Eco-Environmental Knowledge Web

生态毒理学报
Asian Journal of Ecotoxicology

第 17 卷 第 2 期 2022 年 4 月
Vol. 17, No.2 Apr. 2022

DOI: 10.7524/AJE.1673-5897.20211025001
刘晓晨, 刘璟. 环境内分泌干扰物影响垂体促性腺激素的研究进展[J]. 生态毒理学报,2022, 17(2): 1-19
Liu X C, Liu J. Influences of endocrine-disrupting chemicals on pituitary gonadotropins: A review [J]. Asian Journal of Ecotoxicology, 2022, 17(2): 1-19 (in Chinese)

环境内分泌干扰物影响垂体促性腺激素的研究进展

刘晓晨[1,2], 刘璟[1,2,*]

1. 污染环境修复与生态健康教育部重点实验室,浙江大学环境与资源学院,杭州 310058
2. 环境健康研究所,浙江大学环境与资源学院,杭州 310058

收稿日期:2021-10-25　　**录用日期**:2021-12-15

摘要: 通过工业和农业生产活动排入环境的多种农药、阻燃剂、多氯联苯、塑料包装成分、防腐剂、工业副产物和重金属等化学物质,已被证明是内分泌干扰物(endocrine-disrupting chemicals, EDCs),通过各种途径干扰内分泌系统,例如作用下丘脑-垂体-性腺(hypothalamic-pituitary-gonad, HPG)轴。垂体是 HPG 轴中联系下丘脑与性腺的重要内分泌器官,合成和分泌 2 种促性腺激素,即黄体生成素(luteinizing hormone, LH)和卵泡刺激素(follicle-stimulating hormone, FSH),在调控性成熟与生殖发育过程中起到不可或缺的作用。如果垂体促性腺细胞作为 EDCs 作用的靶标,LH 和 FSH 的合成、分泌、转运或者代谢受到干扰,可能会引起生殖系统的内分泌紊乱,影响性成熟和生殖功能,甚至增加生殖障碍等相关疾病风险。已有一些环境流行病学调查和动物实验报道 EDCs 暴露与人体及哺乳动物体内 LH 和 FSH 水平改变相关,但影响促性腺激素的作用机制研究却相对有限。本文对近年来 EDCs 影响促性腺激素的环境流行病学调查、动物实验以及毒理学机制研究的进展进行综述,并探讨未来的研究方向。

关键词: 内分泌干扰物;垂体;促性腺激素;黄体生成素;卵泡刺激素
文章编号: 1673-5897(2022)2-001-19　　**中图分类号**: X171.5　　**文献标识码**: A

Influences of Endocrine-disrupting Chemicals on Pituitary Gonadotropins: A Review

Liu Xiaochen[1,2], Liu Jing[1,2,*]

1. MOE Key Laboratory of Environmental Remediation and Ecosystem Health, College of Environmental and Resource Science, Zhejiang University, Hangzhou 310058, China
2. Institute of Environmental Health, College of Environmental and Resource Science, Zhejiang University, Hangzhou 310058, China

Received 25 October 2021　　**accepted** 15 December 2021

Abstract: A variety of pesticides, flame retardants, polychlorinated biphenyls, chemical in plastic articles, preservatives, industrial by-products, heavy metals and other pollutants, which are discharged into the environment through industrial and agricultural activities, have been proven to be endocrine-disrupting chemicals (EDCs). Disruption of endocrine system by EDCs can occur in various ways, such as acting on the hypothalamic-pituitary-gonad (HPG) axis. The pituitary is an important endocrine organ in the HPG axis that connects the hypothalamus and the gonads.

基金项目:中央高校基本科研业务费专项资金(2021FZZX002-07);浙江省自然科学基金资助项目(LZ21B070001);国家自然科学基金资助项目(22076166,21876151,21621005)
第一作者:刘晓晨(1998—),女,硕士研究生,研究方向为环境健康与毒理学,E-mail: 21914029@zju.edu.cn
* **通讯作者**(Corresponding author), E-mail: jliue@zju.edu.cn

The gonadotropic cells in pituitary synthesize and secrete two gonadotropins, i.e. luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which play an essential role in sexual maturation and reproduction. When the gonadotropin cells act as the targets of EDCs, the synthesis, secretion, transportation or metabolism of LH and FSH may be disturbed, resulting in hormone imbalance, altering sexual maturity, impairing reproduction and even increasing the risk of endocrine and reproductive diseases. Some environmental epidemiological investigations and animal experiments have reported that EDCs exposure was associated with the changes in the serum levels of LH and FSH in humans and mammals. However, the studies on the toxicological mechanisms of EDCs affecting the synthesis and secretion of these two gonadotropins are relatively limited. This review aims to summarize the environmental epidemiological investigations, animal studies, and toxicological mechanisms regarding the effects of EDCs on gonadotropins, as well as discuss future research directions.

Keywords: endocrine-disrupting chemicals; pituitary; gonadotropin; luteinizing hormone; follicle stimulating hormone

随着农业和工业发展被不断排入环境的化学污染物,已对人类健康构成威胁,这是目前全球环境健康领域最令人关切的问题之一。已有流行病学和实验研究表明,很多污染物与人类健康密切相关,存在内分泌干扰效应。其中部分干扰生物体内分泌系统正常功能与作用的外源性化合物被称为内分泌干扰物(endocrine-disrupting chemicals, EDCs),它们可干扰内源激素的产生、分泌、运输、代谢及作用,从而影响生物体的生长、发育和生殖等生理过程[1-2]。环境中 EDCs 主要包括各种农药、阻燃剂和重金属等[3]。EDCs 通过各种途径干扰内分泌系统,其中控制生殖功能的下丘脑-垂体-性腺(hypothalamic-pituitary-gonad, HPG)神经内分泌轴是 EDCs 作用的重要靶标[4](图 1),EDCs 对 HPG 轴的干扰可能会造成儿童的青春期启动异常和成人生殖障碍[5-6]。垂体是联系 HPG 轴中下丘脑与性腺的重要内分泌器官,在调控性成熟与生殖发育过程中起到不可或缺的作用。HPG 轴上的下丘脑脉冲分泌促性腺激素释放激素(gonadotropin-releasing hormone, GnRH),刺激垂体促性腺细胞合成和分泌 2 种促性腺激素(gonadotropins),即黄体生成素(luteinizing hormone, LH)和卵泡刺激素(follicle-stimulating hormone, FSH)。LH 和 FSH 与 HPG 轴下游性腺细胞膜上的特异性受体结合,调控性腺类固醇的合成与分泌以及配子生成。此外,性腺合成的类固醇激素还可以通过负反馈机制抑制下丘脑的 GnRH 分泌,以维持 HPG 轴激素的稳态。

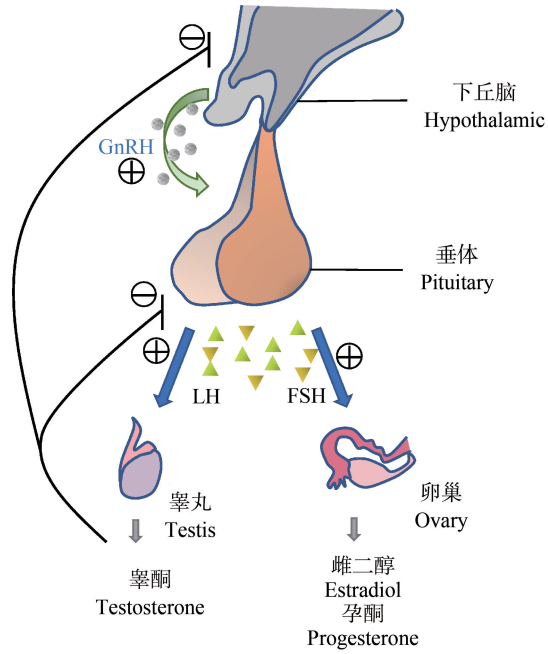

图 1 哺乳动物下丘脑-垂体-性腺轴示意图

注:GnRH 表示促性腺激素释放激素,LH 表示黄体生成素,FSH 表示卵泡刺激素。

Fig. 1 Hypothalamic-pituitary-gonad axis in mammals

Note: GnRH stands for gonadotropin-releasing hormone; LH stands for luteinizing hormone; FSH stands for follicle-stimulating hormone.

促性腺激素 LH 和 FSH 是垂体分泌的异二聚体糖蛋白激素,由非共价结合的共同的 α 亚基(*Cgα*)和特异性 β 亚基(*Fshβ* 和 *Lhβ*)组成[7]。GnRH 以脉冲的方式从下丘脑神经元细胞释放,通过垂体门静脉循环与垂体前叶的促性腺激素细胞表面的 GnRH 受体结合,调控 LH 和 FSH 的合成。GnRH 脉冲频率和振幅的变化对 LH 和 FSH 的合成和释放有不同的影响,LH 优先受高 GnRH 脉冲频率的刺激,而 FSH 主要受低 GnRH 脉冲频率的调控[8]。促性腺激素从垂体释放后进入血液循环,到达女性或雌性哺乳动物的卵巢,与细胞膜上的 LH 或 FSH 的特异性

受体结合。LH 刺激卵泡周围的膜细胞(theca cells)合成雄激素,同时促进包裹在卵母细胞周围的颗粒细胞(granular cells)中孕酮的合成。FSH 与颗粒细胞上的 FSH 受体结合后调控芳香酶的表达,将膜细胞合成的雄激素转化为雌二醇,并刺激卵泡的生长。男性或雄性哺乳动物的睾丸包括间质细胞(leydig cells)和支持细胞(sertoli cells),LH 到达间质细胞后刺激睾酮的产生;与此同时,FSH 与支持细胞表面的 FSH 受体结合可以促进精原细胞的增殖。性腺合成的类固醇激素、抑制素和激活素等又可以通过脑血屏障进入下丘脑和垂体调节 GnRH 和促性腺激素的分泌,维持促性腺激素稳态。由此可见,HPG 内分泌轴十分复杂并且依赖于多个通路和反馈回路,任何扰动都会直接或间接影响女性或男性的性成熟过程和生殖能力[9]。LH 和 FSH 作为生殖内分泌系统的关键激素[3],其水平异常也是许多生殖障碍疾病的诊断指标。例如,男性性腺功能减退特征表现在 GnRH 诱导的 LH 分泌的脉冲幅度减小[10];在女性多囊卵巢综合征病人体内 GnRH 脉冲释放增强导致 LH 水平升高,LH/FSH 比值升高 2 倍 ~3 倍[11-12]。因此,如果垂体促性腺细胞作为 EDCs 作用的靶标,LH 和 FSH 的合成、分泌、转运或者代谢受到干扰,可能会引起生殖系统的内分泌紊乱,影响性成熟和生殖功能,甚至增加生殖障碍等相关疾病风险。

已报道的 EDCs 主要包括普遍使用的农药、阻燃剂、多氯联苯、塑料包装成分、防腐剂、工业副产物和重金属,一些环境流行病学调查和动物实验报道 EDCs 暴露与人体和哺乳动物体内 LH、FSH 水平和生殖功能改变相关,影响促性腺激素稳态的作用机制研究却相对有限且有待深入,目前尚无关于 EDCs 影响促性腺激素的研究进展的综述,因此本文的目的是对近年来相关的环境流行病学调查、动物实验以及毒理学机制研究的进展进行综述,为领域内科学研究和风险评估提供参考。

1　EDCs 暴露与人体促性腺激素水平变化的相关性(Association of EDCs exposure with the gonadotropin levels in human)

GnRH 通过垂体门静脉系统作用于腺垂体的靶细胞,且其半衰期只有几分钟,因此很难在外周血中检测到 GnRH。而促性腺激素从垂体释放进入外周血循环,因此可以通过检测外周血中 FSH 和 LH 水平变化来评估污染物暴露对 HPG 轴调控的相关生殖功能的影响。目前已有一些研究报道了 EDCs 暴露与人体中促性腺激素水平相关,并且与一些不良生殖结局(例如卵巢早衰、更年期提前、精子质量下降和性成熟提前等)也存在相关性(表 1)。

1.1　农药(Pesticides)

