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内分泌干扰物对机体脂质代谢的影响及其机制研究进展

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摘要: 近年来许多动物实验研究表明,内分泌干扰物(endocrine disrupting chemicals, EDCs)暴露除了会损伤生殖、免疫和神经系统等,还能够干扰脂质代谢,增加肥胖、非酒精性脂肪肝和高脂血症等疾病的发病风险。笔者总结了多种 EDCs 对不同动物模型(哺乳动物、硬骨鱼类、两栖动物)脂质代谢的影响,主要包括促进哺乳动物脂肪细胞分化、脂质蓄积和促进肥胖的表观遗传跨代继承,促进硬骨鱼类脂肪从头合成和脂质蓄积,破坏两栖动物的脂质平衡;并从 4 个方面综述了 EDCs 影响脂质代谢的作用机制,包括(1)影响转录因子的表达,从而影响脂质代谢相关酶和蛋白的表达水平;(2)影响调控昼夜节律的时钟基因的活性继而诱导脂质蓄积;(3)影响内源性大麻素和大麻素受体的表达从而改变瘦素或脂肪肝信号神经肽 Y 的表达;(4)影响表观遗传修饰继而影响脂质代谢相关酶、转录因子和脂肪细胞因子的表达。最后,提出今后研究需关注新型 EDCs 对脂质代谢的影响,同时应深入研究昼夜节律、内源性大麻素系统和表观遗传修饰等不同途径之间的交叉作用,以更好地了解 EDCs 通过以上机制影响脂质代谢的过程。

关键词: 内分泌干扰物;脂质代谢;肥胖;非酒精性脂肪肝;作用机制

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Research Progress on Effects of Endocrine Disrupting Chemicals on Lipid Metabolism of Organisms and Underlying Mechanisms

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Abstract: Recent studies on animal experiments have shown that exposure of endocrine disrupting chemicals (EDCs), in addition to damaging reproductive, immune, and nervous systems, can also interfere with lipid metabolism of organisms and increase the risk of diseases such as obesity, non-alcoholic fatty liver, and hyperlipidemia. This article summarized the effects of various EDCs on lipid metabolism in different animal models. In mammals, EDCs were reported to mainly promote adipocyte differentiation, lipid accumulation and epigenetic transgenerational inheritance of obesity. In teleosts, EDCs were found to promote *de novo* synthesis and lipid accumulation. In amphibians, EDCs were reported to be able to destroy the balance of lipid metabolism. Moreover, it is reported that EDCs produce the above adverse effects by: (1) affecting expressions of transcription factors and thus interfering

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with the expression levels of lipid metabolism related enzymes and proteins, (2) disturbing activities of clock genes that regulate circadian rhythm and as such to induce lipid accumulation, (3) changing the expression levels of endogenous cannabinoids and cannabinoid receptors to alter expression levels of leptin or fatty liver signaling neuropeptide Y, and (4) changing epigenetic modifications and then influencing expressions of lipid metabolism related enzymes, transcription factors, and adipokines. In addition, this article proposed that more attention should be paid to the adverse effects produced by new EDCs on animal lipid metabolism, and the interaction between different pathways of circadian rhythm, endocannabinoid system, and epigenetic modifications on lipid metabolism should be further studied, to deepen the understanding towards the mechanisms of EDCs interference on lipid metabolism.
Keywords: endocrine disrupting chemicals; lipid metabolism; obesity; non-alcoholic fatty liver; underlying mechanism

内分泌干扰物(endocrine disrupting chemicals, EDCs)是一种外源性物质,能干扰生物机体内源激素的合成、释放、转运、结合作用或清除过程,从而影响机体内环境稳态、生长、生殖和发育等生理过程[1]。EDCs 主要来源于工农业生产和人们日常生活中产生的废水、废气、废渣,包括天然雌激素如雌二醇、异黄酮类,工业化学品如邻苯二甲酸酯、双酚类、烷基酚,农药如滴滴涕、拟除虫菊酯类,重金属如铅、汞等[1]。人类接触 EDCs 的主要途径是消化道、呼吸道和皮肤,进入体内的 EDCs 会诱发多种不良健康效应。目前,EDCs 的毒理效应研究多集中于对生殖系统、免疫系统、神经系统以及甲状腺内分泌系统等的影响,而近年来 EDCs 对脂质代谢的影响也逐渐引起人们的关注[2]。研究发现化学品暴露能刺激脂肪生成以及干扰脂质代谢和能量平衡,增加肥胖的风险,因此有学者提出了“环境致肥胖因子”假说[2]。脂质由饮食摄入,并能在肝脏、脂肪和肠等许多组织中储存,其在保持能量平衡、控制食物摄入、调节生长、生殖和维持机体健康方面发挥重要作用。脂质代谢紊乱会导致多种疾病的发生,如肥胖、非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)、高脂血症、脂质贮积病和新生儿硬肿症等[3]。因此,了解 EDCs 对脂质代谢的影响和作用机制,对于全面评估 EDCs 的健康风险具有重要意义。本文总结了 EDCs 对不同动物模型脂质代谢的影响及其作用机制,以期为评价 EDCs 的安全性及其对人体健康的潜在风险提供参考。

1　EDCs 对脂质代谢的影响(Effects of EDCs on lipid metabolism)

采用不同的动物模型和暴露途径,很多研究者都发现 EDCs 暴露能够影响机体脂质代谢过程(表 1),具有潜在健康风险。

1.1　哺乳动物

哺乳动物中的研究发现,当机体处于脂肪细胞分化和器官发育的关键时期时,暴露于 EDCs 会导致脂质代谢紊乱,继而引发肥胖、NAFLD 和高血脂症等多种代谢性疾病。EDCs 对哺乳动物脂质代谢的作用主要表现在以下 3 个方面。

