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环境内分泌干扰物对鱼类性别分化的影响

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摘要： 鱼类性别分化是在性别决定机制的控制下，鱼类未分化的性腺向卵巢或精巢发育，并出现第 2 性征的过程，受自身内分泌系统的精确调控。环境内分泌干扰物能通过干扰内源激素的合成、释放、转运、代谢、结合和作用等过程影响鱼类的内分泌机能，从而对鱼类的性别分化产生影响。介绍了鱼类性别分化的模式和过程以及内分泌系统对鱼类性别分化的调控作用，综述了环境内分泌干扰物对鱼类性别比例、配子发生、性腺发育和第 2 性征的影响，从性类固醇激素的合成以及性别分化相关基因的表达两个方面探讨了环境内分泌干扰物影响鱼类性别分化的作用机制，并展望了该领域未来的研究方向。

关键词： 环境内分泌干扰物; 鱼类; 性别分化

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Effects of Endocrine Disrupting Chemicals on Sex Differentiation in Fish

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Abstract: Sex differentiation in fish refers to the development of testes or ovaries from undifferentiated gonads and the expression of male or female secondary sex characteristics under the control of sex determination mechanisms, regulated by the endocrine system. Endocrine disrupting chemicals (EDCs) that can interfere with the production, release, transport, metabolism, binding, action of natural hormones, have potential to disrupt the process of sex differentiation in fish. In this review, the patterns, process and endocrine regulation of sex differentiation in fish were introduced, and adverse effects of EDCs on some events related to sex differentiation in fish were reviewed, including sex ratios, gametogenesis, gonadal development and secondary sex characteristics expression. The potential mechanisms of fish sex differentiation were discussed by synthesis of sex steroid and the expression of genes relating sex differentiation. Finally, future prospects of this field were provided in this paper.

Keywords: endocrine disrupting chemicals; fish; sex differentiation

近年来的研究表明，环境内分泌干扰物(endocrine disrupting chemicals，EDCs)广泛存在于自然水体中，可能导致鱼类及其他水生动物生殖系统发育异常，例如，鱼类间性个体的出现以及雄性个体雌性化等现象[1,2]。与高等脊椎动物相比，鱼类的性别决定机制具有原始性、多样性和易变性，其早期性别发育较易受外界因素的影响[3]，因而 EDCs 对鱼类性别分化的影响受到研究者广泛关注。本文在介绍鱼类性别分化模式、性别分化过程以及内分泌系统

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调控作用的基础上，综述了内分泌干扰物对鱼类性别分化的影响及作用机制，并对今后的研究方向进行了展望。

1 鱼类的性别分化

1.1 鱼类的性别分化模式

鱼类的性别分化大致可分为两种类型：雌雄同体(hermaphrodites)和雌雄异体(gonochorists)[4]。雌雄同体的鱼类能够分化出卵巢和精巢两种性腺类型，其中某些鱼类的卵巢和精巢能够同时存在，比如花斑溪鳉(*Rivulus marmoratus*)[5]；而某些鱼类卵巢和精巢的发育具有次序性，比如黑鲷(*Acanthopagrus schlegeli*)等首先分化成雄性[6]，而裂唇鱼(*Labroides dimidiatus*)等首先分化成雌性[7]。雌雄异体的性别分化可分为两种情况，多数鱼类未分化的性腺直接分化成卵巢或精巢；而某些鱼类会首先发育出一个卵巢样的性腺，随后约50%的个体卵巢样结构退化，逐步发育成精巢结构，如斑马鱼(*Danio rerio*)[8]等。

1.2 鱼类性腺的分化过程

鱼类的性腺起源于胚胎发育时期形成的原始生殖细胞(PGCs)。一般认为PGCs形成后，会通过特定路线迁移至生殖嵴(genital ridges)，并与生殖上皮细胞(随后发育为原始性腺的体细胞)共同形成原始性腺。在自身性别决定机制和外部环境因子的共同作用下，原始性腺开始向卵巢或精巢分化，PGCs有丝分裂形成卵原细胞或精原细胞，性腺体细胞也随之分化。

