧化应激和脂质过氧化等各种途径导致肝纤维化。不仅如此,ZHANG J L 等[68]研究表明香烟烟雾通过 N^6-甲基腺苷(N^6-methyladenosine,m^6A)刺激 miR-25-3p 过度成熟促进了胰腺癌的发展。WITTEL U A 等[69]却认为烟草产品对胰腺癌的诱导是多因素的。他们认为香烟烟雾成分可通过两种作用方式促进胰腺癌的发生,第一种是通过干扰生理途径,第二种是通过与 DNA 的相互作用。LIAN S 等[70]发现尼古丁通过 ROS/NF-κB 和 ROS/MAPK(Erk1/2,p38)/AP-1 轴诱导 IL-8 的表达,从而刺激肿瘤微环境中内皮细胞的增殖和血管生成,这项研究揭示了尼古丁可促进胃癌进展的事实。WIDBOM L 等[71]测定血浆中的可替宁的浓度后发现吸烟是晚发性炎症性肠病(inflammatory bowel disease,IBD)的一个危险因素。ZHOU X 等[72]通过双样本孟德尔随机分析后发现吸烟、甲基化对结肠癌(colorectal cancer,CRC)的风险归因于两个 CpG 位点。

7 表现在免疫系统的毒性

吸烟会影响先天免疫和适应性免疫,并通过加剧致病性免疫反应或减弱防御性免疫而在调节免疫中起双重作用。受吸

烟影响的适应性免疫细胞主要包括辅助性 T 细胞、$CD4^+$ $CD25^+$ 调节性 T 细胞、$CD8^+$ T 细胞、B 细胞和记忆 T/B 淋巴细胞，而受吸烟影响的先天免疫细胞主要是 DCs 巨噬细胞和 NK 细胞[73]。VALIATHAN R 等[74]研究了吸烟对 HIV 感染者免疫激活、微生物易位、免疫衰竭和 T 细胞功能的影响，结果表明吸烟和 HIV 感染分别影响 T 细胞免疫激活和功能，并共同造成最差的免疫状况。LIANG F 等[75]分析了香烟烟雾提取物对吲哚胺 2，3 - 双加氧酶 1（Indoleamine2，3 - dioxygenase 1，IDO1）表达的影响，并探讨了其潜在机制。他们发现 NNK 通过（nAChR）- c - JUN - IDO1 通路诱导 Trp/Kyn 失衡，抑制 $CD8^+$ T 细胞以及促进调节性 T 细胞。烟草有毒物质除了影响免疫细胞群的循环水平外，还会损害气道上皮细胞的屏障功能，影响免疫活性物质的释放。HAM J 等[76]研究表明，吸烟通过诱导激活因子 IL - 1β，促进 3 型先天性淋巴细胞（natural - cytotoxicity - receptor - non - expressing type 3 innate lymphoid cells，ILC3）的产生，从而加重哮喘和非过敏性炎症。微生物脂多糖（lipopolysaccharides，LPS）与类风湿性关节炎（rheumatoid arthritis，RA）的发病机制有关，可能导致全身炎症反应。MEYER P W A 等[77]发现接触烟草制品可能是 LPS 的来源。尽管有证据表明成人接触镉（cadmium，Cd）会引起免疫系统的变化，但关于产前接触 Cd 而损害免疫系统的报道有限。HANSON M L 等[78-79]将受孕小鼠暴露于环境剂量的 CdCl2，并在小鼠出生后两个时间点评估 Cd 对后代免疫系统的影响，研究表明即使妊娠期间 Cd 暴露水平很低，也可能对后代的免疫系统造成长期不利影响，并且这些有害影响在一定程度上具有性别特异性。吸烟不仅有害健康，更重要的是，吸烟造成的损伤往往是不可逆的。一项关于吸烟如何影响健康女性的白细胞亚群比例的研究发现，主动吸烟引起的外周血中免疫细胞组成的变化主要影响免疫抑制分子标记的细胞亚群，且吸烟引起的变化即使在戒烟后数年内也不会完全恢复[80]。

