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环境污染物对硬骨鱼肾间应激轴影响的研究进展

钟艳, 汝少国*

中国海洋大学海洋生命学院,青岛 266003
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摘要: 具备神经内分泌应激反应能力是一个健康有机体的基本特征,它可以使动物应对威胁其体内平衡的紧急情形。鱼类在遭受环境胁迫时,通过启动肾间应激轴分泌应激激素皮质醇,为机体动员和分配能量以维持体内平衡。虽然近来大多数研究的焦点一直是污染物对生殖轴线以及性类固醇激素的影响,但是污染物对其它内分泌系统包括肾间应激轴的干扰也越来越受到关注。环境污染物干扰肾间应激轴不仅损害鱼类正常的应激反应能力,还会进一步危害其生长、生殖、免疫等生理功能。本文在简要介绍硬骨鱼肾间应激轴结构组成及调控机制的基础上,综述了多种环境污染物对硬骨鱼肾间应激轴的干扰作用及其机制,展望了该领域今后的研究重点和方向。
关键词: 硬骨鱼; 肾间应激轴; 皮质醇; 环境污染物
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Research Progress in the Effects of Environmental Pollutants on the Interrenal Stress Axis of Teleosts

Zhong Yan, Ru Shaoguo*
College of Marine Life Science, Ocean University of China, Qingdao 266003, China
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Abstract: The capacity to mount the neuroendocrine stress response is a fundamental characteristic of a healthy organism, which enables the animal to cope with acutely stressful situations threatening homeostasis. By activating the interrenal stress axis to secrete stress hormone like cortisol, the fish could mobilize and allocate energy to maintain homestasis when subjected to extrinsic stress. Despite most of recent researches focused on the impact of pollutants on the reproductive axis and sex steroid hormones, growing attention has been paid to the effect of pollutants on other endocrine systems including the interrenal stress axis. Exposure to environmental pollutants not only damages the normal ability to response to stress, but also harms the growth, reproduction, immunity and other physiological functions in fish. In this paper, based on a brief introduction about the composition and regulatory mechanism of the interrenal stress axis, the disruption and underlying mechanisms of various environmental pollutants on this axis of teleosts will be reviewed, and then future prospects in this field will be discussed.

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作者简介: 钟艳(1988-),女,硕士,研究方向为生态毒理学,E-mail: zhongyan1023@163.com;
* **通讯作者**(Corresponding author),E-mail: rusg@ouc.edu.cn

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在自然水环境中,鱼类常常会遭受各种各样的环境胁迫,如捕食者的威胁、温度的骤变等,为了应对外环境的胁迫,鱼体通过激活肾间应激轴(即下丘脑-垂体-肾间腺轴,hypothalamic-pituitary-interrenal, 简称 HPI 轴)合成并分泌应激激素皮质醇,启动应激反应(stress response),调节机体的能量分配从而维持体内平衡。应激反应在动物界中是一种普遍的、高度保守的适应性反应[1-2]。然而,有大量文献报道了多种环境污染物的慢性或亚慢性暴露会导致鱼类的肾间应激轴损坏或肾间组织损伤,致使机体无法正常启动应激反应。Mishra 和 Mohanty[3] 研究发现 2 mg·L^{-1} 或 4 mg·L^{-1} 六价铬盐慢性暴露一个月,可导致淡水鲶鱼(Channa punctatus)血浆皮质醇水平较对照组显著降低,肾间细胞萎缩,在二次急性胁迫下 HPI 轴调节皮质醇水平升高的能力缺失,表明六价铬盐慢性暴露损坏了鲶鱼 HPI 轴应激功能。环境污染物包括金属的长期暴露导致鱼类无法正常启动适应性应激反应,可能带来严重的后果[4],如导致鱼类在严寒冬季条件下存活能力降低[5]; 面对捕食者时的反应和应对能力减弱[6]。应激功能的异常是污染物胁迫条件下鱼体的一种早期生理反应,肾间应激轴的损坏还可能进一步危害生物体的生长、生殖、代谢、免疫、行为等功能,使鱼类的健康水平降低。因此,利用鱼类应激功能的变化可检测、评估和预警污染物的毒性效应。Pankhurst[7] 甚至认为,动物应激功能的变化在评估环境质量以及预测极端环境(如洪涝、暴风雨)来临方面也会有广阔的应用前景。然而在鱼类应激功能异常研究方面,以往只是利用血浆皮质醇水平作为单一指示指标,忽略了皮质醇水平受到肾间应激轴的严格调控。本文通过对肾间应激轴结构及调控机制的简要介绍,系统的综述了多种环境污染物对应激轴线的干扰效应,初步探讨污染物干扰硬骨鱼应激轴的作用机制,以期为深入研究环境污染物对鱼类应激功能的作用机理提供一定理论基础。