原始性腺若开始向卵巢发育，生殖细胞将经历有丝分裂及减数分裂活动逐步发育为成熟的卵母细胞，而体细胞则分化成两种滤泡细胞(follicle cells)——膜细胞(theca cells)和颗粒细胞(granulosa cells)，滤泡细胞包被卵母细胞共同构成卵泡结构(ovarian follicle)[9]。在卵巢分化的过程中，部分体细胞大量增殖，卵巢内部会逐渐形成一个空腔结构——卵巢腔(ovarian cavity)，为成熟卵子的释放提供通道。研究认为，卵原细胞和卵母细胞的早期分化以及卵巢腔的形成是多数鱼类卵巢分化开始的两个标志[10]。

鱼类的精巢分化通常在其卵巢分化开始后的数周或数月后进行[4]。精巢开始发育后，生殖细胞进行有丝分裂，形成精原细胞及初级精母细胞，精小囊和精小叶开始形成[11]。由于鱼类精巢内生殖细胞的分化较晚，因此，由生殖细胞的发育特征难以判断精巢分化的开始，一般通过体细胞的发育活动进行判断。输出管(efferent duct)的形成是精巢开始分化发育的重要标志[10]。另外，体细胞在精巢分化期间将分化形成两类细胞——间质细胞(leydig cells)和支持细胞(sertoli cells)，其中间质细胞能够分泌雄性激素，支持细胞能够为精细胞的发育提供营养[12]。

1.3 鱼类性别分化的内分泌调控

研究认为，下丘脑-垂体-性腺(HPG)轴和生长激素-胰岛素样生长因子-Ⅰ(GH-IGF-Ⅰ)轴中的相关激素参与了鱼类性别分化的调控过程，其中，研究者最为关注的是性类固醇激素的作用。Yamamoto[13]发现外源性激素能够致使鱼类性反转，由此推测内源性类固醇激素——雌激素和雄激素，可能分别对鱼类的卵巢分化和精巢分化起诱导作用。多项研究已经证实了这一推测，罗非鱼(*Oreochromis niloticus*)、虹鳟鱼(*Oncorhynchus mykiss*)、玫瑰大麻哈鱼(*O. rhodurus*)、大鳞大麻哈鱼(*O. tshawytscha*)以及日本鳗鲡(*Anguilla japonica*)等鱼类的性类固醇激素生成细胞或类固醇合成酶在其性别分化之初已经发挥功能，表示性激素可能诱导并维持了这些鱼类的性别分化过程[10]。此外，性类固醇激素不仅能够作为鱼类性别分化的诱导因子，还能够直接影响性腺生殖细胞的发育，并且间接调控其他与性别分化相关的细胞和器官[4]，其对鱼类性别分化的调控最为关键。

除性类固醇激素外，HPG轴中的促性腺激素释放激素(GnRH)和促性腺激素(GtH)以及GH-IGF-Ⅰ轴均能够对鱼类的性别分化起到一定的调控作用。GnRH和GtH并不直接参与雌雄异体鱼类性别分化的诱导，但对其性别分化过程的完成至关重要，此外，GtH还能够引发雌雄同体鱼类的性转化过程[3,14,15]。GH和IGF-Ⅰ在鱼类性别分化过程中，能够通过自分泌和旁分泌的作用，影响促性腺激素的释放和性类固醇激素的合成，参与调控性腺生殖细胞和体细胞的分化发育[16-20]。

2 环境内分泌干扰物对鱼类性别分化的影响

2.1 环境内分泌干扰物对鱼类性别比例的影响

EDCs能够对鱼类产生雌性化或雄性化作用，导致某些个体改变性别分化的方向，影响鱼类种群正常的性别比例。环境雌激素类物质能够致使鱼类雌性个体的比例显著上升，Xu等[21]采用不同浓度17α-乙炔雌二醇(EE_2)暴露2 dph的斑马鱼至性腺发育成熟(90 dph)，发现2和10 ng·L^{-1} EE_2能够导

