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Research Progress of Developmental Toxicity of Acrylamide

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Abstract

In China, polyacrylamide used for municipal water supply and oil exploitation can be degraded to acrylamide which is harmful to human body under natural conditions. Swedish National Food Administration also found high content of acrylamide in fried and baked starchy foods in 2002. At present, most studies focus on the neurotoxicity and carcinogenicity of acrylamide. There is limited research on its developmental toxicity. This article introduces the basic properties and metabolism of acrylamide, and summarizes the food rich in acrylamide. This review focuses on the embryonic, nervous system, cardiac and reproductive organ developmental toxicity of acrylamide.

Keywords

Acrylamide, Developmental Toxicity

丙烯酰胺发育毒性的研究进展

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摘　要

在我国，用于市政供水和石油开采的聚丙烯酰胺可在自然条件下降解为对人体有害的丙烯酰胺。瑞典国

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家食品管理局2002年在油炸烘焙的淀粉食品中也发现高含量的丙烯酰胺。目前研究多集中于丙烯酰胺的神经毒性和致癌性，缺乏对其发育毒性的系统研究。本文介绍了丙烯酰胺的基本性质、丙烯酰胺含量较高的食品种类和丙烯酰胺体内代谢情况，并重点综述了丙烯酰胺的胚胎发育、神经发育、心脏发育和生殖器官发育的毒性研究。

关键词

丙烯酰胺，发育毒性

1. 引言

丙烯酰胺(Acrylamide)是无色无味的白色晶体，相对分子质量为 71.08。图 1 即为丙烯酰胺的结构示意图。丙烯酰胺用作单体可以合成具有增稠絮凝作用的聚丙烯酰胺，应用于供水处理、废水处理和实验室凝胶电泳操作等领域[1]。丙烯酰胺也用于造纸、木材和纺织行业，在化妆品和香烟中也可以检测到丙烯酰胺的残留，每支香烟的烟雾含有大约 1.10~2.34 μg 丙烯酰胺[2] [3] [4]。2002 年瑞典国家粮食管理局和斯德哥尔摩大学的科学家发现油炸和高温烘焙食品中的丙烯酰胺含量远远高于世界卫生组织(WHO)规定的饮水中的丙烯酰胺的含量[5] [6]。联合国粮农组织(FAO)和 WHO 下的食品添加剂联合专家委员会(JECFA)在第 64 次会议上宣布共获得 6752 个食品样本中丙烯酰胺的检测数据，涵盖的食品种类包括早餐谷物、土豆制品、咖啡制品、奶类、糖以及蜂蜜、蔬菜和饮料等主要消费食品[7]。其中又以高温加工的土豆制品(薯片、薯条)中丙烯酰胺的含量最高，平均含量达到 0.477 mg/kg，而最高含量可达 5.312 mg/kg。此外，坚果和咖啡也属于高丙烯酰胺含量的食品。WHO 和 FAO 通过对 17 个国家丙烯酰胺摄入量的评估，发现一般人群平均摄入量为 0.3~2.0 μg/kg BW/day，其中 90~97.5 百分数位的高消费人群摄入量在 0.6~3.5 μg/kg BW/day。如果按体重计，儿童丙烯酰胺的摄入量是成年人的两到三倍[8]。因为丙烯酰胺含量较高的食物主要是油炸薯类食品、咖啡食品和烘烤谷类食品，而我国人群摄入这三类食品的水平低于西方国家，因此推测中国人群的丙烯酰胺摄入水平应该低于 JECFA 评估的摄入水平。

丙烯酰胺的半数致死剂量(LD_{50})通常高于 150 mg/kg BW，当口服剂量大于 100 mg/kg BW 时，丙烯酰胺就能够产生急性毒性作用[8]。人群实验和动物实验均已证实长期暴露于丙烯酰胺会造成神经系统的损伤[9] [10]。而在体内和体外实验中，丙烯酰胺均表现出了致突变性和致癌性，这说明其具有潜在的基因毒性和生殖毒性[11] [12] [13]。