(1)诱导脂肪细胞分化

脂肪细胞起源于多功能干细胞,多功能干细胞在激素、转录因子等的调控下依次分化为脂肪母细胞、前脂肪细胞、不成熟脂肪细胞和成熟脂肪细胞。体外试验发现多种 EDCs 可诱导脂肪细胞分化:三丁基锡(tributyltin, TBT)可诱导小鼠 3T3-L1 脂肪细胞分化[4],也可促进前脂肪细胞增殖,增加脂肪细胞的大小[5];二丁基锡(dibutyltin, DBT)会促进人和小鼠间充质干细胞脂肪细胞分化[6];有机锡化合物可诱导不完全分化培养基中脂肪细胞的分化[7],双酚 A(bisphenol A, BPA)通过影响人类 3T3-L1 前脂肪细胞分化促进前脂肪细胞增殖,导致脂肪细胞肥大[8];2,2’,4,4’-四溴联苯醚(brominated diphenyl ether 47, BDE-47)染毒小鼠 3T3-L1 脂肪细胞,结果显示暴露浓度越高,脂肪细胞分化程度越高[9]。

(2)促进脂质蓄积

有的 EDCs 仅会增加哺乳动物脂肪细胞中脂质的积累,而有的 EDCs 引起的生物效应较严重,可导致非脂肪细胞特别是肝细胞中甘油三酯(triacylglycerol, TAG)(中性脂肪)过度堆积即脂肪变性。例如,围产期 C57BL/6J 小鼠暴露于低剂量的 DBT,导致后代雄性小鼠的脂肪储存量增加[6];TBT 会增加小鼠 3T3-L1 脂肪细胞的脂质积累[10],还会增加雌性大鼠白色脂肪组织中脂滴的数量[11];孕期多环芳烃(polycyclic aromatic hydrocarbons, PAHs)过量暴露会增加母代和子代小鼠的脂肪质量和体质量[12]。邻苯

二甲酸二(2-乙基)己酯(di(2-ethylhexyl) phthalate, DEHP)暴露破坏了 HepG2 细胞的氧化应激平衡,最终促进肝细胞脂质积聚[13];四氯二苯并-*p*-二噁英暴露增加了雌性 C57BL/6J 小鼠肝脏 TAG 的含量[14];BPA 诱导人肝细胞 HHL-5 细胞发生肝脂肪变性[15];邻苯二甲酸单乙基己酯诱导胆固醇在小鼠肝脏中的沉积[16];有机磷阻燃剂会导致人肝细胞中 TAG 和总胆固醇沉积,诱发肝脂肪变性[17]。而肝脂肪变性会继而引起 NAFLD 的发生,如 DEHP 通过增加肝脏脂质积累以及引起脂质过氧化和炎症使高脂饮食的 SD 大鼠诱发 NAFLD,导致肝细胞形态学改变(小空泡和轻度炎症)[13];壬基酚(nonylphenol, NP)与 DEHP 类似,也可能使高糖/高脂饮食的 SD 大鼠诱发 NAFLD,表现为大鼠囊泡性脂肪变性,以及肝脏炎性细胞浸润[18]。

(3)促进肥胖的表观遗传跨代继承

如果环境因素导致亲代生殖系细胞发生表观遗传修饰,然后在代间生殖系传递,那么没有直接暴露于环境因子的后代仍然表现出相关的表观遗传改变或表型,则称为表观遗传的跨代继承[19]。如孕期大鼠(F0 代)暴露于 EDCs,发育中的胚胎(F1 代)和胚胎中的生殖细胞(F2 代)也直接暴露于环境污染物中,那么 F0、F1 和 F2 代属于多代暴露,而 F3 代则属于跨代继承[20]。Manikkam 等[21]研究发现,大鼠妊娠 8 ~ 14 d 暴露于 BPA、DEHP 和邻苯二甲酸二丁酯的混合物,低剂量的混合物会导致 F3 代雌性肥胖率显著增加,并且 F3 代精子 DNA 中出现差异 DNA 甲基化区域。在另一个类似研究中,研究者采用甲氧滴滴涕染毒妊娠期大鼠,并将 F3 代的雌雄大鼠与野生的雌雄大鼠分别杂交,然后测定 F4 代的肥胖率,发现肥胖表型主要是通过雌性生殖系实现跨代传递的[20]。Skinner 等[19]的研究中用滴滴涕染毒大鼠,发现低剂量暴露导致 F3 代雌雄肥胖率均显著增加,但高剂量暴露仅显著升高了 F3 代雄性肥胖率;类似地,研究者发现 F3 代精子 DNA 中出现差异 DNA 甲基化区域,而且肥胖也是通过雌性生殖系传播。因此,目前的研究已经可以证明污染物暴露可以诱导 F0 代妊娠雌性大鼠疾病的表观遗传,这种遗传机制可以通过种系的表观遗传变化来跨代传递疾病,与这些跨代疾病发生率相关的是精子 DNA 的跨代表观遗传突变,而女性生殖系表观遗传效应尚待阐明。

1.2 硬骨鱼类

由于脊椎动物脂质代谢过程中涉及的主要基因、关键信号通路和代谢通路高度保守,而鱼类与哺乳动物相比饲养简单、成本低、繁殖能力强、伦理道德要求低,所以很多研究也采用鱼类为模式生物探讨 EDCs 对机体脂质代谢的影响。目前研究发现的 EDCs 对硬骨鱼类脂质代谢的影响主要包括以下 2 个方面。

(1)促进脂肪从头合成

相比小肠和脂肪等组织,肝脏的脂肪从头合成能力最强,研究发现,TBT、BPA、二乙二醇二苯甲酸酯、DEHP 和邻苯二甲酸二异壬酯(di-isononylphthalate, DINP)暴露均会促进斑马鱼、大西洋鲷或稀有鮈鲃等鱼类肝脏中脂肪的从头合成,导致脂质和 TAG 的含量增加,糖原和磷脂的含量降低[22-25]。