致雌性个体比例上升。Mikula 等[22] 采用含 500 mg·kg^{-1}尼泊金丙酯(propylparaben)的饲料喂养 20 dph 的斑马鱼至 45 d 性别分化结束,发现雌性个体比例高达 70.9%,而未处理组雌性比例仅为 40%。Knörr 和 Braunbeck[23] 将受精后的日本青鳉(*Oryzias latipes*)暴露于 50 μg·L^{-1}辛基酚(OP)至性成熟,发现雌性比例显著升高,其他酚类物质如壬基酚(NP)、双酚 A(BPA)和 2,4 – 二硝基苯酚(2,4 – dinitrophenol)等也有类似的雌性化作用[24-27]。植物雌激素也能够影响鱼类的性别比例,Yang 等[28] 发现在高水温(27℃)条件下饲养基因型为雌性的褐牙鲆(*Paralichthys Olivaceus*)幼鱼导致部分个体雄性化,发育成雌性个体的比例仅为 16.7%,而喂食含 10 和 100 μg·g^{-1}的金雀异黄素(Genistein)饲料后,其雌性比例能够分别增至 46.7% 和 96.7%。

合成雄激素及抗雌激素能够对鱼类产生雄性化作用,采用 1 mg·L^{-1}群勃龙醋酸酯(TBA)定期浸泡处理处于性别分化关键时期的黑莓鲈(*Pomoxis nigromaculatus*),导致所有个体全部发育为雄性[29]。甲基睾酮(MT)能够诱导日本青鳉、赤点石斑鱼(*Epinephelus akaara*)、东大西洋石斑鱼(*E. marginatus*)和许氏平鲉(*Sebastes schlegeli*)等鱼类出现不同程度的雄性化[27,30-32]。Park 等[33] 发现抗雌激素他莫昔芬(tamoxifen)对黄颡鱼(*Pseudobagrus fulvidraco*)有雄性化的作用,向雄性分化的个体比例随暴露浓度的升高而升高,最高剂量组雄性个体可达 90%。芳香化酶是鱼类体内雄激素向雌激素转化的关键酶,芳香化酶抑制剂能够通过抑制芳香化酶的表达或活性,对鱼类产生雄性化作用,Uchida 等[34] 用含法倔唑(fadrozole)的饲料喂食处于性别分化时期的基因型雌性斑马鱼,发现 10 μg·g^{-1}法倔唑致使 62.5% 的个体雄性化,而 100 和 1000 μg·g^{-1}法倔唑使得 100% 个体性反转。福美斯坦(OHA)、依西美坦(EM)和雄烷二酮(ATD)等芳香化酶抑制剂具有类似作用[35-37]。其他环境污染物如杀真菌剂咪鲜胺(prochloraz)、三丁基锡(TBT)等也被证明能够致使鱼类的性别比例向雄性偏移[38-40]。

一般认为,环境雌激素类物质致使鱼类雌性化,而环境雄激素等则导致鱼类雄性化,但研究也发现有相反情况。Green 和 Kelly[41] 长期给斑点叉尾鮰(*Ictalurus punctatus*)喂食植物雌激素金雀异黄素(4 ~ 8 mg·g^{-1}),成年后雄性个体比例升高,这可能是因为金雀异黄素不仅能发挥雌激素作用,一定剂量下还可能作为拮抗剂阻断鱼体内天然雌激素作用。10 μg·L^{-1} MT 处理性别分化时期的斑马鱼,所有个体全部发育成雌性[42],可能是一定浓度的 MT 在鱼体内经芳构化作用转变成雌激素 17α-甲雌二醇(ME_2),与雌激素受体结合后发挥了雌性化效应[43]。