大量研究发现人类广泛暴露于各类农药,其中不乏持久性化合物,例如大多数国家已禁用有机氯杀虫剂(dichlorodiphenyltrichloroethane, DDT),但至今其污染仍然存在。英国一项研究根据农药的暴露源和健康影响评估确定了 127 种具有内分泌干扰特性的杀虫剂[13]。有机氯农药是目前普遍存在的高持久性污染物,其中围绕杀虫剂 DDT 及其代谢物(dichlorodiphenyldichloroethylene, DDE) 和 (dichlorodiphenyldichloroethane, DDD)的研究尤为集中。南非一项研究显示,与居住在非喷洒残留室内的男子相比,居住在喷洒残留室内的男子血液中 DDT 和 DDE 浓度更高,在检出 DDT 的男性中血清 LH 和 FSH 浓度低于未检出组(P=0.02, P=0.001),在检出 DDE 的男性中 FSH 浓度显著下降(P=0.02)[14]。巴西农村有机氯农药严重污染地区的围绝经期和绝经后女性的血清 LH 水平降低与六氯苯(hexachlorobenzene, HCB)、*p,p*'-DDT、*p,p*'-DDD、硫丹(endosulfan)、艾得灵(aldrin)和灭蚁灵(mirex)的血清浓度显著相关,FSH 下降则与 *p,p*'-DDD、硫丹和艾得灵的暴露水平相关[15]。在人的生长发育早期(例如产前的孕期和产后母乳喂养阶段)暴露于污染物是最易导致健康问题的时期,这段时间内激素活动异常可能会影响发育和生殖健康等[9]。美国一项针对男孩在宫内和儿童期暴露的研究表明,随着母亲血清中 *p,p*'-DDT 浓度每增加 10 倍,12 岁男孩 LH 水平降低 18.5%(95% CI: −29.8 ~ −5.4),而母亲血清中 *p,p*'-DDE 浓度每增高 10 倍,男孩 LH 水平则降低 18.3%(95% CI: −32.9 ~ −0.6)[16]。

有机磷农药(organophosphate pesticides, OPs)和拟除虫菊酯也是在世界范围内大量用于家庭和农业的 2 种非持久性杀虫剂。一项墨西哥的研究中发现,从事花卉业的男性工人尿液中 OPs 的 6 种二烷基磷酸酯(dialkyl phosphate, DAP)代谢物的水平和血清 FSH 水平均呈正相关,其中总二甲基磷酸酯(dimethyl phosphate, DMP)与 FSH 呈单调正相关(P_{trend}<0.002),而 LH 水平随二乙基硫代磷酸酯(diethyl thiophosphate, DETP)水平升高而显著降低;睾

酮水平与尿中二甲基磷酸酯(dimethylphosphate, DMP)、二乙基磷酸酯(diethylphosphate, DEP)和总DAP浓度显著负相关,其中与DEP存在剂量效应关系(P_{trend}<0.003)[17]。在西班牙接受不孕症治疗的男性尿液中OPs代谢物二乙基二硫代磷酸酯(diethyl dithiophosphate, DEDTP)与血清LH(β=11.4, 95% CI: 0.81 ~ 22.1)和FSH(β=3.2, 95% CI: 0.08 ~ 6.20)呈显著正相关;部分DAP代谢物与精子质量下降有关,精子计数与尿中DMP、二甲基硫代磷酸酯(dimethylthiophosphate, DMTP)、二甲基二硫代磷酸酯(dimethyldithiophosphate, DMDTP)和总DAP的浓度显著负相关,活动精子计数与尿中DMP和二甲基二硫代磷酸酯(dimethyldithiophosphate, DMDTP)浓度显著负相关[5]。中国山东省发现母亲尿液中DMP与脐带血中FSH水平呈负相关(β = −0.03, 95% CI: −0.05 ~ −0.01),此外产前OPs暴露与脐带血生殖激素之间的相关性存在性别差异,仅在女婴中发现OPs暴露与脐带血中的雌二醇和睾丸水平呈显著负相关,这可能与不同性别胎儿的胎盘对环境波动的反应不同有关[18]。3-苯氧基苯甲酸(3-phenoxybenoic acid, 3-PBA)是多种拟除虫菊酯杀虫剂的共同代谢产物,其在尿液中的浓度通常作为评估拟除虫菊酯暴露水平的生物标志物。本课题组的环境流行病学调查发现,中国浙江省女性尿液中拟除虫菊酯代谢产物3-PBA的最高四分位数浓度与卵巢早衰风险增加显著相关(校正比值比(odds ratio, OR)=2.334, 95% CI: 1.193 ~ 4.607, P=0.013),卵巢早衰患者血清中LH和FSH水平随着尿液3-PBA浓度的增加而升高(P_{trend}=0.001)[19]。波兰接受不孕治疗的女性尿液中3-PBA浓度与血清FSH水平显著正相关(P=0.04),而FSH水平升高是卵巢储备功能降低的指标之一,说明拟除虫菊酯可能会影响不孕女性卵巢储备[20]。本课题组的研究还发现9 ~ 16岁青春期男孩尿液中3-PBA水平与性成熟发育阶段3和4时体内的LH和FSH水平显著正相关(OR_{G3}=3.751, OR_{G4}=3.801),这些男孩尿液中3-PBA浓度与LH和FSH水平正相关,3-PBA浓度每增加10%,LH和FSH浓度分别升高2.4%和2.9%[6]。

1.2 阻燃剂(Flame retardants)

溴代阻燃剂(brominated flame retardants, BFRs)用于制造各种商业和家庭材料以及消费品,通过内分泌干扰和发育神经毒性对人类健康产生不利影响。其中多溴二苯醚(polybrominated diphenyl ethers, PBDEs)在环境中被普遍检出[21−24],已有一些研究证明PDBEs与人体血清LH水平正相关。例如,有研究发现母亲产前血清2,2',4,4',5,5'-六溴联苯醚(BDE-153)和2,2',4,4',6-五溴联苯醚(BDE-100)浓度增加与12岁男孩血清LH升高有关[16]。美国室内八溴二苯醚(octaBDE)灰尘浓度也与进行不孕治疗的夫妇中的男性血清中LH呈正相关(95% CI: 0.6 ~ 32.6, P=0.05),说明暴露于室内灰尘中的阻燃剂可能是导致男性不孕的原因之一[25]。然而PBDEs暴露与FSH水平变化的相关性在不同人群中的结果存在差异。例如母亲产前血清BDE-153浓度每升高10倍,12岁男孩FSH水平升高22.2% (95% CI: 1.0 ~ 47.9)[16]。40岁以上成年男性血清中2,2',4,4'-四溴二苯醚(BDE-47)和BDE-100浓度与FSH水平呈显著正相关(P=0.03, P=0.008)[26]。室内五溴二苯醚(pentaBDEs)灰尘浓度与不孕男性血清FSH呈负相关(95% CI: −34.7 ~ −2.5, P=0.03)[25]。中国山东省孕妇血清中BDE-47和BDE-100浓度与FSH水平呈显著负相关(95% CI: −0.14 ~ −0.01, P=0.03; 95% CI: −0.13 ~ −0.01, P=0.04),此外多种阻燃剂还与先兆流产、早产风险增加和孕期延长有关,表明孕妇接触多溴二苯醚可能与不良生殖结局相关[27]。有证据表明PBDEs的替代品有机磷阻燃剂(organic phosphorus flame retardants, OPFRs)代谢物也与人体促性腺激素水平变化存在相关性。加拿大成年男性血清中FSH水平随着尿液中三(1,3-二氯-2-丙基)磷酸酯(TDCiPP)的代谢物双(1-氯-2-丙基)1-羟基-2-丙基磷酸盐(BCiPHiPP)浓度升高而显著降低(−10%, 95% CI: −18 ~ −1.1)[28]。

1.3 多氯联苯(Polychlorinated biphenyls)

多氯联苯(polychlorinated biphenyls, PCBs)是一类工业持久性有机污染物,主要在变压器中用作传热流体。笔者课题组的流行病学研究发现,PCBs暴露与我国浙江省女性罹患卵巢早衰的风险相关,女性血清中PCBs浓度与体内LH水平显著正相关(P<0.05)[29]。中国浙江省嵊泗列岛新生儿脐带血清中PCB-52与LH呈显著负相关(β=0.45, 95% CI: −0.89 ~ −0.01, P<0.05),PCB101与FSH水平显著正相关(P<0.05)[30]。日本和美国的研究表明母亲孕期血清PCBs与男婴脐带血以及12岁男孩血清中FSH水平显著正相关(95% CI: 0.01 ~ 0.57; 95% CI: 8.6 ~ 149.0)[16, 31]。

1.4 塑料包装成分(Chemicals in plastic article)

双酚A(bisphenol A, BPA)类物质常用于食品、

表 1　环境内分泌干扰物(EDCs)和人群促性腺激素相关性的流行病学研究进展

Table 1　Association of endocrine-disrupting chemicals (EDCs) exposure with the gonadotropin levels in human

环境内分泌干扰物 Environmental EDCs		地区 Regions	研究人群 Population	健康结局 Health outcomes	参考文献 Reference
农药 Pesticides	有机氯农药 Organochlorine pesticides	南非,巴西,美国 South Africa; Brazil; USA	居住在残留和非残留村庄的男性;严重污染农村地区的围绝经期和绝经后女性;宫内和儿童期暴露的男孩及其母亲 Men living in IRS/non-IRS villages; peri-/postmenopausal women in a rural area contaminated; adolescent boys exposed in utero and childhood and their mothers	有机氯农药的血清浓度与血清 LH 和 FSH 水平降低显著相关;母亲血清中 *p,p'*-DDT 和 *p,p'*-DDE 浓度与 12 岁男孩 LH 水平负相关 The serum levels of organochlorine pesticides were negatively associated with LH and FSH; prenatal maternal serum concentrations of *p,p'*-DDT and *p,p'*-DDE were associated with the decreased LH levels in 12-year-old boys	[14-16]
	有机磷农药 Organophosphorus pesticides	墨西哥,西班牙,中国山东 Mexico; Spain; Shandong, China	从事花卉业男性工人;接受不孕症治疗男性;健康孕妇 Male floriculture workers; men attending infertility clinic; healthy pregnant women	尿液中母体和 DAP 代谢物水平与血清 LH、FSH 水平相关 The urinary levels of parent compounds and DAP metabolites were correlated with serum LH and FSH levels	[5,17-18]
	拟除虫菊酯 Pyrethroids	中国浙江,波兰 Zhejiang, China; Poland	卵巢早衰患者和对照女性;接受不孕治疗的女性;9～16 岁青春期男孩 POI patients and control women; women attending infertility clinic; boys aged 9～16	尿液中代谢产物 3-PBA 与卵巢早衰风险增加相关,与血清中 LH 和 FSH 水平相关,与男孩性成熟发育阶段 G3 和 G4 显著相关 Urinary levels of metabolite 3-PBA were associated with the increased risk of POI; urinary 3-PBA concentrations in boys were correlated with the inductions in odds of being in G3&G4 and levels of LH and FSH	[6,19-20]
阻燃剂 Flame retardants	溴代阻燃剂(BFRs) Brominated flame retardants (BFRs)	美国,中国山东 USA; Shandong, China	宫内和儿童期暴露男孩及其母亲;不孕不育男性;40 岁以上成年男性;前瞻性出生队列 Adolescent boys exposed in utero and childhood and their mothers; men recruited from infertility clinic; ≥40-year-old adult male officers; prospective birth cohort	母亲血清 BDE-153 和 BDE-100 浓度增加与 12 岁男孩 LH、FSH 升高有关;孕妇血清中 BDE-47 和 BDE-100 与 LH 和 FSH 负相关;室内阻燃剂灰尘浓度与血清中 LH、FSH 相关;成年男性血清中 BDE-47 和 BDE-100 浓度与 FSH 水平正相关 Maternal serum levels of BDE-153 and BDE-100 were associated with the increased LH and FSH levels in 12-year-old boys; maternal serum levels of BDE-47 and BDE-100 were inversely associated with LH and FSH levels; the concentrations of BFRs in house dust were associated with serum levels of LH and FSH; the serum concentrations of BDE-47 and BDE-100 were positively associated with LH and FSH levels in adult men	[16,25-27]
	有机磷阻燃剂 Organic phosphorus flame retardant	加拿大 Canada	电子回收和商业废物回收工人 Workers in e-recycling facilities and one commercial-recycling facility	尿液中 BCiPHiPP 浓度与血清 FSH 水平负相关 Urinary concentrations of BCiPHiPP were negatively associated with serum FSH levels	[28]