(2)促进脂质积累

与哺乳动物类似,EDCs 也可诱导鱼类脂肪细胞脂质积累、肝脂肪变性和 NAFLD。TBT 和三苯基锡能促进虹鳟脂肪细胞脂质积累[26]。二苯甲酮-2 (benzophenone 2, BP-2)可促进斑马鱼胚胎卵黄囊脂质积累[27]。双酚 S(bisphenol S, BPS)、TBT、BPA、DINP、三氯生(triclosan, TCS)、NP 和 4-叔辛基苯酚会诱导斑马鱼、大西洋鲷和青鳉肝脂肪变性和肝脏细胞组织学形态变化[15,22,24-25,28-35];还有研究发现,由于不同化学品之间存在的拮抗作用,BPA、NP 和 4-叔辛基苯酚任意 2 种混合暴露,使大西洋鲷肝脏脂质积累与单一化学品暴露相比均有所降低,但仍明显高于对照组[36]。BPA、BPS、TCS 和 DEHP 会增加与 NAFLD 发展相关肝脏基因的表达,从而增加成年斑马鱼 NAFLD 的发病风险[37-39]。

1.3 两栖动物

目前关于 EDCs 对两栖动物脂质代谢的研究较少,有研究表明,TBT 和视黄醇类 X 受体/维甲酸 X 受体(retinoid X receptor, RXR)的特异性配体 LG100268、AGN195203 作用于非洲爪蟾后会导致性腺周围形成异位脂肪细胞,刺激脂肪酸摄取和 TAG 合成,破坏脂质平衡[5]。

2 EDCs 影响脂质代谢的机制研究(Research on the mechanisms of EDCs affecting lipid metabolism)

脂质代谢过程分为合成代谢和分解代谢。脂肪在肝脏、小肠和脂肪组织中合成,合成后与载脂蛋白结合成极低密度脂蛋白进入血液,然后运送到脂肪组织进行储存,或者进入肝脏进行 β-氧化产生能量。脂质代谢过程主要受到过氧化物酶体增殖物激

活受体(peroxisome proliferators-activated receptors, PPARs)、CCAAT 增强子结合蛋白(CCAAT enhancer binding protein, C/EBP)、固醇调节元件结合蛋白(sterol-regulatory element binding proteins, SREBP)和肝 X 受体(liver X receptors, LXRs)等转录因子的调控。近年来发现昼夜节律、内源性大麻素系统以及表观遗传修饰也参与了脂质代谢的调控。

内分泌系统即激素系统,除了包括遍布全身的腺体以及腺体分泌的激素外,还包括识别和响应激素的各种器官和组织中的受体;因而,对内分泌相关核受体直接或间接的影响都可以被归为是对内分泌系统功能的影响。比如,PPARs 是典型的内分泌相关核受体,因此可以认为污染物对 PPARs 的直接影响体现了其对内分泌系统功能的影响。此外,EDCs 也可以通过 LXRs、C/EBP 和 SREBP 等其他转录因子间接影响 PPARs 功能,同时也能通过影响昼夜节律、内源性大麻素系统和表观遗传修饰等因素间接调控核受体 PPARs,进而影响脂质代谢过程。因此,围绕 EDCs 对内分泌相关核受体特别是对 PPARs 的影响,本研究将从干预转录因子表达以及影响昼夜节律、内源性大麻素系统和表观遗传修饰等 4 个方面,综述 EDCs 扰乱脂质代谢的作用机制。

2.1　EDCs 通过影响转录因子干扰脂质代谢

上述提到的转录因子在调控脂质代谢的过程中会相互影响、共同发挥作用,调节脂质合成和分解相关基因的表达水平(图 1)。其中,PPARs 对脂质代谢的调控最为关键,它可以与 RXR 形成二聚体,控制与脂肪细胞分化和脂肪酸氧化有关基因的表达[40],

