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典型 SSRIs 类抗抑郁药对鱼类的毒性效应研究进展

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摘要: 选择性血清素再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)是一类在临床上具有良好治疗效果的抗抑郁药物,由于使用量巨大,在水环境中频繁被检出,其潜在生态毒性效应引起人们的广泛关注。鱼类作为水生脊椎动物,具有和人类相似的神经调控系统,更易受到水体中残留的 SSRIs 的影响。本文综述了 SSRIs 在鱼类体内的代谢和生物积累效应,以及 SSRIs 对鱼类产生的生长发育毒性、生殖毒性和神经行为毒性,并对未来该领域的研究进行了展望。

关键词: 选择性血清素再摄取抑制剂;鱼类;生长发育毒性;生殖毒性;神经行为毒性
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Research Progress on Toxic Effects of Typical SSRIs Antidepressants on Fish

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Abstract: Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants which are used widely in human clinical medicine. Due to high prescription rates and ubiquitous use, SSRIs are frequently detected in the aquatic environment, and their potential ecotoxic effects have caused widespread global concern. As vertebrates, fish show some homology in neuroregulatory system compared to humans, and thus, can be susceptible to effects due to psychotropic drug contaminants in the water. This review outlines the metabolism and bioaccumulation of SSRIs in fish and introduces the influence of SSRIs on the growth and development, reproduction, and behavior of fish. Based on published data, we point out the limitations of current toxicological research on SSRIs and propose future studies for this important class of chemicals in aquatic toxicology.

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Keywords: selective serotonin reuptake inhibitors; fish; growth and development toxicity; reproductive toxicity; neurobehavioral toxicity

药物活性化合物(pharmaceutically active compounds, PhACs)是一类数量巨大、种类繁多和生物活性复杂,且具有潜在生态毒性的新型有机污染物,包括人用和兽用的抗生素、激素、消炎镇痛药、精神类药物和降压药等[1]。由于 PhACs 的广泛使用,其产生的环境污染问题已经成为社会关注的焦点和环境科学研究的热点课题。近年来,选择性血清素再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)是临床上治疗抑郁症、焦虑症和强迫障碍等精神疾病的常用药物。目前国内外最常用的 SSRIs 有 6 种:氟西汀、帕罗西汀、舍曲林、西酞普兰、艾司西酞普兰和氟伏沙明(图 1)。在我国使用的治疗类药品中,抗抑郁药物的分布仅次于抗生素类药物(42%),占 10%[2],其年消费总量可达 27 t,而 SSRIs 的消费量占总消费量的 30%[2]。此外,水环境中的 SSRIs 主要来源于污水排放,大多数污水处理厂对 SSRIs 的去除率较低(<56%)[3-5],致使处理后仍有大量的 SSRIs 及其代谢产物进入河流和湖泊等地表水体。SSRIs 在污水处理厂出水的浓度为 ng·L^{-1} ~ μg·L^{-1}水平,而在地表水中的浓度为 ng·L^{-1}水平。例如,舍曲林在污水处理厂污水和地表水中的最高浓度分别为 2.19 μg·L^{-1}[6-8]和 0.22 μg·L^{-1}[6,9-11]。因此,由于 SSRIs 的使用量巨大,在水环境中被频繁检出,其潜在生态毒性效应引起了广泛关注。

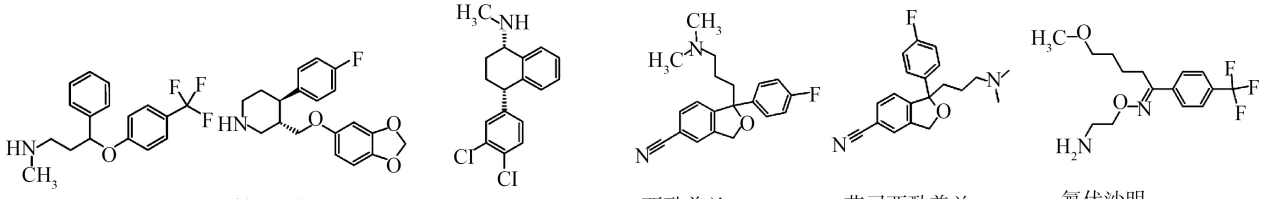

图 1　选择性血清素再摄取抑制剂(SSRIs)的结构和物理化学特性

注:CAS No.表示化学文摘社登记号码;pK_a 表示解离常数;logK_{ow} 表示正辛醇-水分配系数。

Fig. 1　Structure and physicochemical characteristics of selective serotonin reuptake inhibitors (SSRIs)

Note: CAS No. stands for Chemical Abstracts Service Registry Number; pK_a stands for dissociation constant; logK_{ow} stands for octanol-water partition coefficient.