2.2　环境内分泌干扰物对鱼类配子发生的影响

配子发生(gametogenesis)包括雄性生殖细胞(精子)和雌性生殖细胞(卵子)的发生,是鱼类性别分化的首要特征。EDCs 能够抑制或促进鱼类的配子发生过程,改变性腺内所含生殖细胞的类型和比例,从而扰乱鱼类的性别分化。将雌性褐菖鲉(*Sebastiscus marmoratus*)幼鱼暴露于 TBT 中 50 d,未暴露个体卵巢内存在初级生长期(primary growth stage)、卵黄泡期(yolk vesicle stage)及卵黄生成期(vitellogenic stage)3 种类型的卵母细胞,而 10 ng·L^{-1}处理组初级生长期卵母细胞增多,卵黄生成期卵母细胞缺失,100 ng·L^{-1}处理组仅存在初级生长期卵母细胞[44]。采用 250 μg·L^{-1}全氟辛烷磺酸盐(PFOS)处理 14 dpf 斑马鱼幼鱼至性成熟,雄性个体精巢内仅有精原细胞(spermatogonia)和精母细胞(spermatocyte),而精子细胞(spermatid)基本未能发育[45]。Sone 等[46] 证明 17β-孕三烯酮(17β – TB)能够促进食蚊鱼(*Gambusia affinis*)的精子发生过程,将刚出生的食蚊鱼暴露于 1 ~ 10 μg·L^{-1}17β-TB,28 d 后幼鱼精巢内除存在精母细胞外,还存在性成熟个体特有的精子(spermatozoa)。此外,17β-雌二醇(E_2)、EE_2、烷基酚类、邻苯二甲酸二乙基己基酯(DEHP)、2,3,7,8-四氯二苯并二恶英(TCDD)、*o*,*p*′-滴滴涕(DDT)、植物雌激素以及芳香化酶抑制剂等均能干扰鱼类的卵子或精子发生[25,47-54]。某些 EDCs 能够同时对鱼类的卵子发生和精子发生起干扰作用,Weber 等[55] 发现,EE_2(1 ~ 100 ng·L^{-1})或 NP(100 μg·L^{-1})处理处于性别分化关键期斑马鱼幼鱼,能够同时对其卵子发生和精子发生起抑制作用。Kinnberg 等[38] 认为,咪鲜胺(16 ~ 202 μg·L^{-1})能够显著促进斑马鱼幼鱼的精子发生从而延迟其卵子发生过程。

EDCs 除能够对鱼类的配子发生过程产生促进或延迟作用,还能够影响配子的正常发育,导致畸形配子的产生。斑马鱼在性别分化期间暴露于 TBT(0.1 ~ 100 ng·L^{-1}),导致性成熟后雄性个体精子的鞭毛缺失,精子运动能力下降[40]。一般情况下,萎缩卵母细胞仅在排卵后的卵巢中残留,而 0.8 μg·L^{-1}金雀异黄素会诱导雌性日本青鳉正在发育的卵巢中形成萎

缩卵母细胞(atretic oocytes)[56],其原因可能是在发育过程中卵黄的形成受到阻碍,致使卵母细胞不能正常发育,逐渐萎缩[57-58]。

2.3 环境内分泌干扰物影响鱼类性腺的正常发育

研究表明,EDCs能够抑制或延迟鱼类性腺的分化及发育。Tanaka和Grizzle[47]将雌雄同体鱼类花斑溪鳉在孵化后暴露于300 μg·L^{-1}NP中至性别分化结束,发现所有个体性腺内的精巢结构都未能分化。李祥军等[59]发现,壬基酚对河川沙塘鳢(*Odontobulis potamophila*)精巢的发育有抑制作用。Van den Belt等[60]用不同浓度的EE_2处理斑马鱼胚胎,3个月后部分个体解剖后未能发现性腺,其中25 ng·L^{-1}处理组性腺全部未能发育。Kim等[49]采用10和50 μg·L^{-1} DEHP处理孵化后的日本青鳉,3个月后暴露组雌性个体性腺成熟系数(GSI)分别只达到正常个体的33%和38%。