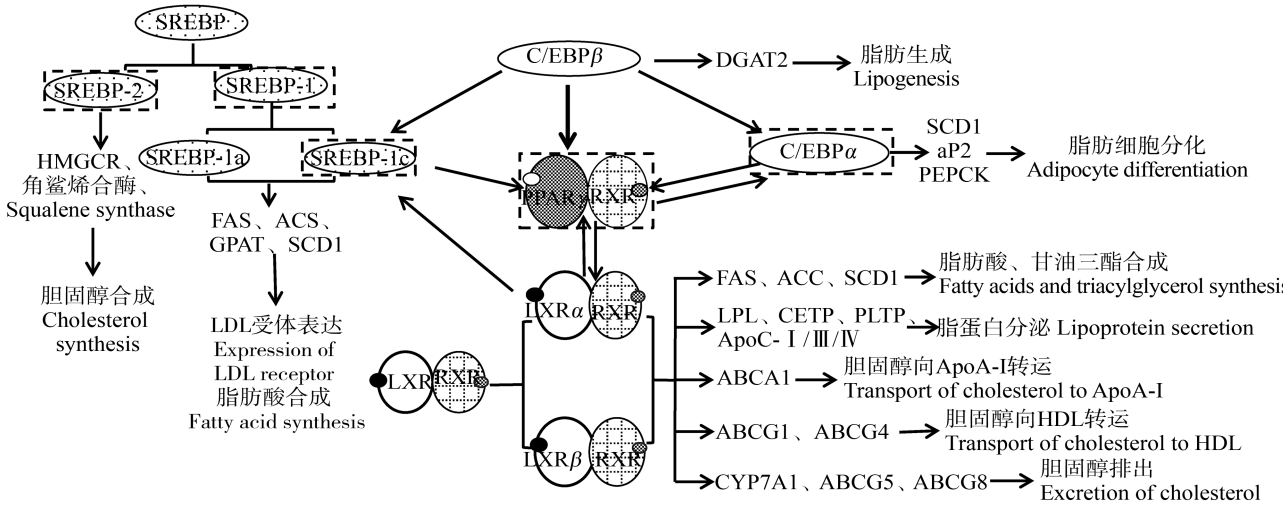

图 1　转录因子在脂质代谢中的调控作用

注:SREBP 表示固醇调节元件结合蛋白;C/EBP 表示 CCAAT 增强子结合蛋白;PPAR 表示过氧化物酶体增殖物激活受体;RXR 表示视黄醇类 X 受体/维甲酸 X 受体;LXR 表示肝 X 受体;HMGCR 表示 3-羟基-3-甲基戊二酸单酰辅酶 A 还原酶;FAS 表示脂肪酸合成酶;ACS 表示乙酰辅酶 A 合成酶;GPAT 表示甘油三磷酸酰基转移酶;SCD1 表示硬脂酰辅酶 A 去饱和酶 1;LDL 表示低密度脂蛋白;DGAT2 表示二酯酰甘油酰基转移酶 2;aP2 表示脂肪酸结合蛋白;PEPCK 表示磷酸烯醇式丙酮酸羧激酶;ACC 表示乙酰辅酶 A 羧化酶;LPL 表示脂蛋白脂肪酶;CETP 表示胆固醇酯转移蛋白;PLTP 表示磷脂转移蛋白;ApoC-Ⅰ/Ⅲ/Ⅳ表示载脂蛋白 C-Ⅰ/Ⅲ/Ⅳ;ABCA1、ABCG1、ABCG4、ABCG5、ABCG8 表示 ATP 结合盒转运体 A1/G1/G4/G5/G8;CYP7A1 表示胆固醇 7α-羟化酶;ApoA-Ⅰ表示载脂蛋白 A-Ⅰ;HDL 表示高密度脂蛋白;虚线框表示目前研究中发现的 EDCs 的可能作用靶标。

Fig. 1　Regulation of transcription factors in lipid metabolism

Note: SREBP stands for sterol-regulatory element binding proteins; C/EBP stands for CCAAT enhancer binding protein; PPAR stands for peroxisome proliferators-activated receptors; RXR stands for retinoid X receptor; LXR stands for liver X receptors; HMGCR stands for 3-hydroxy-3-methylglutaryl coenzyme-A reductase; FAS stands for fatty acid synthetase; ACS stands for acyl-CoA synthetase; GPAT stands for glycerol-3-phosphate acyltransferases; SCD1 stands for stearoyl-CoA desaturase 1; LDL stands for low density lipoprotein; DGAT2 stands for diacylgycerol acyltransferase 2; aP2 stands for adipocyte fatty acid binding protein; PEPCK stands for phosphoenolpyruvate carboxykinase; ACC stands for acetyl CoA carboxylase; LPL stands for lipoprotein lipase; CETP stands for cholsterol ester transfer protein; PLTP stands for phospholipid transfer protein; ApoC-Ⅰ/Ⅲ/Ⅳ stands for apolipoprotein C-Ⅰ/Ⅲ/Ⅳ; ABCA1, ABCG1, ABCG4, ABCG5, ABCG8 stand for ATP-binding cassette A1/G1/G4/G5/G8; CYP7A1 stands for cholesterol 7 alpha-hydroxylase; ApoA-Ⅰ stands for apolipoprotein A-Ⅰ; HDL stands for high-density lipoprotein; the dotted box stands for the possible target of EDCs found in the current study.

C/EBP、SREBP 和 LXRs 也是脂质代谢的主要参与者,它们可与 PPARs 相互作用,调控对脂质合成和摄取以及胆固醇代谢有关基因的表达[41-44]。C/EBP 中的亚型 C/EBPβ、C/EBPα 和 PPARγ 在脂肪形成过程中参与级联反应:C/EBPβ 会激活 C/EBPα 和 PPARγ 的转录,C/EBPβ 激活 PPARγ 因子可介导脂质生成,影响全身脂肪含量。SREBP-1c 在脂肪细胞分化以及形成过程中会与 C/EBPβ、PPARγ 共同作用。

研究发现,环境中很多 EDCs 可以通过影响脂质代谢中关键转录因子的表达,干扰脂肪的生成和代谢[7,9]。TBT 和 BDE-47 都可通过上调 PPARγ 的表达来促进小鼠 3T3-L1 脂肪细胞分化。邻苯二甲酸单乙基己酯通过上调 C/EBPα、磷酸烯醇式丙酮酸羧激酶、肠脂肪酸结合蛋白和脂联素表达水平诱导分化脂肪细胞产生炎症[45]。人类 3T3-L1 前脂肪细胞暴露于 BPA 以及人类干细胞暴露于 DBT 后,均会激活 PPARγ 和 C/EBPα 的表达,促进脂肪细胞分化和脂质蓄积[4,6]。DEHP 可上调 SD 大鼠和 HepG2 细胞中 PPARα 和 SREBP-1c 的表达,促进了肝脏脂肪的生成,导致肝细胞脂质积聚[13,46]。NP 暴露干扰了 Wister 大鼠脂肪生成关键调控因子基因 *pparγ*、*srebp-1*、脂肪酸合成酶(fatty acid synthase, FAS)和脂蛋白脂肪酶(lipoprtein lipase, LPL)的表达,增加了脂肪细胞数量及大小[47];还能通过上调成脂基因 *srebp-1c*、*fas* 和解偶联蛋白 2 等,增加高脂饮食大鼠患 NAFLD 的风险[18]。BALB/cByj 小鼠产前暴露于 PAHs,脂肪组织中 PPARγ、C/EBPα、FAS、环氧合酶-2 和脂联素的表达增加,促进脂肪细胞增大和脂肪生成[12]。氯氰菊酯、阿特拉津和 17α-乙炔雌二醇混用时,PPARα、PPARγ 和 SRBEP-1c 及其与肝脏脂肪酸合成和氧化相关的靶基因也受到影响,抑制脂肪酸合成底物的供应,影响脂肪酸代谢[48]。

大西洋鲷暴露于 BPA 和 NP,PPARs、FAS、LPL 和 TAG 脂肪酶的表达上调,从而促进了脂质的运输和积累[24]。Santangeli 等[24]研究发现,高浓度的 BPA 暴露可以增加斑马鱼 SREBP-2 和 FAS 的表达水平,从而增加脂质的合成和积累。斑马鱼暴露于较低浓度的二乙二醇二苯甲酸酯,会上调 SREBP-2、FAS 和甘油二酯酰基转移酶、溶血磷脂酰基转移酶的表达水平,促进脂肪从头合成[24];还会上调肝 PPARα、SREBP 水平,促进脂肪细胞肥大和脂肪细胞增生[23]。TBT 和三苯基锡暴露增加了虹鳟前脂肪细胞中 PPARγ 和 C/EBPα 的表达,进而增强了脂肪细胞的分化能力[26]。TBT 暴露还能上调雄性斑马鱼脂肪生成基因 *pparγ*、*c/ebpβ*、*srebp-1*、*fas* 和甘油二酯酰基转移酶的表达,促进脂质积累;而 BPS 暴露下调了 PPARα、SREBP-1 的表达,促进雄性斑马鱼肝脏脂质堆积,产生肝脏炎症[22,28]。邻苯二甲酸二异癸酯可激活 PPAR-RXR 异二聚体,促进大西洋鲷脂质稳态的长期变化[49]。Fong 等[27]研究了 BP-2 对斑马鱼胚胎脂质代谢的影响,发现 BP-2 通过干扰 PPARα 抑制了 β-氧化过程,导致斑马鱼胚胎卵黄囊脂质积累。