1　硬骨鱼肾间应激轴

当人或动物自身完整性受到挑战并处于危险状态的时候,我们称人或动物受到“胁迫(stress)”[8]。动物应对环境胁迫的关键反应,则称为“应激反应(stress response)”,包括一系列的行为、生理以及细胞的变化。急性应激反应通常是短期的、适应性的反应,它能使机体应对潜在的威胁; 而慢性应激反应被认为是长期的、不利的反应,它能够对生长、生殖和免疫反应等产生不利的影响[9-11]。

硬骨鱼的应激反应主要受到下丘脑-垂体-肾间腺轴的调节[12-13]。肾间应激轴的激活首先从下丘脑开始,下丘脑接收从中枢和周边神经系统发出的“应激”信号,“应激”信号促进下丘脑视前核(preoptic nucleus, NPO)神经细胞分泌并释放促肾上腺皮质激素释放因子(corticotrophin releasing factor, CRF)[14]。CRF 在鱼类 HPI 轴的调控中发挥关键性作用[15],CRF 通过与垂体前叶促肾上腺皮质细胞膜上的鸟嘌呤核苷酸结合蛋白(G-蛋白)偶联受体结合,促进垂体分泌促肾上腺皮质激素(adrenocorticotropic hormone, ACTH),ACTH 由前体激素阿黑皮素原(pro-opiomelanocortin, POMC)衍生而来,在脊椎动物应激反应中处于中心角色[16]。垂体分泌并释放的 ACTH 与头肾肾间细胞上的黑皮质素 2 型受体(melanocortin type 2 receptor, MC2R)结合后[17],激活 MC2R,经过 cAMP 信号转导途径,一些调节类固醇激素生成的蛋白被磷酸化,这些蛋白质磷酸化后由非活性变成活性,将皮质类固醇合成原料—胆固醇由线粒体外膜转运至线粒体内膜,在一系列皮质类固醇生成酶的作用下,最终合成大量的应激激素皮质醇(cortisol,最主要的皮质类固醇激素)(图 1)。皮质醇经血液循环到达靶组织并与靶组织上的糖皮质激素受体(glucocorticoid receptor, GR)结合,调控一些与糖代谢、免疫功能以及行为等相关目的基因的转录[18-19]。GR 是类固醇激素受体家族的成员之一,属于核受体超家族[20],主要存在于硬骨鱼的鳃、肝脏、大脑和肠中[21-23]。大多数硬骨鱼如虹鳟鱼(Oncorhynchus mykiss)[24]、棘鳍类热带淡水鱼伯氏朴丽鱼(Haplochromis burtoni)[25]等均具有两种 GRs(GR1 和 GR2),斑马鱼(Danio rerio)是迄今为止被报道的只有一种 GR 的硬骨鱼。通过皮质醇的合成与释放,生物体的能量得以重新分配,从而满足应激引起的机体能量增加的需求[12,26]。

2　环境污染物对肾间应激轴的干扰效应及其潜在干扰机制

2.1　环境污染物对肾间应激轴的干扰效应

环境污染物可通过降低鱼体皮质醇水平和糖原含量,减弱其对二次胁迫的应答能力。Benguira 等[27] 利用体内试验研究表明,5、20、50 mg·kg^{-1} 有机