续表1

环境内分泌干扰物 Environmental EDCs		地区 Regions	研究人群 Population	健康结局 Health outcomes	参考文献 Reference
多氯联苯(PCBs) Polychlorinated biphenyls (PCBs)		中国浙江，日本，美国 Zhejiang, China; Japan; USA	卵巢早衰患者和对照女性；新生儿；母婴对；宫内和儿童期暴露男孩及其母亲 POI patients and control women; newborns; mother-to-child pairs; adolescent boys exposed in utero and childhood and their mothers	PCBs 暴露与罹患卵巢早衰的风险相关；血清中 PCBs 浓度与体内 LH、FSH 水平显著相关；母亲孕期血清 PCBs 与男婴脐带血清和 12 岁男孩血清中 FSH 水平显著正相关 Exposure to PCBs was associated with the increased risk of POI; serum concentrations of PCBs were significantly associated with LH and FSH levels; maternal serum PCBs were positively correlated with the levels of FSH in cord serum and the serum of 12-year-old boys	[16,29-31]
塑料包装成分 Chemicals in plastic article	双酚 A(BPA)类 Bisphenol A (BPA) analogues	中国深圳，中国贵州，中国上海，西班牙，丹麦，美国 Shenzhen/Guizhou/Shanghai, China; Spain; Denmark; USA	男大学生；工业密集区工人；健康男性；男性吸烟者；进行不育治疗的男性；患特发性中枢性性早熟的学龄女孩 Male undergraduate students; workers in dense industrial area; healthy men; male smokers; men seeking subfertile treatment; school-aged girls diagnosed with idiopathic central precocious puberty	尿液和血清中 BPA 及类似物浓度与血清 LH、FSH 水平之间显著相关 Concentrations of BPA and analogues in urine and serum were significantly correlated with LH and FSH levels in serum	[33-38]
	邻苯二甲酸酯(PAEs) Phthalates (PAEs)	中国天津，中国重庆，中国浙江，韩国，丹麦， Tianjin/Chongqing/Zhejiang China; Korea; Denmark	青春期前儿童；不育男性；男大学生；母婴对；卵巢早衰患者和对照女性 Prepubescent children; male partners of couples and diagnosed as infertile; male college students; mother-to-child pairs; POI patients and control women	尿液和血清中母体及代谢物含量与 LH、FSH 水平显著相关；母亲尿液中 PAEs 含量与男婴 FSH 水平负相关；尿液中 PAEs 浓度与卵巢早衰风险显著正相关； Concentrations of parent compounds and metabolites in urine and serum were significantly correlated with LH and FSH levels; maternal urinary PAEs were negatively associated with the levels of FSH in male infants; urinary PAEs levels were positively correlated with the risk of POI	[39-43]
防腐剂 Preservatives	对羟基苯甲酸酯(PBs) Parabens (PBs)	加拿大，丹麦，德国，美国，波兰 Canada; Denmark; Germany; USA; Poland	6～17 岁女孩；母婴对；健康男性；寻求不孕治疗女性 Girlsaged 6 ~ 17; mother-to-child pairs; healthy men; women seeking fertility treatment	尿液中 PBs 与 LH 和 FSH 水平相关，与窦卵泡计数负相关 Urinary concentrations of PBs were positively associated with LH and FSH levels in serum and negatively correlated with AFC	[44-47]

续表1

环境内分泌干扰物 Environmental EDCs		地区 Regions	研究人群 Population	健康结局 Health outcomes	参考文献 Reference
工业副产物 Industrial by-products	二噁英 Dioxins	意大利，美国 Italy; USA	事故暴露母亲及其成年男性后代；绝经后妇女 Accidentally exposed mothers and their adult sons; postmenopausal women	子宫内和哺乳期暴露男性成年后精子活力受到永久性损伤，FSH 水平显著升高；血清中二噁英类物质的毒性当量与 LH 水平负相关 Sperm motility of adult men exposed in utero and lactation was permanently damaged, and FSH levels in them were significantly increased; dioxin-like toxic equivalents were inversely associated with serum LH levels	[51－52]
	多环芳烃(PAHs) Polycyclic aromatic hydrocarbons (PAHs)	中国浙江，中国重庆 Zhejiang/Chongqing, China	卵巢早衰患者和对照女性；母婴对；男大学生 POI patients and control women; mother-to-child pairs; male college students	尿液和血清中母体及代谢物与 LH 和 FSH 水平显著相关；与罹患卵巢早衰风险相关 Parent compounds and metabolites in urine and serum are significantly correlated with LH and FSH levels; the serum levels of PAHs were associated with increased risk of POI	[53－55]
重金属 Heavy metals	镉 Cadmium	意大利，美国，中国浙江 Italy; USA; Zhejiang, China	12～14 岁男孩；城乡男性工人；绝经前女性；卵巢早衰患者和健康女性 Boys aged 12 ~ 14; male workers in urban and rural areas; healthy premenopausal women; POI patients and control women	血液/尿液/空气中镉浓度与 LH、FSH 显著负相关；尿镉与男孩性成熟和女性患卵巢早衰风险相关 The levels of cadmium in the blood/urine/air samples were inversely associated with LH and FSH levels; urinary cadmium was correlated with onset of puberty in boys and the risk of POI in women	[56－60]
	铅 Lead	韩国，美国 Korea; USA	绝经女性；铅烟雾暴露焊接工人和对照组 Postmenopausal women; welders exposed to lead-containing fumes and control group	血铅水平与 LH、FSH 正相关 Blood lead levels were positively related with LH and FSH in serum/blood	[61－62]

注：IRS 代表室内喷洒残留；OR 代表比值比；AFC 代表窦卵泡计数；LH 表示黄体生成素；FSH 表示卵泡刺激素；DAP 表示二烷基磷酸酯；POI 代表卵巢功能减退；BCiPHiPP 表示双(1-氯-2-丙基)1-羟基-2-丙基磷酸盐。

Note: IRS stands for indoor residual spraying; OR stands for odds ratio; AFC stands for antral follicle count; LH stands for luteinizing hormone; FSH stands for follicle-stimulating hormone; DAP stands for dialkyl phosphate; POI stands for primary ovarian insufficiency; BCiPHiPP stands for bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate.

饮料罐的漆面包装,也可用于一些牙科密封剂和复合材料,是一类广泛存在于环境的内分泌干扰物。由于 BPA 聚合后未结合的单体仍然存在,BPA 分子可能会从饮料和食品容器中释放出来,因此人类广泛暴露 BPA[32]。西班牙男性大学生尿液中 BPA 浓度与血清 LH 水平之间存在显著正相关(β=0.07, 95% CI: 0.02 ~ 0.12, P<0.01)[33]。我国深圳市工业密集区工人血清中 BPA 类似物 4,4'-二羟基二苯甲酮(DHBP)与 LH 水平正相关(P<0.05),双酚 AF(bisphenol AF, BPAF)和双酚 B(bisphenol B, BPB)与 FSH 水平显著正相关(P<0.001)[34]。一项丹麦的研究显示,尿液中 BPA 浓度处于最高四分位数的男性血清 LH 水平比 BPA 浓度处于最低四分位数的男性高出 22%(95% CI: 6% ~ 39%)[35]。成年男性吸烟者中,尿液中 BPA 水平与高 FSH 风险增加相关(校正相对风险度(RR)=1.64, 95% CI: 1.01 ~ 2.67)[36]。对于正在进行不育治疗的男性,尿液 BPA 浓度增加一个四分位距(IQR),其 FSH 水平增加 1.23 IU·L^{-1}(95% CI: 1.10 ~ 1.40 IU·L^{-1}, P=0.0005),BPA 四分位数浓度与血清 FSH 水平呈正剂量效应趋势(P=0.002)[37]。以上多项流行病学研究表明,BPA 暴露水平与成人体内促性腺激素水平正相关,提示 BPA 可能通过作用垂体或者 HPG 轴刺激促性腺激素合成与分泌。然而中国上海市一项儿童的研究发现,患有特发性中枢性性早熟(idiopathic central precocious puberty, ICPP)的学龄女孩尿液中 BPA 浓度与 FSH 基础水平(r=−0.236, P=0.006)和峰值水平(r=−0.172, P=0.045)之间均存在显著负相关;与最低四分位数浓度相比,最高四分位数浓度 BPA 的女孩罹患 ICPP 的 OR 值增加 9.08 倍(OR=9.08,95% CI: 2.83 ~ 29.15)。该研究结果提示 BPA 暴露与 ICPP 风险升高有关,其潜在机制可能与 FSH 水平降低有关[38]。

邻苯二甲酸酯(phthalic acid ester, PAEs)具有软化塑料的作用,常被用作食品包装、玩具、建筑用品、医疗设备和个人护理产品的塑化剂。PAEs 与聚合物基质非共价结合且非常容易释放出来,因此 PAEs 极易污染食物,尤其是肉和奶制品,并且几乎在室内环境中随处可见[32]。韩国青春期前儿童血清邻苯二甲酸二丁酯(dibutyl phthalate, DBP)、邻苯二甲酸单乙基己基酯(monoethylhexyl phthalate, MEHP)含量与 LH 显著正相关(P<0.05)[39]。中国天津市不育男性血清中邻苯二甲酸单酯的浓度总和(∑mPAE)与 LH 呈负相关(β = −0.017, 95% CI: −0.031 ~ −0.004)[40]。中国重庆市男性大学生尿液中邻苯二甲酸甲酯(monomethylphthalate, MMP)、邻苯二甲酸异丁酯(monoisobutylphthalate, MiBP)和单(2-乙基-5-氧己基)邻苯二甲酸酯(mono(2-ethyl-5-oxohexyl) phthalate, MEOHP)的肌酐校正浓度与血清 FSH 水平显著负相关[41]。当丹麦母亲尿液中总邻苯二甲酸二异壬酯(diisononyl phthalate, DiNP)处于最高三分位数浓度时,男婴的 FSH 水平比处于最低的三分位数浓度时降低了 14%(95% CI: −1 ~ −25)且呈剂量效应关系(P_{trend}=0.037)[42]。笔者课题组发现中国浙江省女性尿液中 MiBP 浓度与卵巢早衰风险显著正相关,MiBP 浓度处于最高四分位数的卵巢早衰患者的 OR 比浓度处于最低四分位数增加 38%(OR=1.38, 95 % CI: 0.73 ~ 2.61, P=0.01)。卵巢早衰患者血清 FSH 水平与 PAEs 代谢物呈正相关,较高水平的 MiBP、邻苯二甲酸单正丁酯(mono-*n*-butylphthalate, MnBP)、MMP、MEOHP 和 MEHHP 与 FSH 的 OR 之间存在明显的剂量效应关系[43]。

1.5 防腐剂(Preservatives)

对羟基苯甲酸酯(parabens, PBs)作为抗菌防腐剂常被用在化妆品、个人护理品、药品和食品中,在多种环境介质中均有检出。加拿大的研究发现 6 ~ 17 岁女孩尿液中 PBs 总量增加 1 倍,LH 和 FSH 水平分别降低 10.8%(95% CI: −17.4 ~ −3.7)和 4.2%(95% CI: −7.9 ~ −0.3)[44]。丹麦妊娠早期母亲尿液中对羟基苯甲酸甲酯和对羟基苯甲酸正丙酯浓度与 3 个月女婴血清中 LH 和 FSH 负相关,尿液最高三分位数对应的女婴血清中 FSH 分别降低 0.15 IU·L^{-1}(P_{trend}=0.06)和 0.14 IU·L^{-1}(P_{trend}=0.08),母亲中尿液中对羟基苯甲酸甲酯第二和第三三分位数浓度对应的女婴血清中 LH 较第一三分位数降低(OR_{2th}=0.31, OR_{3rd}=0.33, P_{trend}=0.06)[45]。德国一项研究发现男性志愿者全身涂抹含对羟基苯甲酸丁酯的乳霜 120 h 后的 FSH 水平较涂抹对照乳霜组显著升高(P<0.05)[46]。然而美国和波兰的 2 项研究均表明成年女性 FSH 水平随尿液中对羟基苯甲酸丙酯浓度增加而升高[47-48]。其中美国的研究发现随着尿液中对羟基苯甲酸丙酯三分位数的增加,窦卵泡计数有降低趋势,第二和第三较第一三分位数的平均变化分别为−5.0% 和−16.3%(P_{trend}=0.07)[47]。