2.2 EDCs 通过影响昼夜节律干扰脂质代谢

昼夜节律是一种生物过程,表现为 24 h 左右生物体体内所有生化过程的周期性变化,昼夜节律由时钟基因(生物钟基因)调控,主要包括 *clock*、*bmal1*、*cry*、*per*、*npas2*、*rev-erbα*、*rorα* 等[50],时钟基因的表达与能量代谢密切相关[51]。具体来说,生物时钟既能调控 PPARs 的表达,又能影响其生理功能:BMAL1 和 CLOCK 可直接调控 PPARα 的表达[52],REV-ERBα 和 DEC1 分别间接抑制 PPARα、PPARγ 的表达[51,53],PER2 可以和 PPARα 相互作用,影响肝脏代谢基因的转录[54];PER2 通过阻断 PPARγ 向其靶基因启动子募集发挥其抑制作用[51,54]。此外,BMAL1 和 CLOCK 能通过转录因子 PPARγ 及其共激活剂 PGC1α 促进脂联素的表达,BMAL1 也会负向调控瘦素的分泌。

有研究表明,化学品还可以通过扰乱昼夜节律影响脂质代谢过程。Weger 等[55]研究发现,TBT、磷酸三(1,3-二氯异丙基)酯、2-羟基-4-甲氧基二苯甲酮和四溴双酚 A 都会引起斑马鱼昼夜节律的改变,从而诱导脂质积累引起肥胖。该研究中,作者在斑马鱼模型中构建了一个受时钟基因调控的荧光素酶报告系统,通过观察荧光素酶的活性间接反映核心时钟基因的活性。然后采用转基因斑马鱼幼鱼暴露于上述化学品 5 d,通过监测 24 h 转基因 *Tg* 斑马鱼的荧光素酶活性,发现在控制的光暗周期中,幼鱼表现出报告基因活性的特征性振荡(具有精确周期长度的每日双相振荡模式),TBT 处理能减小振幅,并能延长最大和最小活性之间的周期,磷酸三(1,3-二氯异丙基)酯进一步延长了这一周期,在暴露于四溴双酚 A 和 2-羟基-4-甲氧基二苯甲酮的幼鱼中观察到特征性振荡的丧失,昼夜节律稳健性降低,即所有测试的 EDCs 均影响了核心时钟活动[52]。

2.3　EDCs 通过影响内源性大麻素系统干扰脂质代谢

内源性大麻素系统是一种信号传导系统,参与食物摄入、能量平衡等的调节。内源性大麻素系统由内源性大麻素物质和大麻素受体 2 个部分组成[56],典型的内源性大麻素物质包括花生四烯酸乙醇胺(anandamide, AEA)和 2-花生四烯酸甘油(2-arachidonoylglycero, 2-AG),大麻素受体包括 CB1 和 CB2 共 2 种。其中,CB1 存在于下丘脑的饥饿饱食中枢以及白色脂肪组织中,结合内源性大麻素后被激活,通过影响内分泌系统中的核受体 PPARs 以及脂肪细胞因子瘦素和脂联素,参与调节脂质的食物摄入、体内合成以及分解过程[57-58]。内源性大麻素发挥作用是通过与表面受体结合来介导的[57]。许多证据表明,内源性大麻素是 PPARα 的天然激活剂,一些内源性大麻素也能激活 PPARγ[59]。而且内源性大麻素不仅可以直接激活 PPARs,也可以通过大麻素受体刺激 PPARγ。因此,内源性大麻素和 PPARs 之间的结合可能介导大麻素的许多生物学作用,包括调节进食行为和脂质代谢。

最近的研究证明了污染物调节内源性大麻素系统的能力[29-30]。特别是在斑马鱼中,DEHP 通过上调 CB1 的水平诱导脂肪细胞分化[23];还能通过上调肝 PPARα、SREBP 和 CB1 的水平,并刺激脂肪酸从头合成和肝脂肪变性而发挥其致肥胖作用,这种肝脏状态可能通过上调瘦素(能量的典型传感器)抑制食物摄入刺激,同时在大脑中可能会对 CB1 产生负面影响,进而降低 *srebp* 基因的表达[23]。Martella 等[15]研究发现,BPA 可通过上调内源性大麻素系统在斑马鱼和人肝细胞中产生肝脂肪变性,BPA 导致肝脏中内源性大麻素 2-AG 和 AEA 的水平升高,棕榈酰乙醇酰胺降低,受体 CB1 的表达增加,并发现 BPA 以 CB1 依赖的方式诱导 HHL-5 细胞中 TAG 积累。斑马鱼暴露于 DINP 会引起食欲和脂肪肝信号神经肽 Y 和 CB1 的上调,在较低浓度下可能通过 CB1 调节食欲,最终导致脂质代谢损伤和肝脏脂肪变性[30]。Forner-Piquer 等[25]研究还发现,大西洋鲷暴露于 BPA 和 DINP,均降低了 AEA、CB1 和神经肽 Y 的表达水平,进而导致食欲下降。