SSRIs 是通过抑制人体突触前膜血清素转运体对血清素(serotonin, 5-HT)的再摄取,从而促进突触后膜 5-HT 能的神经传导,达到抗抑郁的效果(图 2)[12]。先前的研究预测,当鱼类暴露在 1 μg·L^{-1}以及低于 1 μg·L^{-1}的 SSRIs 时,其血浆中的 SSRIs 浓度会达到与人类治疗剂量(peak concentration, C_{max})相等的水平[13]。作为中枢神经系统的神经递质之一,5-HT 在调节鱼类的生长发育、生殖和行为等方面同样具有重要作用[14-17]。外源 SSRIs 的非正常摄入可能引起 5-HT 功能异常,从而干扰鱼类正常的生理功能,产生潜在的生长发育、生殖和神经行为毒性等毒性效应。此外,鱼类终身生活在水中,能够直接接触并持续暴露于水体中的 SSRIs,更易受到水体中 SSRIs 的影响。本文在大量查阅近期 SSRIs 相关研究成果的基础上,以 SSRIs 抗抑郁的药物作用机制入手,分析 SSRIs 在鱼体内的代谢特征,并总结了 SSRIs 对鱼类的生长发育、生殖和神经行为等方面的毒性效应,并对存在的问题以及今后的发展提出了几点建议和展望。

1　SSRIs 在鱼类体内的代谢及生物积累(Metabolism and biological accumulation of SSRIs in fish)

1.1　SSRIs 在鱼类体内的代谢途径

细胞色素 P450 酶(cytochrome P450, CYP450)是哺乳动物和鱼类体内药物代谢的关键酶。其中,SSRIs 在人体内主要由 CYP2D6 或 CYP2C19 代谢[18],