8 表现在神经系统的毒性

烟草烟雾不仅损害免疫系统，而且还会引发神经系统疾病，例如阿尔茨海默病（Alzheimer's disease，AD）。研究表明，长时间暴露于香烟烟雾和尼古丁会造成氧化应激，导致淀粉样 Aβ 蛋白异常沉积和 τ 蛋白过度磷酸化，最终加快 AD 进程[81]。WU P L 等[82]研究吸烟对认知正常的老年人中多种 AD 生物标志物的影响，发现吸烟与记忆障碍、海马体萎缩和脑葡萄糖代谢低有关。LU R 等[83]通过调查大量样本后发现每日接触 SH 与缺血性脑卒中的高风险相关。可替宁通过胶质纤维酸性蛋白（glial fibrillaryacidic protein，GFAP）和 2，3 - 环核苷酸 3 - 磷酸二酯酶（2，3 - cyclic nucleotide 3 - phosphodiesterase，CNP）的表达对脊髓损伤（spinal cord injury，SCI）产生有害影响[84]。丙烯醛通过 TRPA1 通道对 SCI 后脆弱的中枢神经系统构成威胁，加剧神经性疼痛[85]。一项荟萃分析显示，与健康成年人相比，吸烟使睡眠质量降低[86]。除上述危害外，有研究表明吸烟会损害子代的神经系统。SALIHU H M 等[87]发现吸烟会造成脐带血中控制胎儿大脑生长和发育的基因 BDNF、PLP1 和 MBP 下调。此外，一项涉及 9000 例成人的样本数据显示孕期暴露于吸烟环境对胎儿大脑皮质发育有长期负面影响[88]。LEE M 等[89]发现孕期接触二手烟可能会影响婴儿的智力发育商数（Mental developmental index，MDI）。KARIN O 等[90]强调了儿童早期暴露于烟草烟雾与自身执行能力缺陷之间的关联。以上研究都显示，女性孕期和儿童早期暴露于烟草烟雾均会损害孩童的大脑发育。然而有趣的是，自 DORN H 在 60 年前首次提出吸烟可以降低患帕金森病（Parkinson's disease，PD）的风险后，越来越多的研究证明了烟草产品对 PD 死亡风险的保护作用[91-92]。

表 1 烟毒各成分作用机制/作用途径

文献	成分	作用机制/作用途径
[8]	NNK	诱导趋化因子 CCL20
[29]	NNK	介导非神经性 α7 - nAChR 通路
[75]	NNK	损害（nAChR）- c - JUN - IDO1 通路
[9]	BaP	诱导趋化因子 CXCL13
[57]	BaP	下调 Hsp70 - MK2 - p38MAPK
[97]	BaP	DNA 甲基化、DNA 加合物和 DNA 损伤增加
[12]	尼古丁	下调 IL - 22 - IL - 22R 轴
[24]	尼古丁	下调下丘脑 - 垂体 - 甲状腺轴
[25]	尼古丁	激活下丘脑 - 垂体 - 肾上腺轴
[35]	尼古丁	结合内源性烟碱胆碱能受体 nAChRs
[43]	尼古丁	ROS 水平增加
[46]	尼古丁	CXCR4 和 MMP9 上调
[70]	尼古丁	通过 ROS/NF - κB 和 ROS/MAPK/AP - 1 轴诱导 IL - 8 表达
[81]	尼古丁	Aβ 蛋白异常沉积和 τ 蛋白过度磷酸化
[36]	CO	抑制血红蛋白与氧气结合
[59]	邻甲酚、苯乙酸	抑制肌肉线粒体功能
[78]	镉	减少 $CD8^+CD223^+$ 细胞数量
[84]	可替宁	影响 GFAP 和 CNP 的表达
[85]	可替宁	上调 TRPA1 阳离子通道
[99]	丙烯醛	诱导丙烯醛 - DNA 加合物，抑制 DNA 修复

9 表现在泌尿系统的毒性

膀胱癌（bladder cancer，BC）是泌尿道最常见的癌症，是全球第九大常见癌症。吸烟是 BC 发展的主要危险因素，可使患膀胱癌的风险增加 2 ~ 4 倍。CUMBERBATCH M G 等[93]用 Meta 分析证明吸烟会显著增加膀胱癌和肾细胞癌（renal cell cancer，RCC）的发病风险，且吸烟意味着更高的疾病特异性死亡率（disease - specific mortality，DSM）。HOU L 等[94]的研究同样支持了这一结论。REZAEI F 等[95]通过一项生态学分析发现亚洲国家膀胱癌发病率与癌症患者每日烟草使用量之间存在显著关系。GROTENHUIS A J 等[96]评估了吸烟状况、吸烟强度以及戒烟时机对非肌肉浸润性膀胱癌（non - muscle - invasive bladder cancer，NMIBC）患者的影响，研究结果显示，在诊断前任何时候的吸烟状况、吸烟强度和是否戒烟似乎都不会改变 NMIBC 的复发风险。JIN F 等[97]探究 BC 吸烟者和非吸烟者的代谢特征，最终得出 NNK 和 BaP 会导致 BLCA 细胞中甲基化代谢物、DNA 加合物水平增加和广泛的 DNA 损伤。而 MIASKOWSKA W 等[98]认为这是 BC 患者暴露于致癌物质改变蛋氨酸代谢的结果。大部分二手烟源自侧流烟雾（side stream smoke，SSS），与主流烟气相比，SSS 含有更多的致瘤性的多环芳烃和丙烯醛（acrolein，Acr）。LEE H W 等[99]将小鼠暴露于 SSS 16 周后发现，SSS 通过诱导丙烯醛 - DNA 加合物，抑制 DNA 修复和促进细胞转化导致膀胱癌发生。BEEGAM S 等[100]建立小鼠慢性肾功能衰竭模型旨在探讨吸入水烟后加重小鼠慢性肾功能衰竭的程度，以及产生这种危害的可能机制。结果表明吸入水烟会加重 CKD 小鼠的肾损伤、氧化应激、炎症、DNA 损伤和纤维化，这些作用与 NF - κB、ERK 和 p38 的激活机制有关。