鱼类在性别分化时期若受到EDCs的暴露,可能导致其性腺发育出现异常。研究表明,EDCs能够致使鱼类性腺分化成非正常的间性结构——卵精巢,雄性个体还可能同时出现精巢纤维化等异常情况。Seki等[61]将日本青鳉胚胎暴露于4-叔戊基苯酚(4-PP)中至101 dpf,雄鱼精巢内出现卵巢结构,部分区域呈纤维化。17β-TB处理雌性食蚊鱼幼鱼28 d后,在其卵巢内发现有精子[46]。此外,合成雄激素MT、杀真菌剂咪鲜胺、杀虫剂β-六六六(β-HCH)、*o*,*p*′-DDT以及各种酚类化合物等均能够导致卵精巢及精巢纤维化等现象[26,30,38,53,62-65]。EDCs还能够干扰鱼类性腺内部结构如雌鱼卵巢腔、雄鱼精巢内腔以及生精小管等的正常分化。Rodgers-Gray等[66]采用具有雌激素活性的污水处理斜齿鳊(*Rutilus rutilus*)幼鱼,100 d后所有个体不论雌雄全部发育有卵巢腔结构。用雌马酚(equol)处理刚孵化的日本青鳉至100 dph,雌性个体的卵巢腔扩大,内部基质组织增殖[56]。北美大梭鱼(*Esox masquinongy*)口服MT 60d后,雄性个体的精巢发育受到干扰,内部多处出现空腔[67]。Balasubramani和Pandian[68]采用醋酸炔诺酮(NE)浸泡处理幼龄暹罗斗鱼(*Betta splendens*)至性成熟,导致部分个体精巢生精小管萎缩,卵巢和精巢内部空腔面积增大。Zaroogian等[52]发现2龄幼年雄性大西洋牙鲆(*P. dentatus*)分别注射E_2、*o*,*p*′-DDT或OP,4周后导致雄性个体精巢萎缩,生精小管壁增厚,细胞出现透明滴(hyaline material)样变。

2.4 环境内分泌干扰物对鱼类第二性征的影响

第二性征是鱼类某些与性别相关的形态特征,比如雄鱼的婚姻色(nuptial coloration)、追星(nuptial tubercle)和雌鱼的产卵管(ovipositors)等,它们与生殖行为相互联系。一方面,EDCs能够对鱼类第二性征的正常发育或表现起抑制或促进作用。Bogers等[69]将黑头呆鱼幼鱼长期暴露于0.1~1 μg·L^{-1}加氢甲基睾酮(MDHT),发现雄性个体的追星提早出现;Balch和Metcalfe[70]发现,烷基酚类物质能够抑制雄性日本青鳉臀突(papillae on the anal fin)的发育。用EE_2处理幼龄三刺鱼(*Gasterosteus aculeatus*),致使成年后的雄性个体表现出的婚姻色较为暗淡[71]。

另一方面,鱼类在性别分化关键时期暴露于EDCs,可能会诱导其表现出与原性别相反的第二性征。用3.2%~50%漂白亚硫酸盐木浆厂废水处理黑头呆鱼(*Pimephales promelas*)受精卵至125 dph,某些雌性个体出现雄性第二性征——追星,而某些雄性个体则出现雌性特有的产卵管[72]。Sone等[46]用0.3、1和10 μg·L^{-1} 17β-TB处理刚出生的食蚊鱼,28 d后雌雄个体均分化出雄性特有的生殖足类结构。MT和法倔唑联合暴露黑头呆鱼幼鱼13 d,致使所有个体全部表现出雄性特有的第二性征——追星和多斑点的背鳍[73]。