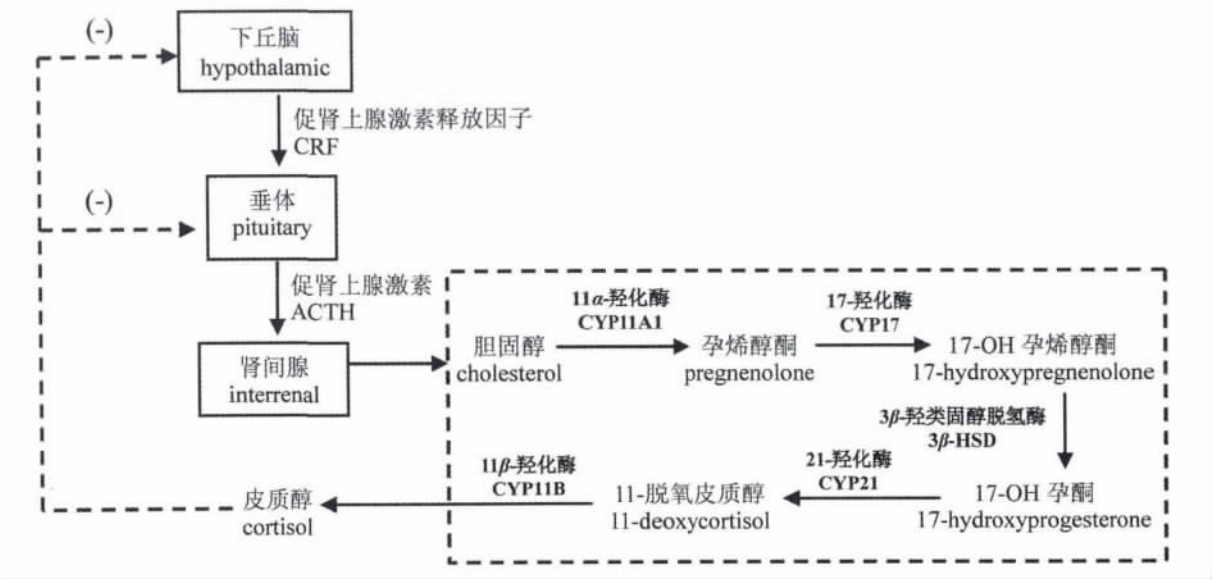

图1 鱼类皮质醇合成途径

Fig. 1 Cortisol biosynthesis pathway in fish

氯农药 o,p'-DDD 注射 14 d 可引起虹鳟鱼血浆皮质醇水平降低、高浓度处理组肝脏糖原含量显著减少，从而导致鱼体对二次胁迫的应答能力减弱。某些污染物还有可能通过直接损伤肾间组织、破坏肾间细胞以及垂体促肾上腺皮质细胞，干扰 HPI 轴的正常运行。Brodeur 等[28]认为肾间组织功能异常是导致黄色河鲈(Perca flavescens)皮质醇应激反应损坏的原因之一，受重金属污染水域黄色河鲈的肾间组织(体外)在 ACTH 的刺激下皮质醇分泌水平显著低于对照组。因此，环境污染物对 HPI 轴的干扰效应最终表现为血浆皮质醇水平的降低，导致机体不能正常启动应激反应，从而无法提供充足能量应对二次胁迫，使鱼体处于亚健康状态。

2.2 肾间应激轴的干扰对其它生理学功能的影响

污染物对肾间应激轴的干扰导致皮质醇水平的异常，可能会进一步影响鱼类的代谢、离子平衡的调节以及免疫等生理功能[29-30]。

皮质醇参与调节机体的能量代谢。Aluru 和 Vijayan[31]研究证实皮质醇通过与肝脏 GR 结合，上调肝脏葡糖异生作用的限速酶磷酸烯醇式丙酮酸羧激酶(phosphoenolpyruvate carboxykinase, PEPCK)，使肝细胞葡萄糖含量升高，为恢复体内平衡提供能量来源。污染物可能通过干扰皮质醇合成、GR 途径等，进一步影响鱼类的代谢[32]。Gagnon 等[33]研究发现，Cu(80 μg·L^{-1})暴露 30 d，导致虹鳟鱼急性皮质醇反应能力降低，同时伴随血浆葡萄糖水平和肝脏糖原含量的降低。Ings[2]研究表明，100% 市政污水暴露导致虹鳟鱼在二次胁迫下皮质醇应答减弱，同时肝脏己糖激酶(hexokinase, HK)和葡糖激酶(glucokinase, GK)的活性显著降低，表明虹鳟鱼的能量代谢能力也受到了抑制。