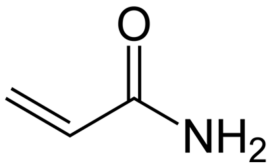

Figure 1. The structure of acrylamide
图 1. 丙烯酰胺的结构

2. 丙烯酰胺的代谢

丙烯酰胺可以通过真皮、呼吸系统和消化系统等多种途径被人体吸收，并可以广泛分布于各组织器官当中[14]。大鼠灌胃实验结果显示丙烯酰胺在肌肉中分布含量最高，可以达到 48%，皮肤占到 15%，血液占到 12%，肝脏占到 7%，只有不到 1%分布于大脑和脊髓当中[15]。丙烯酰胺还可以通过人类的胎盘屏障，并且母乳中也可以检测到其存在，说明丙烯酰胺可以通过母乳威胁婴儿的生长发育[16]。

丙烯酰胺可以通过细胞色素 CYP2E1 的代谢生成毒性更强的环氧丙酰胺[17]。丙烯酰胺也可在谷胱甘肽-S-转移酶的作用下与谷胱甘肽结合，代谢产物通过泌尿途径以巯基尿酸的形式排出体外[18]。在啮齿动物中，灌胃 0.1 mg/kg BW/day 的丙烯酰胺，生物利用度的范围在 23%到 48% [17]。丙烯酰胺在人体当中的半衰期大约是 4~6 小时[14]。环氧丙酰胺可以与 DNA 分子形成加合物，丙烯酰胺和环氧丙酰胺都可以与血红蛋白形成加合物，这些加合物均可以用来作为丙烯酰胺的生物暴露标志物[19]。丙烯酰胺及其代谢物环氧丙酰胺与人体内生物大分子的加合物很可能导致丙烯酰胺的生殖毒性、基因毒性、潜在的致癌性和发育毒性。

3. 丙烯酰胺的发育毒性

3.1. 胚胎发育毒性

越来越多的研究表明丙烯酰胺对妊娠和胚胎发育均能造成不良的影响。丙烯酰胺喂养(5 mg/kg BW/day, 10 mg/kg BW/day)能够显著减少小鼠和大鼠体内的精子数量($P < 0.05$)，并减弱精子的运动性，而且使得精子头部发育异常($P < 0.05$)，降低雄性小鼠和雄性大鼠的交配频率和受孕率($P < 0.05$) [20] [21]。丙烯酰胺处理(5~50 mg/kg BW/day)也可以改变雌性小鼠的动情周期，降低生殖器官的质量和体重，减少雌性体内黄体的数量并抑制雌性小鼠体内黄体酮的产生[22]。妊娠期内干预丙烯酰胺(10 mg/kg BW/day, 50 mg/kg BW/day)会降低活胎数，降低胚胎和胎盘的相对质量和绝对质量，并且可以下调胚胎发育关键基因 *Esx1*、*Hand1*、*Hand2* 的表达水平同时诱导细胞凋亡[23]。胚胎和婴幼儿的体型和成人相比更小，所以丙烯酰胺暴露水平可能更高，从而引起终身损伤[24]。两个欧洲大型母婴队列研究均证实怀孕期间丙烯酰胺的摄入与胎儿的生长状态呈负相关，丙烯酰胺的摄入显著影响了出生体重和胎儿头围等重要的胎儿发育指标[25] [26]。