2.4　EDCs 通过影响表观遗传机制干扰脂质代谢

表观遗传是指在不改变 DNA 序列的情况下,改变基因的表达水平并且可以遗传和逆转[60];表观遗传机制包含 DNA 甲基化、组蛋白修饰、微小 RNA (microRNA/miRNA)、非编码 RNA 以及染色质重塑等[61]。近年来的研究表明,表观遗传机制在调节血脂水平、脂质代谢相关表型和疾病中发挥着重要作用[61]。表观遗传机制不仅可以调控核受体 PPARs 表达,而且 PPARs 发挥生理功能也需要表观遗传机制的配合。其中,DNA 甲基化会通过影响核受体 PPARs 的表达调控脂质代谢过程。在脂肪细胞分化过程中,DNA 甲基化会调控 PPARγ 的表达;在 3T3-L1 前脂肪细胞分化为成熟脂肪细胞的过程中,PPARγ 的基因启动子区会逐渐去甲基化[62-63];在新分离的间充质干细胞和分化后的间充质干细胞中,PPARγ 的基因启动子区都是低甲基化的[64]。此外,DNA 甲基化也会通过调控 PPARγ 的表达促进脂肪产热以及参与脂肪沉积过程。关于组蛋白修饰研究最多的是甲基化和乙酰化修饰,目前已知多个组蛋白甲基转移酶和去甲基化酶与 PPARγ 和 C/EBP 共同调控脂肪的生成[61,65-68];并且有部分研究对于去乙酰化酶对脂质代谢的影响做了表述[69-72]。与脂质代谢有关的 miRNA 种类多集中于 *miR-27*、*miR-33*、*miR-122*、*miR-143* 和 *miR-370*,它们也可以通过影响 PPARs 的表达调控脂质代谢[72],miR-*27* 负向调控 PPARγ 和 RXRα 的表达抑制脂肪生成,*miR-122* 调控 PPARβ 和 SREBP-1 的表达参与胆固醇合成。

研究表明,EDCs 可以通过改变 DNA 甲基化水平影响 PPARs 的表达进而干扰脂质代谢过程。比如,在跨代研究中,滴滴涕、甲氧滴滴涕以及 BPA、DEHP 和邻苯二甲酸二丁酯的混合物都会诱导 F3 代大鼠精子 DNA 中出现差异 DNA 甲基化区域(DMR),促进肥胖的跨代继承[19-21]。BALB/cByj 小鼠暴露于 PAHs 的混合物后,在 F1 和 F2 的雄性和雌性中,均检测到 *pparγ* 启动子中 1 个 CpG 位点甲基化的降低,并且与 *pparγ* 的表达成反比[12]。小鼠 3T3-L1 脂肪细胞暴露于 BDE-47 后,观察到 *pparγ2* 启动子中的 3 个 CpG 位点明显去甲基化[9],而 TBT 会使 *fapb4* 的启动子/增强子区域的甲基化不足,并没有降低 *pparγ2* 的甲基化[8]。围产期小鼠暴露于 4-硝基酚会影响 F1 代的脂肪生成,这种影响可通过母系遗传到 F2 代。

在 miRNA 相关研究中,发现 TCS 显著调节了 4 个负责脂肪酸合成和代谢基因调控的 miRNA,即 *miR-125b*、*miR-205*、*miR-142a* 和 *miR-203a* 的表达[73]。Cocci 等[74]的研究也表明,TCS 直接参与了斑马鱼 *miR-125b* 的上游调控,最终导致脂质积聚和

表1 内分泌干扰物对不同动物模型脂质代谢的影响

Table 1 Effects of endocrine disrupting chemicals on lipid metabolism in different animal models

动物模型 Animal model	内分泌干扰物(EDCs) Endocrine disrupting chemicals (EDCs)	对脂质代谢的影响 Effects on lipid metabolism	参考文献 Reference
小鼠3T3-L1前脂肪细胞 Murine 3T3-L1 adipocytes	TBT	诱导脂肪细胞分化 Induction of adipocyte differentiation	[5,7-8,10]
	MEHP	诱导分化脂肪细胞产生炎症 Induction of differentiated adipocyte inflammation	[45]
	BPA	诱导脂肪细胞分化,促进脂质蓄积,胰岛素信号受损,葡萄糖利用率降低,导致炎症 Induction of adipocyte differentiation and lipid accumulation; impairment of insulin signaling and decrease of glucose utilization; induction of inflammation	[6]
	TCDD	诱导脂肪细胞分化 Induction of adipocyte differentiation	[75]
	4,4'-DDT、4,4'-DDE	诱导脂质积累 Induction of lipid accumulation	[76]
	DINP	诱导脂肪细胞分化,促进脂肪生成 Induction of adipocyte differentiation and promotion of lipogenesis	[77]
人类间充质干细胞(HMSCs) Human mesenchymal stem cells (HMSCs)	DBT	诱导脂肪细胞分化,促进脂质蓄积 Induction of adipocyte differentiation and lipid accumulation	[4]
HepG2细胞 HepG2 cells	DEHP	破坏氧化应激平衡,促进脂质蓄积 Destruction of the balance of oxidative stress and promotion of lipid accumulation	[13]
	OPFRs	诱导脂质积累 Induction of lipid accumulation	[16]
人类肝HHL-5细胞 Human liver HHL-5 cells	BPA	肝脂肪变性 Hepatic steatosis	[15]
昆明小鼠 Kunming mice	TBT	增加脂肪生成和减少分解代谢 Increase of lipogenesis and reduction of steatolysis	[78]
Wister大鼠 Wistar rats	NP	诱导脂肪细胞分化,促进脂肪生成 Induction of adipocyte differentiation and promotion of lipogenesis	[47]
	TBT	促进脂质蓄积,导致肝脏炎症 Induction of lipid accumulation and liver inflammation	[11]
	OT	肝脂肪变性 Hepatic steatosis	[79]
	DEHP	增加脂肪细胞的体积和数量,肝脂肪变性 Increase of the size and number of adipocyte; hepatic steatosis	[80]
	DEHP、DBP和BPA的混合物 DEHP, DBP and BPA mixture	促进脂质积累 Induction of lipid accumulation	[81]
BALB/cByj小鼠 BALB/cByj mice	PAHs	促进脂肪细胞分化 Induction of adipocyte differentiation	[12]
C57BL/6小鼠 C57BL/6 mice	TBT	肝脂肪变性,促进脂肪组织脂质积累 Hepatic steatosis; induction of lipid accumulation in adipose tissue	[5]
	MEHP	脂肪细胞和肝脏脂质积累 Lipid accumulation in adipocytes and liver	[17]
	TCDD	促进脂质蓄积 Induction of lipid accumulation	[14]
	BPA	可能影响脂肪组织的脂质储存 Influence on lipid storage in adipose tissue	[82]
	CYP、ATZ和EE2的混合物 CYP, ATZ and EE2 mixture	抑制脂肪酸合成底物的供应 Inhibition on the supply of synthetic substrates for fatty acids	[48]
	DEHP	肝脏脂质积聚 Lipid accumulation in the liver	[83]