皮质醇涉及鱼类离子平衡的调节。由于硬骨鱼不能像哺乳动物一样合成盐皮质激素如醛固酮，皮质醇在硬骨鱼中除了发挥糖皮质激素功能外，还具有盐皮质激素的作用[12,34]。污染物干扰皮质醇应激反应可能会进一步影响鱼类的离子平衡。皮质醇能够促进鳃氯细胞的增殖和分化[35-36]。Laflamme 等[32]认为，污染最严重湖泊(Osisiko)中的黄鲈血浆氯离子水平减少可能是急性应激反应能力降低导致的生理学后果。Na^+,K^+-ATPase 涉及硬骨鱼类鳃的离子摄取和盐分泌[37]。皮质醇能够提高大西洋鲑鱼(Salmo salar)鳃 Na^+,K^+-ATPase 的活性和 mRNA 水平，提高耐盐性[38]。Levesque 等[39]研究发现，金属污染水域中黄鲈急性皮质醇反应损坏的同时伴随鳃 Na^+,K^+-ATPase 活性的改变。Lerner 等[29]认为 17β-雌二醇(2 μg·L^{-1})通过降低 GR 水平减少大西洋鲑鱼鳃 Na^+,K^+-ATPase 的活性，使其离子调节能力和海水中的耐盐性减弱。

除了能够干扰能量代谢和离子平衡，皮质醇的变化还会抑制鱼类的生殖、生长以及免疫等功能。如大量的文献已经证实高于生理水平的皮质醇不仅对生殖功能具有有害影响，还能抑制鱼类的生长。

Poursaeid 等[40]研究发现皮质醇长期处理不仅导致大鲟鱼 Huso huso 血浆睾酮和 17β-雌二醇水平降低，而且最高浓度处理组身体增长指数(包括体重增加率、比生长速率、肥满度)也显著下降。过高水平的皮质醇对免疫功能也具有抑制作用。Castillo 等人[41]的研究则表明皮质醇能够抑制分离巨噬细胞细胞因子(TNF、TGFb、IL-6)的表达，当皮质醇和脂多糖(LPS)同时加入到巨噬细胞中，细胞因子的诱导也被皮质醇显著抑制。

2.3　环境污染物对肾间应激轴的潜在干扰机制

研究表明环境污染物主要通过干扰下丘脑和垂体促皮质类固醇激素的分泌、皮质醇的合成与代谢、cAMP 信号转导以及皮质醇负反馈途径等，最终抑制皮质醇的合成与分泌，减弱鱼类的应激反应能力。通常情况下，某一种污染物往往是以 HPI 轴的多个位点为靶目标发挥干扰效应。就目前报道的文献来看，多数污染物主要通过干扰类固醇生成和大脑糖皮质激素信号这两条途径影响 HPI 轴的功能[42-44]。

2.3.1　对 HPI 轴的过度刺激

皮质醇和 ACTH 等激素分泌亢进可能是环境污染物导致 HPI 轴功能损坏的机制之一。如在野外环境下，污染物本身就作为一个“应激源(stressor)”，长期、过度激活肾间应激轴，引起慢性应激反应即皮质醇分泌亢进，可能进一步导致鱼类 HPI 轴功能受损或衰竭，对二次胁迫的应答能力下降[45-46]。Hontela 等[47]研究表明，加拿大一条被污染河流中的黄色河鲈和白斑狗鱼(Esox lucius)在二次胁迫下应激反应减弱，原因可能是污染物慢性暴露引起 HPI 轴持续活跃、皮质醇分泌系统衰竭所致。Norris 等人[48]的研究进一步证实了 Hontela 的推测，受金属污染水域中的褐鳟鱼(Salmo trutta)因过度分泌 ACTH 导致 HPI 轴功能衰竭，二次应激的血浆皮质醇水平显著低于对照组。