3 环境内分泌干扰物影响鱼类性别分化的作用机制

3.1 环境内分泌干扰物影响性类固醇激素的合成

鱼类性类固醇激素的合成是以胆固醇为前体,经P450胆固醇侧链裂解酶(P450scc)、3β-羟基类固醇脱氢酶(3β-HSD)、P450 17α-羟化酶/17,20-裂解酶(P450c17)和17β-羟基类固醇脱氢酶(17β-HSD)等首先催化生成雄激素睾酮(T),然后再由P450芳香化酶(P450arom)将T转化为雌激素E_2,或由P450 11β-羟化酶(P450c11)和11β-羟基类固醇脱氢酶(11β-HSD)将其转化为雄激素11-酮基睾酮(11-KT)。性类固醇激素主要由性腺合成,其他组织如脑也可合成一定量的性激素。由于性类固醇激素对鱼类的性别分化起关键作用,EDCs可能通过影响性腺或脑等组织中性类固醇激素合成酶的表达或活性,干扰性激素的合成,从而改变体内性激素的正常水平,导致鱼类异常的性别分化。Ruksana等[36]发现,70 dph XX型罗非鱼喂食1000 μg·g^{-1}芳香化酶抑制剂EM至100 dph,性腺芳香化酶的活性下降,血浆E_2水平显著下降,11-KT水平显著上升,致使其全部发育为表型雄

性。Lange 等[74]认为,EE_2处理性别分化关键时期的斜齿鳊导致其雌性化,与 EE_2能够上调脑和性腺芳香化酶 mRNA 的表达有关。除芳香化酶外,EDCs 也可通过干扰性激素合成途径中其他酶的表达或活性,影响性激素的合成。Filby 等[75]研究表明,EE_2能通过抑制 P450c17,17β-HSD 和 11β-HSD 的表达而表现雌激素样作用。Bhandari 等[76]用含合成雄激素 MT(50 $\mu g \cdot g^{-1}$)的饲料喂养 XX 型罗非鱼幼鱼,导致全部个体性反转,推测其原因可能是由于 P450scc、3β-HSD 及 P450arom 的表达量显著下降致使雌激素合成受到抑制所引起的。

3.2　环境内分泌干扰物影响其他性别分化相关基因的表达

除上述性类固醇激素合成酶基因外,研究者还发现了多个在鱼类性别分化中起重要作用的基因,包括一些转录因子和生长因子如 *Dmrt*1、*Sox*-9、*Foxl*2、*Nr*5*a*、*Amh*、*Wt*1、*Dax*1、*Gata*-4 等,EDCs 可能通过影响这些基因的表达,干扰鱼类的性别分化。Liu 等[77]发现法倔唑和他莫昔芬单独或联合处理雌性南方鲶(*Silurus meridionalis*)幼鱼后,卵巢分化相关基因 *Foxl*2 mRNA 表达显著降低,精巢分化相关基因 *Dmrt*1 mRNA 表达显著升高,部分个体发生性反转。Vizziano – Cantonnet 等[78]认为,EE_2通过促进卵巢分化相关基因(*Foxl*2*a*, *Foxl*2*b*) mRNA 的表达并抑制部分精巢分化相关基因(*Amh*, *Sox*9*a*2) mRNA 的表达,致使 XY 型虹鳟鱼发生性反转。EE_2还能够通过降低 *Nr*5*a*2、*Amh* 和 *Dmrt*1 mRNA 的表达,抑制黑头呆鱼精巢发育[79]。

需要注意的是,上述 EDCs 干扰鱼类性别分化的两大作用机制并非完全独立。研究表明,某些转录因子和生长因子能够参与调控性类固醇激素合成酶特别是芳香化酶基因的表达,通过性激素合成途径间接发挥作用[80-86],因此,EDCs 可能是通过干扰这类基因的表达,影响芳香化酶的作用,从而扰乱鱼类的性别分化。Suzawa 和 Ingraham[87]推测除草剂阿特拉津(Atrazine)可能通过激活 *Sf* – 1(*Nr*5*a*1)的表达产物,上调芳香化酶基因的表达,从而诱导斑马鱼雌性化。