1.6 工业副产物(Industrial by-products)

二噁英通常是金属冶炼和燃烧含氯有机化学品工业产生的副产品,主要包括多氯二苯并对二噁英

(polychlorinated dibenzo-*p*-dioxin, PCDD)和多氯二苯并呋喃(polychlorinated dibenzofurans, PCDF)[49−50]。意大利的研究发现在子宫内和哺乳期暴露于相对低剂量的二噁英的男性成年后精子活力受到永久性损伤,二噁英暴露的男性体内 FSH 水平显著高于母乳对照组[51]。美国绝经后妇女 LH 与二噁英类污染物的暴露呈负相关,当血清中二噁英类物质的毒性当量每增加 1 倍,LH 水平降低 11.9% (95% CI: −21.3% ~ −1.4%, P=0.03)[52]。

多环芳烃(polycyclic aromatic hydrocarbons, PAHs)主要由不完全的有机燃烧过程产生,然后排放到大气中。笔者课题组研究发现中国浙江省女性血清中总 PAHs 与 LH 和 FSH 水平呈显著正相关,罹患卵巢早衰的 OR 升高[53]。我国浙江省嵊泗列岛母婴脐带血清中 FSH 的浓度与 16 种 PAHs 和低分子量 PAH 的自然对数浓度显著正相关(P<0.05)[54]。我国重庆市暴露于室外细颗粒物 $PM_{2.5}$ 结合的 PAHs 的男大学生尿液中菲及其代谢产物 1-羟基菲的浓度与 LH 水平正相关(β=3.710, 95% CI: 0.518 ~ 7.004; P=0.023),但 3-羟基菲与 LH 呈负相关(β= −5.937, 95% CI: −10.122 ~ −1.558, P=0.009)[55]。

1.7　重金属(Heavy metals)

镉和铅是广泛存在于环境中的有毒重金属,作为内分泌干扰物可引起类雌激素效应或抗雄激素作用,干扰生殖系统和正常发育。意大利 12 ~ 14 岁男孩尿镉与血清 LH 水平正相关(r=0.048, P≤0.05),性成熟延迟且处于 G3、G4 阶段的男孩睾丸体积显著减小[56]。同时意大利城乡男性工人血液/尿液/空气中镉的对数浓度与 LH、FSH 均呈显著负相关[57]。美国绝经前女性血镉浓度每增加 1 mg·L^{-1},FSH 水平增加 20% (95% CI: −2.9 ~ 46.9)[58],但另一项研究则发现此人群中血清 FSH 水平随着镉含量的增加而下降,与最低镉暴露水平的三分位数相比,最高和中间三分位数的平均 FSH 水平分别降低 10% (95% CI:−17.3% ~ −2.5%)和 8.3% (95% CI: −16.0% ~ −0.1%)[59]。笔者课题组则发现卵巢早衰患者尿镉水平与血清 LH 水平呈显著正相关(P_{trend}=0.001),亦与血清 FSH 水平呈显著正相关(P_{trend}<0.001),这是首次报道镉暴露与女性患卵巢早衰风险呈正相关(OR=2.50, 95% CI: 1.34 ~ 4.65, P_{trend}=0.001)[60]。

韩国绝经后女性血铅水平与 FSH 正相关(β= 2.929, P=0.019)[61]。美国暴露于铅烟雾的工人 LH 和 FSH 水平均显著高于对照组(P<0.05),且与血铅水平正相关(r=0.72, P=0.004; r=0.78, P=0.001)[62]。

2　EDCs 暴露对哺乳动物促性腺激素的干扰作用(Disrupting effects of EDCs exposure on gonadotropins in mammals)

大量流行病学调查证明 EDCs 暴露与人体内促性腺激素水平改变存在相关性,已有的动物实验也证实 EDCs 暴露引起促性腺激素水平变化,对生殖系统功能和性成熟产生影响(表 2)。

2.1　农药(Pesticides)

有机氯农药暴露不仅引起促性腺激素水平变化,对配子发生和性成熟皆产生影响。成年雄性 Wistar 大鼠连续 10 d 腹腔注射 50 mg·kg^{-1}·d^{-1}和 100 mg·kg^{-1}·d^{-1}的 DDT,结果表明农药暴露后体内睾酮减少,LH 和 FSH 水平升高,促性腺激素水平的增加可能与类固醇对下丘脑-垂体轴的负反馈调节有关[63]。雌性 Wistar 大鼠在产后(postnatal day, PND)6 ~ 10 d 皮下注射 10 mg·kg^{-1}·d^{-1}和 100 mg·kg^{-1}·d^{-1}的 *o*,*p*'-DDT 后,在 PND 22 d 时 LH 水平趋于降低,随后观察到阴道口张开和第一次动情期出现的日龄都减小(即性成熟提前),与年龄相关的 LH 对 GnRH 的反应提前下降[64]。成年雄性 Wistar 大鼠连续灌胃 6.75 mg·kg^{-1}·d^{-1}有机磷农药毒死蜱 12 周后血清 LH 和 FSH 水平较对照组均显著降低(P< 0.05),抑制精子发生,曲细精管发育不良[65]。

不同剂量的拟除虫菊酯杀虫剂暴露不同年龄或者窗口期的啮齿类动物,对促性腺激素的影响不尽相同。笔者课题组研究发现未成熟 ICR 小鼠在 PND 7 ~ 12 暴露于 0.5、5、和 50 μg·kg^{-1}·d^{-1}的氯氰菊酯,暴露组 LH 水平均显著升高且呈剂量效应关系,且中高剂量组 FSH 水平也显著提高(P<0.05),并引起性成熟提前[66]。另一项研究将雄性成年 ICR 小鼠连续暴露于 0、35 或 70 mg·kg^{-1}·d^{-1}的氯菊酯 6 周,附睾精子量和睾酮均显著降低,进而导致 HPG 轴负反馈调节的血清 LH 含量随着暴露剂量增大显著增加[67]。然而,21 日龄雌性昆明小鼠持续暴露 6 个月剂量为 1.38、2.76 和 5.52 mg·kg^{-1}·d^{-1}的 β-氯氰菊酯,与对照组相比暴露组血清 FSH 水平呈剂量依赖性升高,2.76 mg·kg^{-1}和 5.52 mg·kg^{-1}剂量组 LH 浓度显著降低(P<0.05),并且随着剂量的增加小鼠的胚胎着床率和妊娠成功率显著降低[68]。成年雄性 Sprague-Dawley (SD)大鼠以每天 0、7.5、15、30、60 mg·kg^{-1}的剂量口服氯氰菊酯 15 d 后,与对照组相比最高剂量组的体内 FSH 水平显著升高,30 mg·

kg^{-1}组和 60 $mg\cdot kg^{-1}$组大鼠的血清睾酮浓度和每日精子产量均显著降低($P<0.05$)[69]。

新烟碱类是一类目前在世界范围内使用最为广泛的杀虫剂,主要用于农业以保护作物免受昆虫侵害[70-71]。近些年有研究表明暴露于新烟碱农药会造成大鼠体内促性腺激素水平异常,对性腺和配子造成不良影响。成年雌性 Wistar 大鼠经口暴露于 5、10 和 20 $mg\cdot kg^{-1}\cdot d^{-1}$的吡虫啉 90 d 后,最高剂量组的血清 LH 和 FSH 水平显著下降,卵巢质量显著降低并出现明显的病理学变化[72]。在雄性大鼠体内同样发现了新烟碱农药暴露对生殖功能的负面效应,通常 FSH 水平上升指示生殖力下降。50 日龄雄性大鼠每周 5 d 暴露于 9 $mg\cdot kg^{-1}\cdot d^{-1}$的吡虫啉,一个月后发现体内 FSH 水平上升 32.6%,睾酮下降 63.9%,睾丸质量上升 14.2%,精子数量减少 32.1% 并且精子头部出现变形、尾部异常弯曲[73]。8 ~ 10 周龄雄性 SD 大鼠连续暴露于 12.5、25 和 35 $mg\cdot kg^{-1}\cdot d^{-1}$的啶虫脒 90 d,暴露组的雄鼠体内 FSH 水平均显著升高,中低剂量组的 LH 显著升高,中高剂量组精子数量显著减少,高剂量组头部异常精子增多($P<0.05$)[74]。

2.2 阻燃剂(Flame retardants)

长期暴露于 BFRs 会严重影响两性生殖健康。21 日龄雄性 SD 大鼠持续暴露 14 d 剂量为 0、0.1、0.2 和 0.4 $mg\cdot kg^{-1}\cdot d^{-1}$的 2,2',4,4'-四溴二苯醚(BDE-47)后,最高剂量组血清 LH 水平显著降低,睾酮显著升高并且伴随着间质细胞的增殖($P<0.05$)[75]。另外成年雌性 SD 大鼠在交配前 2 ~ 3 周至妊娠(gestation day, GD)第 20 天,经口暴露 0、0.06、20 和 60 $mg\cdot kg^{-1}$的 PBDE 工业混合物(DE-71、DE-79 和 BDE-209),暴露组血清 LH 浓度随剂量增加趋于降低,卵巢中的类固醇生成和卵泡生成显著受损[76]。

2.3 多氯联苯(Polychlorinated biphenyls)

SD 母鼠在胚胎第 16、18 天腹腔注射 0、0.1、1 或 10 $mg\cdot kg^{-1}$的多氯联苯混合物 Aroclor1221,1 $mg\cdot kg^{-1}$组 F1 代血清中 LH 水平显著高于 0.1 $mg\cdot kg^{-1}$和 10 $mg\cdot kg^{-1}$组,且有高于对照组的趋势($P=0.0516$)。在动情前期,与对照组相比暴露组的 F2 雌鼠血清 LH 水平显著降低,Aroclor1221 抑制了发情周期中子宫和卵巢质量的波动,其中卵巢质量显著下降[77]。SD 孕鼠在 GD 7 ~ GD 21 灌胃暴露剂量为 30 $\mu g\cdot kg^{-1}\cdot d^{-1}$的 PCB169,雄性子代出生后第 6 周(postnatal week, PDW)血浆 LH 水平显著降低,然而 PDW 15 雄性子代血浆 FSH 水平显著升高($P<0.05$),同时 PDW 3 和 PDW 6 睾酮浓度下降,睾丸间质细胞减少,表明 PCB169 通过垂体-睾丸轴抑制精子发生[78]。另一项 CD-1 小鼠的暴露实验表明母鼠围产期饮食暴露 1 $\mu g\cdot kg^{-1}\cdot d^{-1}$的 PCB(101+118),雄性后代成年后垂体中 *Lhβ* 和 *Fshβ* 基因的表达水平均显著上调[79]。

2.4 塑料包装成分(Chemicals in plastic article)

已有研究报道,雌性 Wistar 孕鼠在 GD 18 ~ PND 5 皮下注射 0.5 $mg\cdot kg^{-1}$或 5 $mg\cdot kg^{-1}$的 BPA,暴露组雄性后代青春期启动延迟,在 PND 90(成年后)暴露组下丘脑 *Gnrh1* 和 *Esr2* mRNA 相对表达水平增加,5 $mg\cdot kg^{-1}$组血清 LH 浓度显著升高,0.5 $mg\cdot kg^{-1}$组垂体 *Fshβ* 亚基 mRNA 表达增加($P<0.05$),证明在下丘脑性分化期间暴露于低于未见毒性反应水平剂量的 BPA 类物质,会改变雄性后代促性腺激素水平进而扰动 HPG 轴[80]。相似地,SD 母鼠从 GD 6 至哺乳期饮水暴露于 1 $\mu g\cdot mL^{-1}$和 10 $\mu g\cdot mL^{-1}$的 BPA,雌性后代血清 LH 和 FSH 水平均显著升高,青春期启动显著提前[81]。然而,22 日龄断奶雄性大鼠连续 48 周饮水暴露于 5、25 和 50 $\mu g\cdot L^{-1}$的 BPA 或其类似物(BPB、BPF 和 BPS),血浆 LH 和 FSH 水平均显著下降,50 $\mu g\cdot L^{-1}$组相对附睾质量显著降低,每日精子产量显著降低($P<0.01$),附睾头精子数和尾部精子数均有不同程度减少($P<0.05$)[82]。选择处于动情周期的雌性 NMRI 小鼠皮下注射 0、1、5、10、50 和 100 $\mu g\cdot kg^{-1}$的 BPS 连续 21 d,所有暴露组的雌鼠体内 LH 和 FSH 水平均显著降低[83]。