3.2. 神经发育毒性

丙烯酰胺对成年动物的神经毒性已经很明确，但胚胎时期和哺乳时期丙烯酰胺对神经元发育的影响同样也具有研究意义。小鼠孕期连续灌胃 5 mg/kg BW/day 丙烯酰胺会导致胎鼠脑组织神经元结构退化，同时引起出血性损伤，并降低脑源性神经营养因子水平[27]。胚胎时期对大鼠灌胃丙烯酰胺(5 mg/kg BW/day, 10 mg/kg BW/day, 20 mg/kg BW/day)同样会减少新生鼠神经元数量，下调生长相关蛋白 43 (GAP-43)和突触素的表达[28]。孕期干预丙烯酰胺(25 mg/kg BW/day)还可以导致胎鼠脑组织坏死，引起氧化应激损伤，降低脑源性神经营养因子的水平[29]。产前和围产期干预丙烯酰胺(10 mg/kg BW/day)均会引起小脑氧化损伤，减少神经元细胞数量和破坏小脑的超微结构[30]。鸡卵内注射丙烯酰胺(1.25 mg/卵，2.50 mg/卵)虽然不会引起新孵化鸡死亡率和畸形率的显著上升，但是可以破坏新孵化鸡大脑中的抗氧化防御能力[31]。丙烯酰胺在神经组织发育期间主要通过引起氧化损伤、下调神经发育相关蛋白表达从而达到神经元细胞数量减少和神经细胞超微结构被破坏的效果。

3.3. 心脏发育毒性

心脏是脊椎动物体内最早发育和最早工作的器官[32]。胚胎时期心脏和血管的异常发育会导致心脏畸

形和功能异常，进而引发先天性心脏病。丙烯酰胺在斑马鱼早期心脏发育过程中会过度激活心肌细胞中的 Notch 信号通路，导致心室增厚，阻碍心小梁延伸，使得心脏发育异常[33]。另外，丙烯酰胺还可以扰乱心肌细胞中线粒体和肌原纤维的超微结构，可以使得心脏特异性转录因子(*nkx2.5*, *hand2*)的表达上调。在心脏的发育过程中，丙烯酰胺还可以引起心脏部位的氧化应激损伤，并通过减弱心肌细胞的增殖能力使得心肌细胞的数量减少[34]。以上研究结果均表明心脏也是丙烯酰胺发育毒性的潜在靶器官之一。

3.4. 生殖器官发育毒性

丙烯酰胺可以诱导成年雄性大鼠精子形态缺陷、降低睾丸尾部的精子浓度，血清睾酮水平和睾丸间质细胞活性[35]。由于饮食习惯，很多孕妇在产前、妊娠期间以及哺乳期间也会摄入高水平的丙烯酰胺，这些对胎儿早期生殖系统发育的影响难以忽视。雌性 SD 大鼠在怀孕期间和哺乳期间摄入丙烯酰胺(14 mg/kg BW/day)能够减少后代雄性大鼠的睾丸间质细胞、塞托利细胞和生精细胞的数量，增加氧化损伤水平并引起后代雄性大鼠生殖系统发育障碍[36]。雄性 F344 大鼠出生后连续 12 周干预 40 ppm 丙烯酰胺会导致睾丸中生精上皮的局灶性变性和坏死以及附睾管中的上皮脱落[37]。雄性小鼠用 1 μg/kg BW/day 的丙烯酰胺(即剂量相当于人体暴露于 10.5 μg/kg BW/day 的丙烯酰胺)长期干预 6 个月，能导致小鼠精子 DNA 损伤，并会造成后代雄性小鼠精子 DNA 的损伤和生殖细胞中 CYP2E1 酶活性的上升[38]。后代即使没有直接暴露于丙烯酰胺，上一代丙烯酰胺的暴露仍然会对下一代的生殖细胞产生危害。

4. 结论与展望

丙烯酰胺作为一种食品来源加工污染物和内分泌干扰物，具有来源广泛的特点，并且可以干扰代谢、生长和生殖[39]。尤其是在胚胎发育阶段，基因重编程和器官发育很容易受内分泌干扰物的影响。目前关于丙烯酰胺在胚胎期和发育早期的毒理学文章还较少。考虑到内分泌干扰物可能会不遵循经典毒理学剂量效应关系，以及发育早期更容易受到丙烯酰胺的影响，未来关于丙烯酰胺对于各个器官发育的潜在影响还值得进一步系统的研究。同时，也需要更多的研究和技术生产手段革新来确保各个食品体系中丙烯酰胺含量的进一步下降，以保证人体的健康。

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