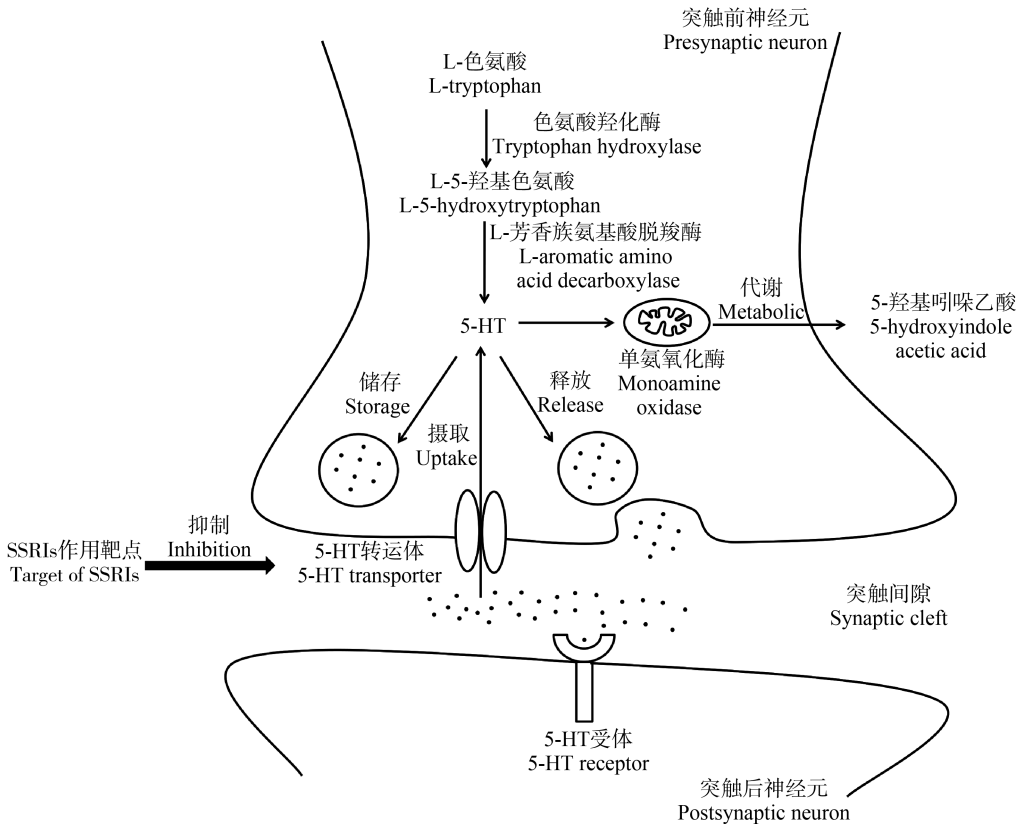

图 2 血清素(5-HT)的合成、释放、摄取、储存、代谢及 SSRIs 作用靶点示意图(参考文献[12])

Fig. 2 Schematic diagram of serotonin (5-HT) synthesis, release, uptake, storage, metabolism and SSRIs targets (reference from literature [12])

而鱼类体内缺乏 CYP2D 和 CYP2C 的同源物,因此 SSRIs 在鱼类体内可能由其他的 CYP450 代谢[19]。SSRIs 在人体内的主要代谢途径为 N-去甲基化,如氟西汀在人体内的 N-去甲基代谢产物为去甲氟西汀[18]。然而,氟西汀在鱼体内的主要代谢产物并非去甲氟西汀[19]。在斑马鱼胚胎中,仅有约 1% 的氟西汀转化为去甲氟西汀,其余可代谢为 10 种其他的代谢产物[20-21]。此外,与哺乳动物相比,鱼类对 SSRIs 的吸收和代谢速率较慢。例如,氟西汀在人体内的半衰期为 1 ~4 d[22],而在青鳉(*Oryzias latipes*)体内的半衰期为 9.4 d[23]。可见,SSRIs 在鱼类和哺乳动物体内的代谢途径可能存在差异,然而目前关于 SSRIs 在鱼体中的主要代谢酶、主要代谢产物以及代谢途径还不明确,仍需进一步的探索。

1.2 SSRIs 在鱼类体内的生物积累

生物富集(bioconcentration)是指水生生物通过非吞食方式从水中吸收化学物质,导致化学物质在水生生物体内的浓度超过水环境中浓度的现象,而生物积累(bioaccumulation)是指水生生物通过所有途径(吞食和非吞食方式)从水中吸收化学物质,导致化学物质在水生生物体内的浓度超过水环境中浓度的现象。生物富集是生物积累的一种情况。正辛醇/水分配系数(octanol-water partition coefficient, K_{ow})能够反映化学物质在油水两相中的分配情况。当化学物质的 $\log K_{ow}$ >4 时,一般认为该化学物质相对亲脂。SSRIs 的 $\log K_{ow}$ 在 3.74 ~5.29 之间,具有一定的亲脂性,能够在鱼类体内积累。生物富集因子(bioconcentration factor, BCF)和生物积累因子(bioaccumulation factor, BAF)能够反映化学物质在鱼类体内的积累能力,其值越大,该化合物在鱼类体内的积累能力越大,反之,积累能力越小。目前,已有研究报道了 SSRIs 能够在多种鱼体内积累,如青鳉、鲫(*Carassius auratus*)和虹鳟(*Oncorhynchus mykiss*)等[9,11,23-29]。

SSRIs 能够在鱼类的不同组织(肝脏、脑、肾脏、肌肉、腮和性腺)中积累,由于暴露时间[28-29]、暴露浓度[11,28-29]和鱼的种类[9,29]的不同,积累能力相差较大,但主要在鱼类的肝脏、肾脏和脑中积累(表 1)。