不同生命时期暴露邻苯二甲酸酯对啮齿动物体内促性腺激素水平均有显著影响。Wistar 孕鼠在 GD 1、GD 7 和 GD 14 分别注射 DBP 100 $mg\cdot kg^{-1}$和 500 $mg\cdot kg^{-1}$,与对照组相比产前暴露的雄性大鼠血清 LH 和 FSH 水平升高,睾酮水平、精子数量和活力显著下降($P<0.05$)[84]。4 周龄雄性 Wistar 大鼠连续 4 周每日灌胃 80、200 和 500 $mg\cdot kg^{-1}$的 DBP,中、高剂量组的雄鼠体内 LH 和 FSH 水平显著增加($P<0.01$),最大分别增加 59.5% 和 51%,同时睾酮水平和类固醇合成急性调节蛋白 *StAR* 基因表达下降[85]。成年雄性 Wistar 大鼠分别于 90、97、104 和 111 日龄腹腔注射 100 $mg\cdot kg^{-1}$和 500 $mg\cdot kg^{-1}$的 DBP,暴露组雄鼠血清 LH 水平显著升高了 82.78% 和 77.24%,FSH 水平升高了 74.06% 和 88.27%,精子数量和活力显著下降($P<0.05$)[86]。然而不同的邻

表 2　环境内分泌干扰物对哺乳动物促性腺激素的影响

Table 2　The effects of EDCs on gonadotropins in mammals

环境内分泌干扰物 Environmental EDCs		研究模型 Models	对促性腺激素及生殖相关功能的影响 Effects on gonadotropins and reproduction functions	参考文献 References
农药 Pesticides	有机氯/有机磷农药 (滴滴涕,2,4-滴滴涕,毒死蜱) Organochlorine/organophosphorus pesticides (DDT, *o*, *p*'-DDT, chlorpyrifos)	Wistar 大鼠 Wistar rats	引起 LH、FSH 和睾酮水平发生变化,雌性性成熟提前,抑制雄性精子发生和曲细精管发育 Exposure to organochlorine pesticides altered serum LH, FSH and testosterone levels and advanced female sexual maturity, and inhibited male spermatogenesis and seminiferous tubule growth	[63-65]
	拟除虫菊酯(氯氰菊酯, 氯菊酯,*β*-氯氰菊酯) Pyrethroids (Cypermethrin, permethrin, *β*-cypermethrin)	CD-1(ICR)小鼠, 昆明小鼠,SD 大鼠 CD-1 (ICR) mice, Kunming mice, SD rats	改变 LH、FSH 和睾酮水平,性成熟提前,降低胚胎着床率、妊娠成功率、附睾精子量和每日精子产量 Exposure to pyrethroids caused changes in LH, FSH and testosterone levels and premature sexual maturity, reduced embryo implantation sites, pregnancy success rate, epididymal sperm count and daily sperm production	[66-69]
	新烟碱农药(吡虫啉,啶虫脒) Neonicotinoids (Imidacloprid, acetamiprid)	Wistar 大鼠,SD 大鼠 Wistar rats, SD rats	引起 LH、FSH 和睾酮水平改变,卵巢和睾丸质量均发生变化,精子数量下降,头部和尾部异常精子数升高 Exposure to neonicotinoids altered serum LH, FSH and testosterone levels and changed the weight of the ovaries and testicles, and reduced sperm count and increased the number of sperm head and tail abnormalities	[72-74]
阻燃剂 Flame retardants	溴代阻燃剂 Brominated flame retardants (BDE-47, PBDE 混合物 PBDE mixture)	SD 大鼠 SD rats	体内 LH、雌二醇和睾酮水平改变,影响卵巢卵泡生成和睾丸间质细胞增殖 Exposure to PBDEs resulted in changes in LH, estradiol and testosterone levels, affected ovarian folliculogenesis and induced leydig cell hyperplasia	[75-76]
多氯联苯 Polychlorinated biphenyls	Aroclor1221, PCB169, PCB (101+118)	SD 大鼠,CD-1(ICR)小鼠 SD rats, CD-1 (ICR) mice	上调雄性后代 *Lhβ*、*Fshβ* 亚基基因表达,改变 LH 和 FSH 水平,降低睾酮水平,影响子宫、卵巢质量和睾丸间质细胞数量和精子发生 PCB exposure up-regulated the expression of *Lhβ* and *Fshβ* subunit genes in male offspring, changed LH and FSH levels, reduced testosterone levels, as well as altered the weight of uterus and ovaries and affected testicular leydig cells count and spermatogenesis	[77-79]

续表2

环境内分泌干扰物 Environmental EDCs		研究模型 Models	对促性腺激素及生殖相关功能的影响 Effects on gonadotropins and reproduction functions	参考文献 References
塑料包装成分 Chemicals in plastic article	双酚A类 Bisphenol A analogues (BPA, BPB, BPF, BPS)	Wistar大鼠,SD大鼠,NMRI小鼠 Wistar rats, SD rats, NMRI mice	体内LH、FSH水平发生变化,上调下丘脑*Gnrh1*和*Esr2*基因和垂体*Fshβ*基因mRNA表达,降低每日精子产量、附睾质量和精子数量,引起后代青春期启动提前 BPA and analogues exposure changed the levels of LH and FSH, increased the expression of hypothalamic *Gnrh1* and *Esr2* and pituitary *Fshβ* mRNA, reduced daily sperm production, epididymal weight and sperm count, and accelerated offspring's pubertal onset	[80-83]
	邻苯二甲酸酯 Phthalates (DBP, DEHP, DMP)	Wistar大鼠,SD大鼠,C57小鼠 Wistar rats, SD rats, C57 mice	改变体内LH、FSH和雌二醇、睾酮水平,下调*Star*基因表达,降低睾丸和附睾质量,精子数量和活力下降 Exposure to phthalates altered LH, FSH, estradiol and testosterone levels, decreased the expression of *Star* gene, the weight of testis and epididymis as well as sperm count and motility	[84-88]
防腐剂 Preservatives	对羟基苯甲酸酯 (对羟基苯甲酸正丁酯) Paraebns (*n*-butylparaben)	Wistar大鼠,Holtzman大鼠 Wistar rats, Holtzman rats	影响LH、FSH和睾酮水平,精子头部异常数量增加,附睾尾部精子数量、每日精子产量降低,包皮分离和睾丸下降时间延迟 Exposure to parabens affected the levels of LH, FSH and testosterone, increased the number of sperm head abnormalities, decreased the caudal epididymal sperm count and daily sperm production, and delayed the ages of preputial separation and testicular descent	[89-91]
工业副产物 Industrial by-products	二噁英 Dioxins (TCDD)	Wistar大鼠,SD大鼠 Wistar rats, SD rats	下调胎儿*Lhβ*、*Fshβ*亚基基因表达,引起LH、FSH水平变化,影响性腺类固醇生成和基因表达,性二型行为紊乱 Dioxins exposure reduced the expression of*Lhβ*, *Fshβ* subunit genes and altered LH and FSH levels, and affected gonadal steroidogenesis and the expressions of steroidogenic genes, and disrupted sexual dimorphic behavior	[92-93]
重金属 Heavy metals	镉,铅(氯化镉,醋酸铅) Cadmium, lead (Cadmium chloride,lead acetate)	昆明小鼠,Wistar大鼠,SD大鼠 Kunming mice, Wistar rats, SD rats	引起LH、FSH和睾酮水平改变,影响下丘脑*Kiss1*和*Kiss1*受体表达水平,造成卵巢储备、卵泡数量和睾丸精子数量、活力均下降 Exposure to metals altered the serum concentrations of LH, FSH and testosterone, affected the expression of hypothalamic *Kiss1* and *Kiss1* receptor, and caused a reduction in ovarian reserve, follicle count, testicular sperm count and motility	[94-98]

注:SD大鼠表示Sprague-Dawley大鼠;BDE-47表示2,2',4,4'-四溴二苯醚;PBDE表示多溴二苯醚;TCDD表示四氯二苯并-*p*-二噁英;BPA表示双酚A;BPB表示双酚B;BPF表示双酚F;BPS表示双酚S;DBP表示邻苯二甲酸二丁酯;DEHP表示邻苯二甲酸二(2-乙基己基)酯;DMP表示邻苯二甲酸二甲酯;*Gnrh1*代表促性腺激素释放激素1基因;*Esr2*代表雌激素受体2基因;*Star*代表类固醇激素合成急性调节蛋白基因;*Kiss1*是编码神经肽-吻肽的基因。

Note: SD rats stand for Sprague-Dawley rats; BDE-47 is 2,2',4,4'-tetrabromodiphenyl ether; PBDE is polybrominated diphenyl ether; TCDD is tetrachlorodibenzo-*p*-dioxin; BPA is bisphenol A; BPB is bisphenol B; BPF is bisphenol F; BPS is bisphenol S; DBP is dibutyl phthalate; DEHP is bis(2-ethylhexyl) phthalate; DMP is dimethyl phthalate; *Gnrh1* stands for gonadotropin releasing hormone 1 gene; *Esr2* stands for estrogen receptor 2 gene; *Star* stands for steroidogenic acute regulatory protein gene; *Kiss1* stands for a gene encoding neuropeptide-kisspeptin.

苯二甲酸酯对促性腺激素水平调控存在差异。例如 18 日龄雄性 SD 大鼠连续 30 d 灌胃 250、500 或 750 mg·kg^{-1}邻苯二甲酸二(2-乙基己)酯(bis(2-ethylhexyl) phthalate, DEHP)后体内促性腺激素水平受到抑制,高剂量组 LH 水平降低 21.1%,中、高剂量组 FSH 水平分别降低 26.4%、28.3%,相对睾丸和附睾质量均表现出剂量依赖性降低,且均具有统计学显著性[87]。C57 雌性小鼠每日灌胃 0、0.5、1 和 2 g·kg^{-1}的邻苯二甲酸二甲酯(dimethyl phthalate, DMP),持续暴露 40 d 后 2 g·kg^{-1}组体内 LH 和雌二醇(E_2)显著升高,FSH 却显著下降(P<0.05),这可能是由于 DMP 对垂体-卵巢轴的双重作用,即刺激垂体 LH 的产生并抑制颗粒细胞中类固醇的产生,推测长期暴露 DMP 会促进血清 E_2 水平,导致 FSH 水平继发性降低[88]。

2.5　防腐剂(Preservatives)

Wistar 大鼠于妊娠期和哺乳期(GD 12 ~ PND 21)皮下注射 10、100 和 200 mg·kg^{-1}对羟基苯甲酸正丁酯(*n*-butylparaben, BP),200 mg·kg^{-1}暴露组的雄性后代在 PND 110 的血清中 LH 和 FSH 浓度显著降低,并且所有暴露组的精子头部异常(主要表现为头部无特征弯曲)数量增加,睾酮浓度显著升高(P<0.05)[89]。母鼠在 GD 7 ~ PND 21 经口暴露 64、160、400 和 1 000 mg·kg^{-1}的 BP 后,暴露组的 PND 21 和 PND 49 的雄性仔鼠血清中 LH 水平以及 PND 35 的雄性仔鼠 FSH 水平显著下降,但 PND 90 的雄性仔鼠的促性腺激素均显著升高,并伴随着最高剂量组的附睾尾部精子数量显著减少约 36%,每日精子产量显著下降约 55% (P<0.01)[90]。然而,Holtzman 大鼠在这一时期皮下注射 0、100 和 1 000 mg·kg^{-1}的 BP,最高剂量组 F1 代雄鼠在 PND 45 和 PND 75 的 LH 水平却显著上升(P<0.05),10 mg·kg^{-1}和 1 000 mg·kg^{-1}组出现包皮分离延迟,100 mg·kg^{-1}和 1 000 mg·kg^{-1}组的睾丸下降延迟并且在成年后评估处于亚生育状态[91]。