10 讨论

尽管人们普遍意识到烟草产品会导致癌症，但世界上仍有

超过 10 亿种此类产品的用户。烟草产品造成的发病率和病死率仍然高得令人无法接受[101]。烟草和烟草烟雾中含有上千种有害物质,各有害物质单独或共同作用于细胞水平,影响细胞的功能与数量,进而影响各组织的正常运作,最终导致各系统的功能异常,疾病由此发生(插页XX图 1)。本文从人体九大系统入手,综述了烟草对人体各系统产生的毒性危害,烟毒各成分作用机制/作用途径如表 1 所示,是烟草毒邪致病理论的重要基石,为完善针对香烟毒邪的中医临床研究体系构建作铺垫。

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独活化学成分及药理作用研究进展

（正文见 129－144 页）

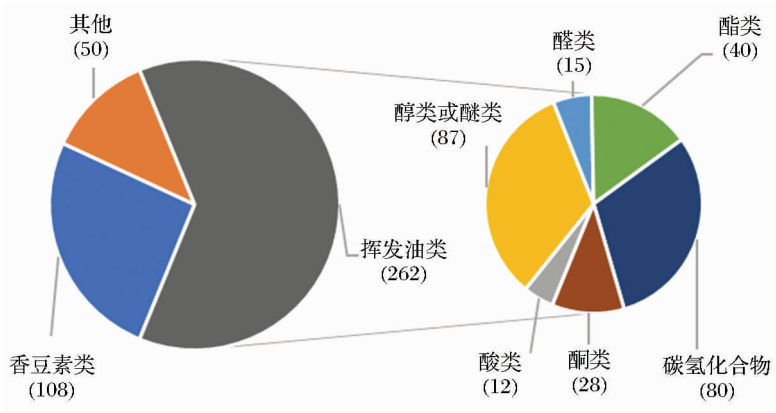


图 1　独活中化合物类别及数量

烟毒暴露的机体毒性研究进展

（正文见 182－188 页）

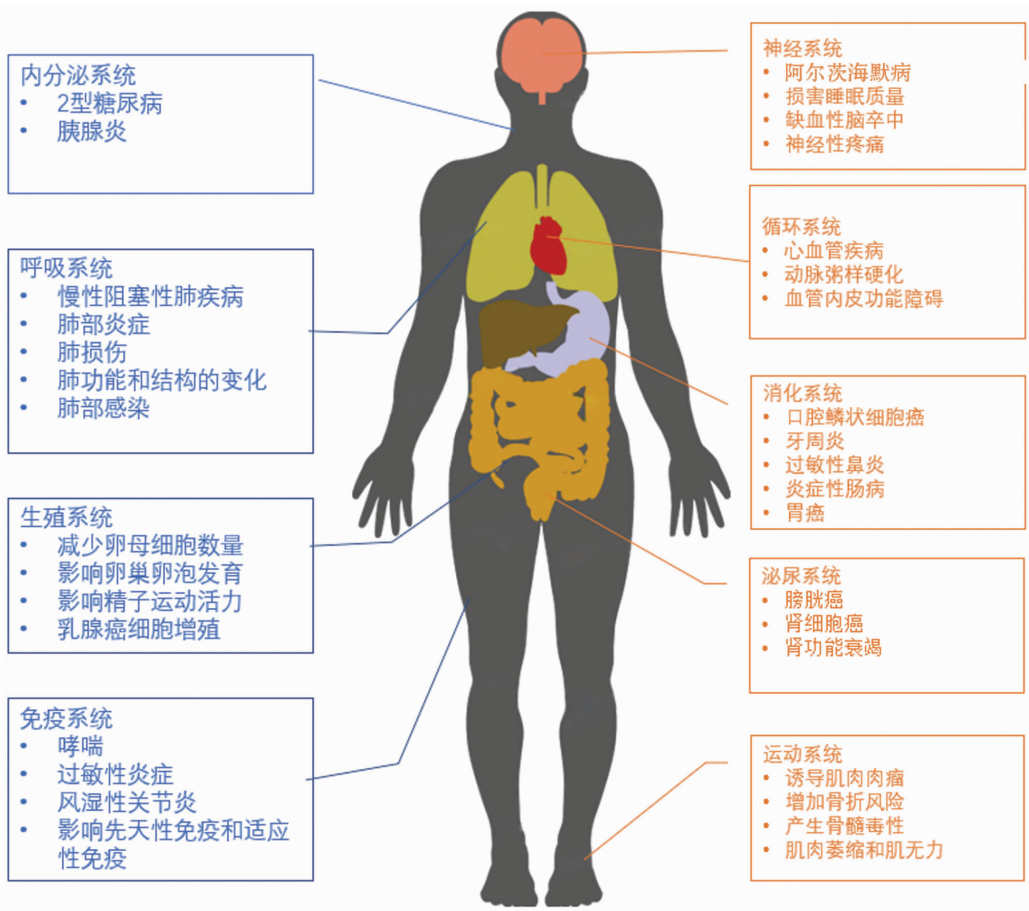


图 1　烟毒相关疾病