表 1　SSRIs 在鱼体内的生物积累

Table 1　Bioaccumulation of SSRIs in fish

生物 Organisms	药物 Pharmaceutical	暴露浓度 Concentration	暴露时间 Exposure duration	组织种类 Tissue	BCF 或 BAF BCF or BAF	参考文献 References
实验室鱼类 Laboratory fish						
青鳉[a] *Oryzias latipes* [a]	氟西汀 Fluoxetine	0.64 μg·L^{-1}	7 d	全鱼匀浆 Whole fish homogenate	BCF:74, 80	[23]
斑马鱼胚胎 *Danio rerio* embryo	氟西汀 Fluoxetine	0.1 ~ 1 000 μg·L^{-1}	68 h 116 h	全鱼匀浆 Whole fish homogenate	BCF: 0.019 ~ 0.220 BCF:1.73 ~ 6.88	[29]
斑马鱼成鱼 Adult *Danio rerio*	氟西汀 Fluoxetine	0.1 μg·L^{-1}	3, 6 d	脑 Brain 内脏 Viscera 肌肉 Muscle	BCF: 10.9 ~ 104 BCF: 5.62 ~ 18.4 BCF: 3.37 ~ 11.2	[29]
鲫 *Carassius auratus*	氟西汀 Fluoxetine	0.1 μg·L^{-1}	3, 6 d	肝脏 Liver 脑 Brain 肌肉 Muscle	BCF: 3.16 ~ 3.23 BCF: 1.33 ~ 3.01 BCF: 0.33 ~ 0.97	[29]
		0.1 ~ 1 000 μg·L^{-1}	30 d	肝脏 Liver 脑 Brain 肌肉 Muscle	BCF: 11.1 ~ 137 BCF: 12.4 ~ 110 BCF: 12.1 ~ 166	
鲫 *Carassius auratus*	舍曲林 Sertraline	4.36 ~ 116 μg·L^{-1}	4, 7 d	肝脏 Liver 脑 Brain 腮 Gill 肌肉 Muscle	BCF: 19.5 ~ 626 BCF: 6.94 ~ 285 BCF: 4.01 ~ 146 BCF: 0.625 ~ 43.1	[28]
虹鳟[b] *Oncorhynchus mykiss* [b]	舍曲林 Sertraline	53 ng·L^{-1}	13 d	肝脏 Liver 脑 Brain	BCF: 85 BCF: 180	[25]
	西酞普兰 Citalopram	260 ng·L^{-1}		肝脏 Liver 脑 Brain	BCF: 47 BCF: 9	
拟鲤[b] *Rutilus rutilus* [b]	氟西汀 Fluoxetine	54 ~ 72 ng·L^{-1}	15 d	脑 Brain 血浆 Plasma	BCF: 68 BCF: 6.3	[24]
	帕罗西汀 Paroxetine	6.6 ~ 9.8 ng·L^{-1}		脑 Brain	BCF: 67	
	舍曲林 Sertraline	47 ~ 65 ng·L^{-1}		脑 Brain 血浆 Plasma	BCF: 361 BCF: 14	
	西酞普兰 Citalopram	211 ~ 340 ng·L^{-1}		脑 Brain	BCF: 1.6	
美洲红点鲑[b] *Salvelinus fontinalis* [b]	氟西汀 Fluoxetine	54 ~ 72 ng·L^{-1}	3 months	肝脏 Liver 脑 Brain 肌肉 Muscle	BCF: 345 BCF: 138 BCF: 224	[24]
	帕罗西汀 Paroxetine	6.6 ~ 9.8 ng·L^{-1}		肝脏 Liver 脑 Brain	BCF: 365 BCF: 198	
	舍曲林 Sertraline	47 ~ 65 ng·L^{-1}		肝脏 Liver 脑 Brain 肌肉 Muscle	BCF: 264 BCF: 191 BCF: 109	
	西酞普兰 Citalopram	211 ~ 340 ng·L^{-1}		肝脏 Liver 脑 Brain	BCF: 39 BCF: 17	
野生鱼类 Wild fish						
鲤鱼[c] *Cyprinus carpio* [c]	舍曲林 Sertraline	1.3 ~ 1.6 ng·L^{-1}	–	肝脏 Liver 肾脏 Kidney 脑 Brain 腮 Gill 肌肉 Muscle	BAF: 2 727.3 BAF: 2 697.6 BAF: 2 655.5 BAF: 1 515.2 BAF: 757.6	[27]