2.3.2　干扰下丘脑以及垂体主要促激素对皮质醇的调节

污染物对 CRF 和 ACTH 的干扰可能直接影响 HPI 轴功能的正常发挥。在哺乳动物中研究发现，Cd 可通过干扰 Y-1 型鼠肾上腺肿瘤细胞 ACTH 的分泌影响皮质类固醇的分泌[49]。因鱼体 CRF、ACTH 等激素水平较难测定，相关研究主要是在基因水平上开展的，如 Fuzzen 等[50]研究表明，100 ng·L^{-1} E_2 暴露 48 h 导致雄性斑马鱼皮质醇应答减弱、crf mRNA 的表达水平降低了三倍。然而，基因水平的变化与激素水平的变化有时并不成正相关关系。因此，未来还需要从蛋白水平进一步研究污染物暴露下 CRF 和 ACTH 对皮质醇的调节作用。

2.3.3　干扰 cAMP 信号途径

普遍认为 cAMP 信号级联反应的过程主要为: ACTH 与受体 MC2R 结合后，激活 G 蛋白，G 蛋白激活后促进腺苷酸环化酶生成大量的 cAMP[51]。cAMP 通过激活多个靶目标如 cAMP-依赖性蛋白激酶 A(protein kinase A, PKA)等促进类固醇激素的生成[52-53]。cAMP 信号途径的各个因子都有可能是环境污染物干扰皮质类固醇合成的关键目标。研究发现，有机氯农药 o,p'-DDD 能显著抑制 G 蛋白激动剂 NaF、腺苷酸环化酶激动剂毛喉素以及 cAMP 类似物对皮质醇生成的促进效应，表明 cAMP 信号途径的多个因子(G 蛋白、腺苷酸环化酶等)均是 o,p'-DDD 干扰虹鳟鱼肾间细胞皮质醇生成的靶位点(体外)[54]。Sandhu 和 Vijayan[55]研究认为镉(10、100、1 000 nmol)干扰虹鳟鱼头肾细胞皮质醇合成的靶目标位于 cAMP 生成的上游，并推测 MC2R 信号途径(ACTH 诱导皮质醇生成首要的一步)可能是镉干扰虹鳟鱼头肾细胞皮质醇生成的关键目标。

2.3.4　干扰皮质醇的合成与代谢

皮质类固醇生物合成途径的关键限速步骤主要包括: 类固醇急性调节蛋白(steroidogenic acute regulatory protein, StAR)和外周型苯二氮受体(peripheral-type benzodiazepine receptor,PBR)共同将胆固醇从线粒体外膜转移到细胞色素 P450 侧链裂解酶(cytochrome P450 side chain cleavage enzyme, P450scc)的活性部位[56-58]; P450scc 将胆固醇转化成孕烯醇酮[59]。皮质类固醇合成途径中关键酶或蛋白转录水平的微小变化可能会对皮质醇激素水平产生显著的影响[44]。多篇文献研究结果表明皮质醇合成限速步骤中的关键酶或蛋白是环境污染物干扰肾间应激轴的关键靶目标，环境污染物可通过降低该限速步骤中关键因子的转录水平，进而干扰皮质醇的合成。Aluru 等[60]研究表明，芳香烃受体(aryl hydrocarbon receptor, AhR)激动剂(β-萘黄酮,BNF)和拮抗剂(α-萘黄酮,ANF)可通过降低 StAR 和 P450scc 的 mRNA 含量使肾间类固醇生成能力减弱，显著抑制了 ACTH 对虹鳟鱼头肾细胞皮质醇分泌的促进效应(体外)。100 mg·kg^{-1} 水杨酸盐喂食虹鳟鱼 3 d，可导致头肾 StAR 和 PBR 的 mRNA 水平显著降低[43]。