2.6　工业副产物(Industrial by-products)

针对二噁英的研究主要集中在探究围产期暴露对子代的影响,子宫内或母乳暴露可以传递给子代,可能影响 F1 代成年后的生殖行为。妊娠 Wistar 大鼠在 GD 15 单次口服 1 μg·kg^{-1}四氯二苯并-*p*-二噁英(tetrachlorodibenzo-*p*-dioxin, TCDD),GD 20 时雌雄胎儿垂体中 *Lhβ* 和 *Fshβ* 亚基基因表达降低,血清 LH 和 FSH 激素水平下降进而导致下游性腺类固醇生成蛋白表达下降,成年后性二型行为紊乱[92]。然而,成年雌性 SD 孕鼠于 GD 8 ~ GD 14 分别灌胃 100 ng·kg^{-1}·d^{-1}和 500 ng·kg^{-1}·d^{-1}的 TCDD,高暴露组的 F3 代血清中 LH 浓度却显著增加(P<0.05)[93]。

2.7　重金属(Heavy metals)

25 日龄雄性昆明小鼠灌胃暴露于 5 mg·kg^{-1}·d^{-1}的 $CdCl_2$,在 20 d 和 30 d 后血清 FSH 水平显著升高(P<0.01),睾酮浓度升高,而与之合成的相关蛋白表达降低,这可能是青春期 HPG 轴负反馈调节的结果[94]。12 周成年雌性 Wistar 大鼠饮水暴露于 100 mg·kg^{-1}的 $CdCl_2$ 持续 30 d 后血清基础 LH 水平增加,下丘脑中 Kiss1 表达水平升高,Kiss1 受体表达下降,同时暴露组大鼠的卵巢储备功能降低,卵泡数显著下降(P<0.05),出现了 HPG 轴受损、卵巢早衰特征[95]。成年 SD 大鼠连续腹腔注射 3.5 mg·kg^{-1}或 2 mg·kg^{-1}的 $CdCl_2$ 一个月后,雌鼠和雄鼠的 LH 水平均显著降低,对卵巢和睾丸均产生了毒性作用[96-97]。另外,成年雄性 Wistar 大鼠灌胃 50 mg·kg^{-1}醋酸铅 4 周后,血清 LH 和 FSH 显著降低,精子数量和活力下降(P<0.001)[98]。以上研究结果显示,未成熟的小鼠暴露于较低剂量的镉,促性腺激素水平上升,然而成年啮齿类动物暴露高剂量镉或铅,促性腺激素水平却下降。不同窗口期暴露不同剂量的重金属,可能通过不同机制调控促性腺激素的合成和分泌。

3　EDCs 干扰促性腺激素合成的机制研究(The mechanisms of interference of EDCs with gonadotropin synthesis)

目前关于 EDCs 调控促性腺激素合成与分泌的作用机制的研究还十分有限。由于垂体促性腺细胞合成和分泌促性腺激素受下丘脑分泌的 GnRH 调控,因此 EDCs 对 GnRH 的干扰作用可间接调控 LH 和 FSH 的合成。在哺乳动物中,下丘脑 GnRH 神经元脉冲式分泌的 GnRH 和垂体促性腺激素细胞膜上的 GnRH 受体结合,从而激活相关通路诱导 LH 和 FSH 的合成和分泌。笔者课题组研究发现,21 日龄小鼠下丘脑外植体暴露于 500 μg·L^{-1}和 5 000 μg·L^{-1}氯氰菊酯后,GnRH 脉冲的间隔时间显著缩短,电压门控钠离子通道(voltage-gated sodium channels, VGSCs)的抑制剂 TTX 可以阻断氯氰菊酯对 GnRH 脉冲频率的调控,表明氯氰菊酯通过干扰 VGSCs 缩短 GnRH 脉冲间隔[66]。另一项研究发现,从体内暴露 500 mg·kg^{-1} DEHP 的大鼠中分离的垂体细胞无论有无 GnRH 的刺激,其释放的 LH 在暴露后都显

著增加;但体外分离的 20 日龄大鼠垂体细胞在暴露于 DEHP 或其代谢物后,只有代谢物 2-乙基己酸(2-ethylhexanoic acid, 2-EHXA)能够显著增强 GnRH 刺激下 LH 的分泌,但是对基础水平没有影响[99]。这说明 DEHP 代谢物可以通过增强垂体对 GnRH 的反应来调节 LH 的分泌。

除了通过干扰 GnRH 间接调控促性腺激素,EDCs 也可能直接作用于垂体促性腺细胞,干扰 LH 和 FSH 的合成。笔者课题组利用 LβT2 细胞以及垂体原代细胞等体外模型开展了一系列研究。LβT2 细胞暴露于 10^{-9} ~ 10^{-7} mol·L^{-1} *p,p*'-DDT 和甲氧滴滴涕(methoxychlor, MXC), *Cg*α、*Lh*β 和 *Fsh*β 基因 mRNA 水平以及 LH 和 FSH 分泌水平显著升高,并呈现剂量效应关系。调控促性腺激素合成的丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)包括细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)、Jun N 末端激酶(Jun N-terminal kinase, JNK)和 p38 MAPK。分别用这 3 种激酶抑制剂预处理 LβT2 后暴露 *p,p*'-DDT 和 MXC,其中 ERK 抑制剂 PD184352 阻断 *p,p*'-DDT 和 MXC 对 *Cg*α、*Lh*β 和 *Fsh*β 亚基基因表达的诱导作用,而 JNK 和 p38 MAPK 抑制剂无显著影响[100],表明 *p,p*'-DDT 和 MXC 通过 ERK 信号通路诱导 LH 和 FSH 的合成。Ca^{2+}信号在垂体前叶合成和分泌促性腺激素所必需的信号转导级联中起着重要作用。笔者课题组研究发现,原代培养的雄性小鼠垂体细胞暴露于 50 μg·L^{-1}氯氰菊酯后以时间依赖性的方式提高了促性腺激素亚基基因 *Cg*α、*Lh*β 和 *Fsh*β 的 mRNA 水平以及细胞培养液中 LH 和 FSH 这 2 种激素的分泌水平。当氯氰菊酯与 L 型电压门控钙离子通道(voltage-gated calcium channels, VGCCs)阻断剂尼莫地平、胞内 Ca^{2+}螯合剂 BAPTA-AM、胞外 Ca^{2+}螯合剂 EGTA 共暴露时,氯氰菊酯诱导的 Ca^{2+}离子内流、促性腺激素亚基基因的表达和激素分泌的增加均被抑制。以上结果证明了氯氰菊酯通过干扰钙离子通道,刺激小鼠垂体细胞 Ca^{2+}离子内流,激活下游 ERK 激酶通路进而诱导垂体促性腺激素亚基基因的表达以及 LH 和 FSH 的分泌,导致血清促性腺激素水平升高,从而加速小鼠性成熟[66]。同时,笔者课题组利用 LβT2 细胞暴露氯氰菊酯发现,该农药还可通过抑制 Ca^{2+}-ATP 酶活性,导致 Ca^{2+}从细胞内质网钙库中释放来调节钙稳态[101]。Ca^{2+}-ATP 酶可将钙离子泵入内质网钙库中贮存,毒胡萝卜素(thapsigargin)是一种 Ca^{2+}-ATP 酶的抑制剂,可增加胞质钙离子水平最终导致内质网钙库中钙离子的耗竭。我们的研究发现毒胡萝卜素预处理可引起 LβT2 细胞内质网钙库中钙离子的耗竭,阻断了氯氰菊酯对 ERK 的激活作用。另外,氯氰菊酯还可剂量依赖性地降低 LβT2 细胞内的 Ca^{2+}-ATP 酶活性。进一步证明了氯氰菊酯通过 Ca^{2+}激活下游的蛋白激酶 C/C-RAF/ERK1/2/即刻早期基因 *Egr-1*、*c-fos* 和 *c-jun* 信号通路,促进促性腺激素亚基基因的转录[101]。

近些年有研究发现 EDCs 引起的不良影响可以在多代和跨代中传递,导致异常发育表型的机制就可能包括与生殖相关的细胞中的表观遗传失调。啮齿动物和人类暴露 EDCs 的表观遗传标记有 DNA 甲基化、组蛋白翻译后修饰和非编码 RNA[102-103]。有研究发现 TCDD 通过诱导组蛋白去乙酰化酶活性,进而抑制促性腺激素基因 *Cg*α、*Lh*β 和 *Fsh*β 表达[104]。GD 15 妊娠大鼠口服 1 μg·kg^{-1} TCDD 后胎儿垂体促性腺激素亚基基因和血清激素水平下降;DNA 微阵列分析和 PCR 验证结果证实暴露 TCDD 的母鼠的胎儿垂体中组蛋白去乙酰化酶(histone deacetylases, HDCAs)1/3/4/5/6/7/9/11 基因的 mRNA 水平升高,在妊娠晚期和新生儿早期观察到 HDAC1/5/7 表达升高并伴随着垂体促性腺激素减少。染色质免疫共沉淀分析显示乙酰化组蛋白 H3 和 H4 与促性腺激素亚基基因的启动子区域相关,TCDD 暴露导致 *Lh*β 启动子上结合的组蛋白的乙酰化程度显著降低,其他基因的乙酰化组蛋白有同样的降低趋势[104]。

4 总结与展望(Conclusions and perspectives)

虽然目前很多环境流行病学的研究结果表明,EDCs 暴露与促性腺激素水平改变相关,但是不同化合物对不同年龄、不同性别、不同地域的人群的影响存在较大差异。目前很多流行病学调查是横断面研究,检测的促性腺激素只能代表瞬时的水平变化,EDCs 的长期暴露对促性腺激素合成以及受促性腺激素调控的相关健康结局的影响仍然缺乏研究。EDCs 暴露、促性腺激素水平的改变以及相关的生殖系统疾病和健康效应之间的相关性和因果关系仍然不明确,需要进一步的大规模人群的前瞻性队列研究。

目前关于 EDCs 暴露对 HPG 轴影响的毒理学研究仍不完善,多为高剂量的短期暴露。由于高剂量的 EDCs 暴露可能导致 HPG 轴的内分泌器官的

细胞凋亡和损伤,从而引起其合成的激素水平下降。然而实际环境中 EDCs 大多是低剂量的长期暴露,对 HPG 轴的干扰作用机制可能与高剂量暴露导致的毒性机制不同。例如有研究报道高剂量的氯菊酯暴露导致雄鼠的睾酮水平下降,是由于睾丸间质细胞的线粒体损伤引起细胞凋亡[67];而笔者课题组前期的研究发现在无细胞毒性的环境相关剂量下的氯氰菊酯暴露干扰睾丸间质细胞的钙离子通道,刺激睾酮的合成[66]。某些 EDCs 的暴露还会引起代际传递效应,子代的促性腺激素水平受到干扰,然而相关的机制仍然不明确,有可能涉及到 EDCs 对子代表观遗传的影响。虽然垂体是 HPG 轴上极为重要的内分泌器官,然而由于垂体在颅内,体积极小,获取原代细胞培养较难,因此关于 EDCs 干扰垂体分泌促性腺激素的毒理机制研究十分有限。笔者课题组的一系列研究表明,小鼠垂体瘤细胞系 LβT2 可以响应 EDCs 对 LH 和 FSH 的亚基基因表达以及促性腺激素分泌的调控,是研究 EDCs 调控促性腺激素作用机制的较好的体外模型。因此未来的研究可以结合体内和体外模型,更多聚焦于低剂量 EDCs 长期暴露对促性腺激素以及 HPG 轴的干扰作用和毒性机制。

通讯作者简介:刘璟(1979—),女,博士,教授,主要研究方向为环境内分泌干扰物的暴露特征、健康效应和毒性机制。

参考文献(References):

[1] Kumar M, Sarma D K, Shubham S, et al. Environmental endocrine-disrupting chemical exposure: Role in non-communicable diseases [J]. Frontiers in Public Health, 2020, 8: 553850

[2] Zoeller R T, Brown T R, Doan L L, et al. Endocrine-disrupting chemicals and public health protection: A statement of principles from The Endocrine Society [J]. Endocrinology, 2012, 153(9): 4097-4110