续表1

动物模型 Animal model	内分泌干扰物(EDCs) Endocrine disrupting chemicals (EDCs)	对脂质代谢的影响 Effects on lipid metabolism	参考文献 Reference
SD 大鼠 Sprague-Dawley rats	DEHP	引起脂质过氧化和肝脏炎症,诱导 NAFLD Induction of lipid peroxidation, inflammation, and NAFLD	[18]
	NP	导致肝脏炎症,诱导 NAFLD Induction of liver inflammation and NAFLD	[79]
	TCDD	肝脏脂质积累,肝炎和肝纤维化 Promotion of lipid accumulation; hepatitis and liver fibrosis	[84]
	DDT、甲氧滴滴涕、BPA、DEHP 和 DBP 的混合物 DDT, methoxychlor, BPA, DEHP and DBP mixture	促进肥胖的代际遗传,表现为体质量增加,腹部肥胖 Promotion of epigenetic transgenerational inheritance of obesity; weight gain and abdominal obesity	[19-21]
虹鳟(*Oncorhynchus mykiss*)初级脂肪细胞 Trout (*Oncorhynchus mykiss*) primary adipocyte culture	TBT	促进脂质积累 Induction of lipid accumulation	[26]
	TPT	促进脂质积累 Induction of lipid accumulation	[26]
大西洋鲷(*Sparus aurata*)肝细胞 Sea bream (*Sparus aurata*) hepatocytes	DIDP、TMCP	肝细胞脂质含量增加 Increase of lipid content of hepatocyte	[74]
草鱼幼鱼(*Ctenopharyngodon idellus*) Juvenile grass carp (*Ctenopharyngodon idellus*)	BPA	肝脂质积累,肝、肾脂质过氧化明显增加 Lipid accumulation in the liver; increase of lipid peroxidation in liver and kidney	[85]
海洋青鳉(*Oryzias javanicus*) Marine medaka (*Oryzias javanicus*)	BPA	促进脂质蓄积 Induction of lipid accumulation	[35]
稀有鮈鲫(*Gobiocypris rarus*) Rare gudgeon (*Gobiocypris rarus*)	BPA	促进雄鱼脂质合成和肝脏脂质积累 Promotion of lipogenesis and lipid accumulation in male fish	[86]
	TBT	促进脂肪生成和肌肉组织脂质积累 Promotion of lipogenesis and lipid accumulation in muscle tissue	[87]
	LNG	肝脏出现细胞空泡,肝细胞肿胀 Increased presence of hepatic lipid vacuoles andoedema of the liver cells	[88]
尼罗罗非鱼(*Oreochromis niloticus*) Nile tilapia (*Oreochromis niloticus*)	DEHP	肝脏脂质代谢紊乱 Alteration of lipid metabolism	[89]
大西洋鲷(*Sparus aurata*) Sea bream (*Sparus aurata*)	BPA	促进脂肪生成,改变肝脏的结构和生化成分 Promotion of lipogenesis; changes in the structure and biochemistry composition of the liver	[25]
	BPA、NP、*t*-OP	肝脏脂肪堆积 Hepatic steatosis	[32-34]
	BPA、NP 和 *t*-OP 的混合物 BPA, NP and *t*-OP mixture	具有较温和的脂肪生成作用 Promotion of lipogenesis	[36]
	DIDP	促进长期的脂质稳态变化 Promotion of long-term lipid homeostasis changes	[82]
	DINP	促进脂肪生成,改变肝脏的结构和生化成分 Promotion of lipogenesis; changes in the structure and biochemistry composition of the liver	[25]

续表1

动物模型 Animal model	内分泌干扰物(EDCs) Endocrine disrupting chemicals (EDCs)	对脂质代谢的影响 Effects on lipid metabolism	参考文献 Reference
斑马鱼(*Danio rerio*) Zebrafish (*Danio rerio*)	BPA	促进脂肪生成和储存 Promotion of lipogenesis and storage	[24]
		促进脂质蓄积 Induction of lipid accumulation	[29]
		诱导 NAFLD Induction of NAFLD	[15]
	BPS	促进脂质积累 Induction of lipid accumulation	[90]
		促进雄性斑马鱼肝脏脂质堆积,肝脏炎症 Promotion of lipid accumulation and liver inflammation in male zebrafish	[28]
		诱导 NAFLD(单纯脂肪变性向非酒精性脂肪性肝炎转化) Induction of NAFLD (the transformation from hepatic steatosis to nonalcoholic steatohepatitis)	[38]
	BP-2	斑马鱼胚胎卵黄囊脂质积累 Promotion of lipid accumulation in yolk sac of zebrafish embryos	[27]
	TCS	加速肝细胞癌的发展,促进肝肿瘤的发生 Acceleration of the development of hepatocellular carcinoma and promotion of the occurrence of liver tumor	[76]
		诱导脂质积聚和脂肪肝疾病 Induction of lipid accumulation and fatty liver disease	[31]
	TCS、BPA	促进肝脏炎症的发展,诱导 NAFLD Promotion of the development of liver inflammation and induction of NAFLD	[39]
	DEHP	诱导脂肪细胞分化 Induction of adipocyte differentiation	[23]
		增加 NAFLD 的发病风险 Induction of NAFLD	[37]
	DINP	肝脂肪变性 Hepatic steatosis	[30]
	DGB	促进脂肪从头合成 Induction of *de novo* lipogenesis	[24]
	TBT	肝脂肪变性 Hepatic steatosis	[91]
		促进脂质蓄积 Induction of lipid accumulation	[22]
		诱导肥胖 Induction of obesity	[52]
	TDCIPP、BP-3、TBBPA	诱导肥胖 Induction of obesity	[52]
非洲爪蟾(*Xenopus laevis*) African clawed frog (*Xenopus laevis*)	TBT	在性腺周围形成异位脂肪细胞 Ectopic adipocyte formation around the gonads	[5]
	RXR 特异性配体 LG100268 和 AGN195203 The RXR-specific ligands LG100268 and AGN195203	在性腺周围形成异位脂肪细胞,刺激脂肪酸摄取和 TAG 合成,破坏脂质平衡 Ectopic adipocyte formation around the gonads. Stimulation of fatty acid uptake and TAG synthesis and alteration of lipid metabolism	[5]