除了限速步骤中的StAR、PBR和P450scc，皮质类固醇合成途径中的主要蛋白还包括下游的17α-羟化酶(CYP17)、3β-羟化类固醇脱氢酶(3β-HSD)、21-羟化酶(CYP21)和11β-羟化酶(CYP11B)[59]。其中11β-羟化酶(CYP11B)是一个重要的多功能类固醇合成酶，它参与皮质醇生物合成的最后一步，将11-脱氧皮质醇转化为皮质醇[61]。Kortner等[62]研究发现，0.1、1、10 mg·kg^{-1}三丁基锡(TBT)灌食幼年大马哈鱼72 h，可显著抑制肾间11β-羟化酶的mRNA水平。但Walsh等[63]认为，与限速步骤因子StAR、P450scc等相比，类固醇合成途径下游的一些酶对污染物的暴露可能表现较低的敏感性。如芳香烃受体(AhR)激动剂(β-萘黄酮,BNF)和拮抗剂(α-萘黄酮,ANF)显著降低了虹鳟鱼头肾细胞StAR和P450scc的转录水平，但对CYP11B表达无影响[60]。Gravel和Vijayan[43]研究表明，水杨酸盐暴露可显著降低虹鳟鱼头肾StAR和PBR的mRNA水平，而11β-羟化酶的mRNA水平无明显变化。

皮质类固醇的代谢对血浆皮质醇水平的维持也起关键性的作用，环境污染物可能通过干扰皮质醇的代谢，促进或抑制皮质醇转化为失活代谢物，进而影响其发挥正常生理功能。Ings等[2]研究发现，城市污水暴露虹鳟鱼14 d，在急性胁迫后24 h，100%未稀释污水处理组皮质醇合成酶(StAR、P450scc、11β-羟化酶)mRNA水平均显著降低，而血浆皮质醇含量较对照组显著升高，由此推测城市污水的暴露可能干扰了皮质醇的代谢。Wiseman等[64]研究表明，用含硒代蛋氨酸8.47 mg·(kg·dm)$^{-1}$的食物喂养雌性虹鳟鱼126 d后，给予空气暴露胁迫，血浆皮质醇水平较对照组降低，而其失活代谢物—皮质酮水平显著升高，进而导致虹鳟鱼对二次胁迫的应激应答能力减弱。虽然现有文献已经证明皮质醇的代谢是污染物干扰鱼类应激反应的靶位点，但是污染物是如何干扰皮质醇的代谢途径尚不清楚。Wiseman等[64]研究中缺少对11β-羟化类固醇脱氢酶(将皮质醇转化成皮质酮的直接指标)水平的测定。

2.3.5 干扰大脑GR信号途径

皮质醇可通过负反馈途径作用于下丘脑和垂体，调节CRF和ACTH的分泌，从而维持血浆中皮质醇的水平。其中大脑GR信号途径是皮质醇负反馈调节环的一个关键组成部分，Alderman等[65]研究表明，GR涉及调节虹鳟鱼下丘脑视前区(preoptic area, POA)CRF转录水平，进而影响血浆皮质醇的水平。大脑GR信号途径是污染干扰肾间应激轴的靶位点之一。在分子水平上，Aluru等[42]研究表明，高浓度PCBs 100 mg·(kg·bm)$^{-1}$暴露北极红点鲑(Salvelinus alpinus)引起神经毒性，使含GR的神经细胞减少，大脑GR基因表达下降，从而干扰了皮质醇的负反馈调节，导致血浆皮质醇水平降低。在蛋白水平上，Gravel和Vijayan[43]的研究也获得了类似结果，100 mg·(kg·bw)$^{-1}$水杨酸盐处理虹鳟鱼3 d导致大脑GR蛋白含量显著降低约50%，从而干扰了皮质醇负反馈调节。