4　展　望

4.1 从分子水平系统研究鱼类性别分化相关基因的功能

目前,已发现了多个与鱼类性别分化相关的基因,这对阐明鱼类性别分化的分子机理有重要帮助。但是,除芳香化酶等少数基因外,大部分基因在鱼类性别分化过程中的功能以及表达调控机制尚不明确,这给在分子水平上探索 EDCs 的作用机制带来了一定的困难。因此,随后的研究中应当首先采用功能基因组学的研究方法,如差异显示(differential display)、消减杂交差异显示(different subtractive screens)或微阵列分析(microarray)等[88],确定所有主要的鱼类性别分化相关基因,并对各个基因的功能以及基因之间的协调表达情况进行系统研究,从而揭示鱼类性别分化的分子机制。只有在充分了解性别分化相关基因作用机理的基础上,才能进一步探讨 EDCs 如何通过影响这类基因的表达扰乱鱼类的性别分化。

4.2　从生化和分子水平深入探究环境内分泌干扰物对性激素的合成、转运、代谢及结合等的影响

目前,EDCs 对鱼类性类固醇激素的影响仍存在以下两个问题需要进一步探讨。其一,在性类固醇激素合成途径中,除性激素合成酶以外,某些调控蛋白也可能成为 EDCs 干扰鱼类性别分化的作用位点。其中,类固醇激素合成急性调节蛋白(steroidogenic acute regulatory protein,StAR)负责类固醇激素前体——胆固醇向线粒体内膜的转运,是性激素合成限速步骤的重要调控因子[89],EDCs 可能通过对 StAR 的表达或活性起促进或抑制作用,影响雌雄激素的合成,从而间接扰乱鱼类的性别分化[90]。目前通过体外实验可以证明,EE_2或 4 – NP 等化学物质能够通过影响 StAR 的表达改变雌雄激素的水平,导致鱼类的卵子发生过程受到干扰[91-92]。其二,EDCs 除能够作用于性激素的合成之外,还能对合成后性激素的转运、代谢或结合等过程产生影响,这些途径可能也与鱼类性别分化的扰乱存在一定关联。研究发现,EDCs 能够干扰鱼类血浆中性激素结合球蛋白(sex hormone binding globulin,SHBG)的水平[93-94],而 SHBG 参与性类固醇激素的转运,并可能对鱼类的性别分化起一定的调控作用[88];Thibaut 和 Porte[95]认为,EDCs 能够干扰性激素的代谢活动,并可能最终影响到鱼类配子的发生过程;Filby 等[75]研究发现,雌激素 EE_2和抗雄激素氟他胺(flutamide)均可能通过上调黑头呆鱼雌激素受体(ER)的表达,促进雌激素与受体的结合,导致雄性个体出现雌性化现象。目前,针对上述两个问题的相关研究仍然处于起步阶段,鉴于性类固醇激素在鱼类性别分化内分泌调控中发挥的中心作用,继续深入探

究 EDCs 如何通过性激素的合成、转运、代谢及结合等多个作用途径影响鱼类的性别分化是今后研究的重点方向。

4.3 明确下丘脑、垂体等其他内分泌器官在鱼类性别分化中的作用

由于 HPG 轴和 GH-IGF-I 轴能直接或间接调控鱼类的性别分化过程，因此 EDCs 对鱼类性别分化的干扰可能与这两大内分泌轴线有一定关联。虽然已有研究证明，EDCs 能够在幼鱼性别分化期间影响这两大轴线中相关激素的水平[96-98]，但此类研究多讨论的是 EDCs 对鱼类生长或繁殖等方面的作用机制，EDCs 能否通过两途径影响鱼类的性别分化尚缺乏直接证据和明确结论。对下丘脑 GnRH、垂体 GtH 和 GH 等其他激素的相关研究有助于完善鱼类性别分化的内分泌调控机制，能够为探讨 EDCs 影响鱼类性别分化的作用途径提供新的思路。

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