[3] Maqbool F, Mostafalou S, Bahadar H, et al. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms [J]. Life Sciences, 2016, 145: 265-273

[4] Oyola M G, Handa R J. Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: Sex differences in regulation of stress responsivity [J]. Stress, 2017, 20(5): 476-494

[5] Melgarejo M, Mendiola J, Koch H M, et al. Associations between urinary organophosphate pesticide metabolite levels and reproductive parameters in men from an infertility clinic [J]. Environmental Research, 2015, 137: 292-298

[6] Ye X Q, Pan W Y, Zhao S L, et al. Relationships of pyrethroid exposure with gonadotropin levels and pubertal development in Chinese boys [J]. Environmental Science & Technology, 2017, 51(11): 6379-6386

[7] Kaprara A, Huhtaniemi I T. The hypothalamus-pituitary-gonad axis: Tales of mice and men [J]. Metabolism, 2018, 86: 3-17

[8] Stamatiades G A, Kaiser U B. Gonadotropin regulation by pulsatile GnRH: Signaling and gene expression [J]. Molecular and Cellular Endocrinology, 2018, 463: 131-141

[9] Plunk E C, Richards S M. Endocrine-disrupting air pollutants and their effects on the hypothalamus-pituitary-gonadal axis [J]. International Journal of Molecular Sciences, 2020, 21(23): 9191

[10] Dwyer A A, Chavan N R, Lewkowitz-Shpuntoff H, et al. Functional hypogonadotropic hypogonadism in men: Underlying neuroendocrine mechanisms and natural history [J]. The Journal of Clinical Endocrinology & Metabolism, 2019, 104(8): 3403-3414

[11] Goodarzi M O, Dumesic D A, Chazenbalk G, et al. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis [J]. Nature Reviews Endocrinology, 2011(7): 219-231

[12] Saadia Z. Follicle stimulating hormone (LH: FSH) ratio in polycystic ovary syndrome (PCOS)-obese vs. non-obese women [J]. Medical Archives, 2020, 74(4): 289

[13] McKinlay R, Plant J A, Bell J N B, et al. Endocrine disrupting pesticides: Implications for risk assessment [J]. Environment International, 2008, 34(2): 168-183

[14] Bornman M, Delport R, Farías P, et al. Alterations in male reproductive hormones in relation to environmental DDT exposure [J]. Environment International, 2018, 113: 281-289

[15] Freire C, Koifman R J, Sarcinelli P N, et al. Association between serum levels of organochlorine pesticides and sex hormones in adults living in a heavily contaminated area in Brazil [J]. International Journal of Hygiene and Environmental Health, 2014, 217(2-3): 370-378

[16] Eskenazi B, Rauch S A, Tenerelli R, et al. *In utero* and childhood DDT, DDE, PBDE and PCBs exposure and sex hormones in adolescent boys: The CHAMACOS study [J]. International Journal of Hygiene and Environmental Health, 2017, 220(2): 364-372

[17] Aguilar-Garduño C, Lacasaña M, Blanco-Muñoz J, et al. Changes in male hormone profile after occupational organophosphate exposure. A longitudinal study [J]. Toxicology, 2013, 307: 55-65

[18] Qin K L, Zhang Y, Wang Y W, et al. Prenatal organophosphate pesticide exposure and reproductive hormones in cord blood in Shandong, China [J]. International Jour-

nal of Hygiene and Environmental Health, 2020, 225: 113479

[19] Li C M, Cao M F, Ma L J, et al. Pyrethroid pesticide exposure and risk of primary ovarian insufficiency in Chinese women [J]. Environmental Science & Technology, 2018, 52(5): 3240-3248

[20] Jurewicz J, Radwan P, Wielgomas B, et al. Exposure to pyrethroid pesticides and ovarian reserve [J]. Environment International, 2020, 144: 106028

[21] Hoh E, Zhu L Y, Hites R A. Dechlorane plus, a chlorinated flame retardant, in the Great Lakes [J]. Environmental Science & Technology, 2006, 40(4): 1184-1189

[22] Zhu J P, Feng Y L, Shoeib M. Detection of dechlorane plus in residential indoor dust in the city of Ottawa, Canada [J]. Environmental Science & Technology, 2007, 41 (22): 7694-7698

[23] Siddique S, Xian Q M, Abdelouahab N, et al. Levels of dechlorane plus and polybrominated diphenylethers in human milk in two Canadian cities [J]. Environment International, 2012, 39(1): 50-55

[24] Ren G F, Yu Z Q, Ma S T, et al. Determination of dechlorane plus in serum from electronics dismantling workers in South China [J]. Environmental Science & Technology, 2009, 43(24): 9453-9457

[25] Johnson P I, Stapleton H M, Mukherjee B, et al. Associations between brominated flame retardants in house dust and hormone levels in men [J]. Science of the Total Environment, 2013, 445-446: 177-184

[26] Makey C M, McClean M D, Braverman L E, et al. Polybrominated diphenyl ether exposure and reproductive hormones in North American men [J]. Reproductive Toxicology, 2016, 62: 46-52

[27] Gao Y, Chen L M, Wang C F, et al. Exposure to polybrominated diphenyl ethers and female reproductive function: A study in the production area of Shandong, China [J]. Science of the Total Environment, 2016, 572: 9-15

[28] Gravel S, Lavoué J, Bakhiyi B, et al. Multi-exposures to suspected endocrine disruptors in electronic waste recycling workers: Associations with thyroid and reproductive hormones [J]. International Journal of Hygiene and Environmental Health, 2020, 225: 113445

[29] Pan W Y, Ye X Q, Yin S S, et al. Selected persistent organic pollutants associated with the risk of primary ovarian insufficiency in women [J]. Environment International, 2019, 129: 51-58

[30] Tang M L, Yin S S, Zhang J Y, et al. Prenatal exposure to polychlorinated biphenyl and umbilical cord hormones and birth outcomes in an island population [J]. Environmental Pollution, 2018, 237: 581-591

[31] Miyashita C, Araki A, Mitsui T, et al. Sex-related differences in the associations between maternal dioxin-like compounds and reproductive and steroid hormones in cord blood: The Hokkaido study [J]. Environment International, 2018, 117: 175-185

[32] Casals-Casas C, Desvergne B. Endocrine disruptors: From endocrine to metabolic disruption [J]. Annual Review of Physiology, 2011, 73: 135-162

[33] Adoamnei E, Mendiola J, Vela-Soria F, et al. Urinary bisphenol A concentrations are associated with reproductive parameters in young men [J]. Environmental Research, 2018, 161: 122-128

[34] Gao C Z, He H H, Qiu W H, et al. Oxidative stress, endocrine disturbance, and immune interference in humans showed relationships to serum bisphenol concentrations in a dense industrial area [J]. Environmental Science & Technology, 2021, 55(3): 1953-1963

[35] Lassen T H, Frederiksen H, Jensen T K, et al. Urinary bisphenol A levels in young men: Association with reproductive hormones and semen quality [J]. Environmental Health Perspectives, 2014, 122(5): 478-484

[36] Liang H, Xu W P, Chen J P, et al. The association between exposure to environmental bisphenol A and gonadotropic hormone levels among men [J]. PLoS One, 2017, 12(1): e0169217

[37] Meeker J D, Calafat A M, Hauser R. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic [J]. Environmental Science & Technology, 2010, 44(4): 1458-1463

[38] Chen Y, Wang Y C, Ding G D, et al. Association between bisphenol A exposure and idiopathic central precocious puberty (ICPP) among school-aged girls in Shanghai, China [J]. Environment International, 2018, 115: 410-416

[39] Hyun Kim D, Min Choi S, Soo Lim D, et al. Risk assessment of endocrine disrupting phthalates and hormonal alterations in children and adolescents [J]. Journal of Toxicology and Environmental Health, Part A, 2018, 81(21): 1150-1164

[40] Wang B, Qin X L, Xiao N, et al. Phthalate exposure and semen quality in infertile male population from Tianjin, China: Associations and potential mediation by reproductive hormones [J]. Science of the Total Environment, 2020, 744: 140673

[41] Chen Q, Yang H, Zhou N Y, et al. Phthalate exposure, even below US EPA reference doses, was associated with semen quality and reproductive hormones: Prospective MARHCS study in general population [J]. Environment International, 2017, 104: 58-68

[42] Muerköster A P, Frederiksen H, Juul A, et al. Maternal

phthalate exposure associated with decreased testosterone/LH ratio in male offspring during mini-puberty. Odense Child Cohort [J]. Environment International, 2020, 144: 106025

[43] Cao M F, Pan W Y, Shen X Y, et al. Urinary levels of phthalate metabolites in women associated with risk of premature ovarian failure and reproductive hormones [J]. Chemosphere, 2020, 242: 125206

[44] Guth M, Pollock T, Fisher M, et al. Concentrations of urinary parabens and reproductive hormones in girls 6-17 years living in Canada [J]. International Journal of Hygiene and Environmental Health, 2021, 231: 113633

[45] Jensen T K, Andersson A M, Main K M, et al. Prenatal paraben exposure and anogenital distance and reproductive hormones during mini-puberty: A study from the Odense Child Cohort [J]. Science of the Total Environment, 2021, 769: 145119

[46] Janjua N R, Mortensen G K, Andersson A M, et al. Systemic uptake of diethyl phthalate, dibutyl phthalate, and butyl paraben following whole-body topical application and reproductive and thyroid hormone levels in humans [J]. Environmental Science & Technology, 2007, 41(15): 5564-5570

[47] Smith K W, Souter I, Dimitriadis I, et al. Urinary paraben concentrations and ovarian aging among women from a fertility center [J]. Environmental Health Perspectives, 2013, 121(11-12): 1299-1305

[48] Jurewicz J, Radwan M, Wielgomas B, et al. Parameters of ovarian reserve in relation to urinary concentrations of parabens [J]. Environmental Health, 2020, 19(1): 26

[49] Liang Y S, Tang Z, Jiang Y S, et al. Serum metabolic changes associated with dioxin exposure in a Chinese male cohort [J]. Environment International, 2020, 143: 105984

[50] Patrizi B, Siciliani de Cumis M. TCDD toxicity mediated by epigenetic mechanisms [J]. International Journal of Molecular Sciences, 2018, 19(12): 4101

[51] Mocarelli P, Gerthoux P M, Needham L L, et al. Perinatal exposure to low doses of dioxin can permanently impair human semen quality [J]. Environmental Health Perspectives, 2011, 119(5): 713-718

[52] Lambertino A, Persky V, Freels S, et al. Associations of PCBS, dioxins and furans with follicle-stimulating hormone and luteinizing hormone in postmenopausal women: National Health and Nutrition Examination Survey 1999-2002 [J]. Chemosphere, 2021, 262: 128309

[53] Ye X Q, Pan W Y, Li C M, et al. Exposure to polycyclic aromatic hydrocarbons and risk for premature ovarian failure and reproductive hormones imbalance [J]. Journal of Environmental Sciences, 2020, 91: 1-9

[54] Yin S S, Tang M L, Chen F F, et al. Environmental exposure to polycyclic aromatic hydrocarbons (PAHs): The correlation with and impact on reproductive hormones in umbilical cord serum [J]. Environmental Pollution, 2017, 220: 1429-1437

[55] Chen Q, Wang F R, Yang H, et al. Exposure to fine particulate matter-bound polycyclic aromatic hydrocarbons, male semen quality, and reproductive hormones: The MARCHS study [J]. Environmental Pollution, 2021, 280: 116883

[56] Interdonato M, Pizzino G, Bitto A, et al. Cadmium delays puberty onset and testis growth in adolescents [J]. Clinical Endocrinology, 2015, 83(3): 357-362

[57] Ciarrocca M, Capozzella A, Tomei F, et al. Exposure to cadmium in male urban and rural workers and effects on FSH, LH and testosterone [J]. Chemosphere, 2013, 90(7): 2077-2084

[58] Jackson L W, Howards P P, Wactawski-Wende J, et al. The association between cadmium, lead and mercury blood levels and reproductive hormones among healthy, premenopausal women [J]. Human Reproduction, 2011, 26(10): 2887-2895