3 研究展望

3.1 开发环境肾间腺干扰物筛选的分子标志物

三大内分泌轴线下丘脑-垂体-性腺轴(hypothalamic-pituitary-gonadal, HPG轴)、下丘脑-垂体-甲状腺轴(hypothalamic-pituitary-thyroid axis, HPT轴)以及HPI轴共同调节鱼体的内分泌平衡。污染物干扰任一内分泌轴线均可导致鱼体内分泌紊乱，甚至威胁个体的存活。利用指示内分泌轴线干扰的分子标志物可以准确、敏感地评价污染物对鱼类早期、低水平的内分泌扰乱作用，例如卵黄原蛋白(vitellogenin, VTG)是指示HPG轴是否受到环境雌激素干扰的理想分子标志物。目前，对HPI轴分子标志物的研究工作还未见开展。而开发指示肾间腺轴干扰的分子标志物，对鉴别和筛选“环境肾间腺干扰物”具有重要意义。早期关于哺乳动物的研究发现，具有皮质类固醇受体启动元件的基因可能是研究污染物干扰皮质醇应答的有效标志物，这可能同样适用于鱼类。Quabius等[66]研究表明，PCBs暴露能引起虹鳟鱼前肾细胞中糖皮质激素受体和白细胞介素-1-β的升高。因此，今后应该着重研究含有皮质醇受体启动元件的基因，在基因表达水平上筛选“环境肾间腺干扰物”的分子标志物。

3.2 环境污染物对肾间应激轴作用机制的深入探讨

目前，环境污染物干扰肾间应激轴的机制研究远不够深入。Ings等[2]研究发现，城市污水暴露导致虹鳟鱼皮质醇合成酶基因表达下降而血浆皮质醇水平显著升高，推测原因是皮质醇的代谢也受到干扰，但是该作者并没有进一步证实。多篇文献表明大脑GR信号途径是污染物干扰HPI轴的靶位点，但垂体水平的负反馈调节却未见报道。其次，环境污染物因其种类、结构和性质的不同，其干扰机制也存在较大差异，有些是对鱼类肾间应激轴直接的作用，还有些可能是污染物对其它内分泌轴线的作用

间接导致肾间轴线的变化。肾间应激轴与生殖轴[67-68]、甲状腺轴均存在交互作用[69]。三大轴线之间也可以进行复杂的交叉反应，Liu 等[70]研究表明咪鲜胺(prochloraz, PCZ)可通过降低雌性斑马鱼血浆 E_2 浓度下调 HPI 轴 CRF 的基因表达，并进一步导致血浆皮质醇水平的降低; 而 CRF 的降低又能够下调 HPT 轴促甲状腺激素(thyroid-stimulating hormone, TSH)水平，最终导致甲状腺素(thyroxine, T_4)含量下降。因此，作用机制的进一步探讨首先要从轴线外角度明确污染物干扰肾间应激轴是直接作用还是间接作用，其次要深入研究轴线内的靶位点，皮质醇代谢途径的酶和因子以及垂体水平的正负反馈调节等应是今后深入探讨污染物干扰 HPI 轴作用机制的研究重点，而污染物对鱼类完整内分泌系统的影响研究应是未来的研究热点和难点。

3.3　大脑神经递质系统与应激轴的联合研究

目前已知大脑单胺能神经递质系统涉及脊椎动物的完整应激反应，其中大脑 5-羟色胺(5-hydroxytryptamine, 5-HT)系统在复杂的神经内分泌环中发挥关键作用，在鼠中已经证实 5-HT 神经末端与室旁核内包含 CRH 的神经元之间存在直接的突触联系[71]，5-HT 能够促进哺乳动物下丘脑 CRF[72]和垂体 ACTH 的释放[73]; 同时，5-HT 活性也受到应激反应中的因子如皮质醇、CRF 等影响[74]。早期文献就已表明大脑 5-HT 能系统在鱼类 HPI 轴的调节中也发挥关键作用[75]，但具体机制还不清楚。近来，Gesto 等[76]研究表明，急性应激能够诱导虹鳟鱼前脑血清素活性和终脑多巴胺能活性的增加。因此，环境污染物对鱼类完整应激反应的影响除了与应激轴有关，应该还要考虑大脑神经递质系统是否也受到干扰，上游神经递质系统受到干扰可能也会影响下游轴线的调节。由于单胺能系统与应激轴之间存在复杂的交互作用，在哺乳动物中相关研究很有限，鱼类中的文献更是非常罕见，鱼类大脑神经递质系统与应激轴的联系还有待于进一步揭示。

通讯作者简介: 汝少国(1967—)，男，博士，教授，博士生导师，主要从事污染生态学和环境内分泌干扰物研究。

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