注:MEHP 表示邻苯二甲酸单乙基己酯;TCDD 表示四氯二苯并-*p*-二噁英;4,4'-DDT 表示 4,4'-滴滴涕;4,4'-DDE 表示 4,4'-滴滴伊;DINP 表示邻苯二甲酸二异壬酯;OPFRs 表示有机磷阻燃剂;OT 表示有机锡;DBP 表示邻苯二甲酸二丁酯;TCDD 表示四氯二苯并-*p*-二噁英;CYP 表示氯氰菊酯;ATZ 表示阿特拉津;EE2 表示 17α-乙炔雌二醇;DDT 表示滴滴涕;TPT 表示三苯基锡;DIDP 表示邻苯二甲酸二异癸酯;TMCP 表示磷酸三间甲苯酯;LNG 表示左炔诺孕酮;*t*-OP 表示 4-叔辛基苯酚;BP-2 表示二苯甲酮-2;DGB 表示二乙二醇二苯甲酸酯;TDCIPP 表示磷酸三(1,3-二氯异丙基)酯;BP-3 表示苯甲酮-3;TBBPA 表示四溴双酚 A;TBT 表示三丁基锡;DBT 表示二丁基锡;BPA 表示双酚 A;BDE-47 表示 2,2',4,4'-四溴联苯醚;PAHs 表示多环芳烃;DEHP 表示邻苯二甲酸二(2-乙基)己酯;NP 表示壬基酚;TCS 表示三氯生;BPS 表示双酚 S;NAFLD 表示非酒精性脂肪肝;TAG 表示甘油三酯。

Note: MEHP stands for mono(2-ethylhexyl) phthalate; TCDD stands for 2,3,7,8-tetrachlorodibenzodioxin; 4,4'-DDT stands for 4,4'-dichlorodiphenyltrichloroethane; 4,4'-DDE stands for *p,p*'-dichlorodiphenyldichloroethylene; DINP stands for di-isononylphthalate; OPFRs stands for organophosphorus flame retardants; OT stands for organotin; DBP stands for dibutylphthalate; TCDD stands for 2,3,7,8-tetrachlorodibenzodioxin; CYP stands for cypermethrin; ATZ stands for atrazine; EE2 stands for 17α-ethynyestradiol; DDT stands for dichlorodiphenyltrichloroethane; TPT stands for tributyltin; DIDP stands for di-isodecyl-phthalate; TMCP stands for tri-*m*-cresyl phosphate; LNG stands for levonorgestrel; *t*-OP stands for tert-octylphenol; BP-2 stands for benzophenone-2; DGB stands for diethylene glycol dibenzoate; TDCIPP stands for tris(1,3-dichloroisopropyl) phosphate; BP-3 stands for benzophenone-3; TBBPA stands for tetrabrominated bisphenol A; TBT stands for tributyltin; DBT stands for dibutyltin; BPA stands for bisphenol A; BDE-47 stands for brominated diphenyl ether 47; PAHs stands for polycyclic aromatic hydrocarbon mixture; DEHP stands for di(2-ethylhexyl) phthalate; NP stands for nonylphenol; TCS stands for triclosan; BPS stands for bisphenol S; NAFLD stands for nonalcoholic fatty liver disease; TAG stands for triglyceride.

脂肪肝疾病[41]。邻苯二甲酸二异癸酯和磷酸三间甲苯酯诱导原代大西洋鲷肝细胞 3 种 miRNAs(即 *miR-133*、*miR-29* 和 *miR-199a*)表达水平下降,导致肝细胞脂质含量增加。尽管生理学的研究证实了 miRNA 会通过影响 PPARs 和 RXR 表达干扰脂质代谢,然而上述研究仅介绍了 miRNA 和脂质代谢的相关性,并未从 miRNA 影响核受体方面进行阐述,因而具体作用机制尚需进一步研究。

3　结论与展望(Conclusion and prospects)

(1)目前多数研究主要关注单一污染物暴露对动物模型脂质代谢过程的毒理效应,鉴于环境中 EDCs 的种类日益增多、多种 EDCs 或 EDCs 与其他污染物的复合暴露风险也愈发严峻,因此今后的研究需要进一步关注新型 EDCs(如全氟烷基和多氟烷基物质、纳米材料或代谢类调节药物)对机体脂质代谢的影响,以及复合暴露条件下不同污染物之间的协同或拮抗作用,从而为复杂环境条件下污染物的健康风险评估提供参考。

(2)在 EDCs 影响脂质代谢的 4 种机制中,大部分研究主要关注了 EDCs 通过影响转录因子改变脂质代谢的作用途径,而关于另外 3 种机制的研究相对较少。此外,研究发现转录因子、时钟基因以及组蛋白修饰等因素在脂质代谢调控中相互作用、相互影响,如在表观遗传机制对脂质代谢的调控中,发现组蛋白乙酰化中,去乙酰化酶 HDAC3 可以调控时钟基因 *rev-erbα* 的表达[64],表明各个机制之间可能存在交叉作用。并且,脂质代谢过程会关联不同的器官、组织,所以 EDCs 在影响脂质代谢的同时,也有可能影响其他系统(比如生殖系统),或者 EDCs 在影响其他系统的同时也会影响脂质代谢。因此,未来的研究也需要关注不同机制以及不同系统之间的作用交叉,以便更全面更深入地解析污染物干扰脂质代谢的作用途径。

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