[59] Pollack A Z, Schisterman E F, Goldman L R, et al. Cadmium, lead, and mercury in relation to reproductive hormones and anovulation in premenopausal women [J]. Environmental Health Perspectives, 2011, 119(8): 1156-1161

[60] Pan W Y, Ye X Q, Zhu Z Y, et al. Urinary cadmium concentrations and risk of primary ovarian insufficiency in women: A case-control study [J]. Environmental Geochemistry and Health, 2021, 43(5): 2025-2035

[61] Lee T W, Kim D H, Ryu J Y. The effects of exposure to lead, cadmium and mercury on follicle-stimulating hormone levels in men and postmenopausal women: Data from the Second Korean National Environmental Health Survey (2012-2014) [J]. Annals of Occupational and Environmental Medicine, 2019, 31: e21

[62] Dehghan S F, Mehrifar Y, Ardalan A. The relationship between exposure to lead-containing welding fumes and the levels of reproductive hormones [J]. Annals of Global Health, 2019, 85(1): 125

[63] Ben Rhouma K, Tébourbi O, Krichah R, et al. Reproductive toxicity of DDT in adult male rats [J]. Human & Experimental Toxicology, 2001, 20(8): 393-397

[64] Rasier G, Parent A S, Gérard A, et al. Early maturation of gonadotropin-releasing hormone secretion and sexual precocity after exposure of infant female rats to estradiol or dichlorodiphenyltrichloroethane [J]. Biology of Reproduction, 2007, 77(4): 734-742

[65] Alaa-Eldin E A, El-Shafei D A, Abouhashem N S. Individual and combined effect of chlorpyrifos and cypermethrin on reproductive system of adult male albino rats [J]. Environmental Science and Pollution Research International, 2017, 24(2): 1532-1543

[66] Ye X Q, Li F X, Zhang J Y, et al. Pyrethroid insecticide cypermethrin accelerates pubertal onset in male mice via disrupting hypothalamic-pituitary-gonadal axis [J]. Environmental Science & Technology, 2017, 51(17): 10212-10221

[67] Zhang S Y, Ito Y, Yamanoshita O, et al. Permethrin may disrupt testosterone biosynthesis via mitochondrial membrane damage of leydig cells in adult male mouse [J]. Endocrinology, 2007, 148(8): 3941-3949

[68] Zhou Y J, Wang X D, Xiao S, et al. Exposure to beta-cypermethrin impairs the reproductive function of female mice [J]. Regulatory Toxicology and Pharmacology, 2018, 95: 385-394

[69] Li Y F, Pan C, Hu J X, et al. Effects of cypermethrin on male reproductive system in adult rats [J]. Biomedical and Environmental Sciences, 2013, 26(3): 201-208

[70] Simon-Delso N, Amaral-Rogers V, Belzunces L P, et al. Systemic insecticides (neonicotinoids and fipronil): Trends, uses, mode of action and metabolites [J]. Environmental Science and Pollution Research International, 2015, 22(1): 5-34

[71] Bass C, Field L M. Neonicotinoids [J]. Current Biology, 2018, 28(14): R772-R773

[72] Kapoor U, Srivastava M K, Srivastava L P. Toxicological impact of technical imidacloprid on ovarian morphology, hormones and antioxidant enzymes in female rats [J]. Food and Chemical Toxicology, 2011, 49(12): 3086-3089

[73] Abdel-Razik R K, Mosallam E M, Hamed N A, et al. Testicular deficiency associated with exposure to cypermethrin, imidacloprid, and chlorpyrifos in adult rats [J]. Environmental Toxicology and Pharmacology, 2021, 87: 103724

[74] Arıcan E Y, Gökçeoğlu Kayalı D, Ulus Karaca B, et al. Reproductive effects of subchronic exposure to acetamiprid in male rats [J]. Scientific Reports, 2020, 10(1): 8985

[75] Li Z Q, Li H T, Li C C, et al. Low dose of fire retardant, 2,2',4,4'-tetrabromodiphenyl ether (BDE47), stimulates the proliferation and differentiation of progenitor Leydig cells of male rats during prepuberty [J]. Toxicology Letters, 2021, 342: 6-19

[76] Lefèvre P L C, Berger R G, Ernest S R, et al. Exposure of female rats to an environmentally relevant mixture of brominated flame retardants targets the ovary, affecting folliculogenesis and steroidogenesis [J]. Biology of Reproduction, 2016, 94(1): 9, 1-11

[77] Steinberg R M, Walker D M, Juenger T E, et al. Effects of perinatal polychlorinated biphenyls on adult female rat reproduction: Development, reproductive physiology, and second generational effects [J]. Biology of Reproduction, 2008, 78(6): 1091-1101

[78] Yamamoto M, Narita A, Kagohata M, et al. Effects of maternal exposure to 3, 3', 4, 4', 5-pentachlorobiphenyl (PCB126) or 3, 3', 4, 4', 5, 5'-hexachlorobiphenyl (PCB169) on testicular steroidogenesis and spermatogenesis in male offspring rats [J]. Journal of Andrology, 2005, 26(2): 205-214

[79] Fiandanese N, Borromeo V, Berrini A, et al. Maternal exposure to a mixture of di(2-ethylhexyl) phthalate (DEHP) and polychlorinated biphenyls (PCBs) causes reproductive dysfunction in adult male mouse offspring [J]. Reproductive Toxicology, 2016, 65: 123-132

[80] Oliveira I M, Romano R M, de Campos P, et al. Delayed onset of puberty in male offspring from bisphenol A-treated dams is followed by the modulation of gene expression in the hypothalamic-pituitary-testis axis in adulthood [J]. Reproduction, Fertility and Development, 2017, 29(12): 2496

[81] Yuan M, Zhao Y N, Lin R, et al. Adverse reproductive function induced by maternal BPA exposure is associated with abnormal autophagy and activating inflamation via mTOR and TLR4/NF-κB signaling pathways in female offspring rats [J]. Reproductive Toxicology, 2020, 96: 185-194

[82] Ullah A, Pirzada M, Jahan S, et al. Impact of low-dose chronic exposure to bisphenol A and its analogue bisphenol B, bisphenol F and bisphenol S on hypothalamo-pituitary-testicular activities in adult rats: A focus on the possible hormonal mode of action [J]. Food and Chemical Toxicology, 2018, 121: 24-36

[83] Nourian A, Soleimanzadeh A, Shalizar Jalali A, et al. Bisphenol-A analogue (bisphenol-S) exposure alters female reproductive tract and apoptosis/oxidative gene expression in blastocyst-derived cells [J]. Iranian Journal of Basic Medical Sciences, 2020, 23(5): 576-585

[84] Giribabu N, Reddy P S. Protection of male reproductive toxicity in rats exposed to di-*n*-butyl phthalate during embryonic development by testosterone [J]. Biomedicine & Pharmacotherapy, 2017, 87: 355-365

[85] 于森, 张林媛, 乔佩环, 等. 邻苯二甲酸二丁酯诱导氧化应激及抑制 CYP17a1 干扰睾酮合成[J]. 卫生研究, 2015, 44(3): 364-370
Yu M, Zhang L Y, Qiao P H, et al. Testicular oxidative

stress and downregulation of CYP17a1 induced by di(*n*-butyl) phthalate inhibit synthesis of testosterone [J]. Journal of Hygiene Research, 2015, 44(3): 364-370 (in Chinese)

[86] Nelli G, Pamanji S R. Di-*n*-butyl phthalate prompts interruption of spermatogenesis, steroidogenesis, and fertility associated with increased testicular oxidative stress in adult male rats [J]. Environmental Science and Pollution Research International, 2017, 24(22): 18563-18574

[87] Ha M, Guan X, Wei L, et al. Di-(2-ethylhexyl) phthalate inhibits testosterone level through disturbed hypothalamic-pituitary-testis axis and ERK-mediated 5α-Reductase 2 [J]. Science of the Total Environment, 2016, 563-564: 566-575

[88] Yue M, Ma R S, Zhang R Z, et al. Effects of dimethyl phthalate (DMP) on serum sex hormone levels and apoptosis in C57 female mice [J]. International Journal of Endocrinology and Metabolism, 2019, 17(2): e82882

[89] Guerra M T, Sanabria M, Leite G A A, et al. Maternal exposure to butyl paraben impairs testicular structure and sperm quality on male rats [J]. Environmental Toxicology, 2017, 32(4): 1273-1289

[90] Zhang L Y, Dong L, Ding S J, et al. Effects of *n*-butylparaben on steroidogenesis and spermatogenesis through changed E2 levels in male rat offspring [J]. Environmental Toxicology and Pharmacology, 2014, 37(2): 705-717

[91] Maske P, Dighe V, Mote C, et al. *n*-butylparaben exposure through gestation and lactation impairs spermatogenesis and steroidogenesis causing reduced fertility in the F1 generation male rats [J]. Environmental Pollution, 2020, 256: 112957

[92] Takeda T, Matsumoto Y, Koga T, et al. Maternal exposure to dioxin disrupts gonadotropin production in fetal rats and imprints defects in sexual behavior [J]. The Journal of Pharmacology and Experimental Therapeutics, 2009, 329 (3): 1091-1099

[93] Yu K L, Zhang X L, Tan X M, et al. Transgenerational impairment of ovarian induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) associated with Igf2 and H19 in adult female rat [J]. Toxicology, 2019, 428: 152311

[94] Li X S, Guo J T, Jiang X W, et al. Cyanidin-3-O-glucoside protects against cadmium-induced dysfunction of sex hormone secretion via the regulation of hypothalamus-pituitary-gonadal axis in male pubertal mice [J]. Food and Chemical Toxicology, 2019, 129: 13-21

[95] da Costa C S, Oliveira T F, Freitas-Lima L C, et al. Subacute cadmium exposure disrupts the hypothalamic-pituitary-gonadal axis, leading to polycystic ovarian syndrome and premature ovarian failure features in female rats [J]. Environmental Pollution, 2021, 269: 116154

[96] Madboli A E N A, Seif M M. Immunohistochemical, histopathological, and biochemical studies of the NF-B P65 marker in rat ovaries experimentally intoxicated by cadmium and the protective effect of the purslane plant extract [J]. Environmental Science and Pollution Research International, 2021, 28(14): 17613-17626

[97] Wang J C, Zhu H L, Lin S, et al. Protective effect of naringenin against cadmium-induced testicular toxicity in male SD rats [J]. Journal of Inorganic Biochemistry, 2021, 214: 111310

[98] Alotaibi M F, Al-Joufi F, Abou Seif H S, et al. Umbelliferone inhibits spermatogenic defects and testicular injury in lead-intoxicated rats by suppressing oxidative stress and inflammation, and improving Nrf2/HO-1 signaling [J]. Drug Design, Development and Therapy, 2020, 14: 4003-4019

[99] Svechnikova I, Svechnikov K, Söder O. The influence of di-(2-ethylhexyl) phthalate on steroidogenesis by the ovarian granulosa cells of immature female rats [J]. The Journal of Endocrinology, 2007, 194(3): 603-609

[100] Zhou J H, Yang Y, Xiong K, et al. Endocrine disrupting effects of dichlorodiphenyltrichloroethane analogues on gonadotropin hormones in pituitary gonadotrope cells [J]. Environmental Toxicology and Pharmacology, 2014, 37 (3): 1194-1201

[101] Li F X, Ma H H, Liu J. Pyrethroid insecticide cypermethrin modulates gonadotropin synthesis via calcium homeostasis and ERK1/2 signaling in LβT2 mouse pituitary cells [J]. Toxicological Sciences, 2017, 162(1): 43-52

[102] Xin F, Susiarjo M, Bartolomei M S. Multigenerational and transgenerational effects of endocrine disrupting chemicals: A role for altered epigenetic regulation? [J]. Seminars in Cell & Developmental Biology, 2015, 43: 66-75

[103] Latchney S E, Fields A M, Susiarjo M. Linking inter-individual variability to endocrine disruptors: Insights for epigenetic inheritance [J]. Mammalian Genome, 2018, 29(1-2): 141-152

[104] Takeda T, Fujii M, Taura J, et al. Dioxin silences gonadotropin expression in perinatal pups by inducing histone deacetylases: A new insight into the mechanism for the imprinting of sexual immaturity by dioxin [J]. Journal of Biological Chemistry, 2012, 287(22): 18440-18450 ◆