续表1

生物 Organisms	药物 Pharmaceutical	暴露浓度 Concentration	暴露时间 Exposure duration	组织种类 Tissue	BCF或BAF BCF or BAF	参考文献 References
褐鳟[cd] *Salmo trutta m. fario* [cd]	舍曲林 Sertraline	10 ng·L^{-1}	1 month	肝脏 Liver 肾脏 Kidney 脑 Brain	BAF: 2 400 BAF: 4 400 BAF: 240, 1 500	[11]
	西酞普兰 Citalopram	3.9 ng·L^{-1}	6 months	肝脏 Liver 肾脏 Kidney 脑 Brain	BAF: 880 BAF: 2 800 BAF: 680	
		4.5 ng·L^{-1}	1 month	肾脏 Kidney	BAF: 70	
		58 ng·L^{-1}	1 month	肝脏 Liver 肾脏 Kidney	BAF: 260 BAF: 710	
		53 ng·L^{-1}	3 months	肝脏 Liver 肾脏 Kidney	BAF: 590 BAF: 2 100	
		24 ng·L^{-1}	6 months	肝脏 Liver 肾脏 Kidney	BAF: 360 BAF: 3 100	
小口黑鲈[ce] *Micropterus dolomieu* [ce]	舍曲林 Sertraline	<LOD～220 ng·L^{-1}	–	脑 Brain 性腺 Gonad	BAF: 24～27 BAF: 27	[9]
大口黑鲈[ce] *Micropterus salmoides* [ce]	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}	–	肌肉 Muscle	BAF: 2	
	舍曲林 Sertraline	<LOD～220 ng·L^{-1}		脑 Brain 肝脏 Liver	BAF: 68 BAF: 5	
	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}		脑 Brain 性腺 Gonad	BAF: 8 BAF: 4～5	
赤眼鳟[ce] *Scardinius erythrophthalmus* [ce]	舍曲林 Sertraline	<LOD～220 ng·L^{-1}	–	脑 Brain	BAF: 18	
	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}		肝脏 Liver 脑 Brain 性腺 Gonad 肌肉 Muscle	BAF: 20 BAF: 4 BAF: 2～4 BAF: 1	
岩钝鲈[ce] *Ambloplites rupestris* [ce]	舍曲林 Sertraline	<LOD～220 ng·L^{-1}	–	脑 Brain 性腺 Gonad	BAF: 29 BAF: 14～15	
	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}		肝脏 Liver 脑 Brain 性腺 Gonad	BAF: 9 BAF: 18 BAF: 2～3	
金眼狼鲈[ce] *Morone chrysops* [ce]	舍曲林 Sertraline	<LOD～220 ng·L^{-1}	–	脑 Brain 性腺 Gonad	BAF: 23 BAF: 2	
	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}		肝脏 Liver 脑 Brain 性腺 Gonad 肌肉 Muscle	BAF: 1～19 BAF: 6 BAF: 9 BAF: 2	
美洲狼鲈[ce] *Morone americana* [ce]	舍曲林 Sertraline	<LOD～220 ng·L^{-1}	–	性腺 Gonad	BAF: 0.5	
	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}		性腺 Gonad	BAF: 8	
玻璃梭鲈[ce] *Sander vitreus* [ce]	舍曲林 Sertraline	<LOD～220 ng·L^{-1}	–	脑 Brain 性腺 Gonad	BAF: 15～20 BAF: 2	
	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}		肝脏 Liver 性腺 Gonad	BAF: 3 BAF: 5	
弓鳍鱼[ce] *Amia calva* [ce]	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}	–	肝脏 Liver	BAF: 1	
虹鳟[ce] *Oncorhynchus mykiss* [ce]	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}	–	肝脏 Liver	BAF: 17	
美国黄金鲈[ce] *Perca flavescens* [ce]	西酞普兰 Citalopram	<LOD～190 ng·L^{-1}	–	脑 Brain 性腺 Gonad	BAF: 4 BAF: 1～4	

注:BCF表示生物富集因子;BAF表示生物积累因子;LOD表示检测限,<LOD表示未检出;“–”表示未给出;[a]鱼类在名义浓度为0.64 μg·L^{-1}的氟西汀中暴露7 d,随后在清水中净化21 d;[b]暴露溶液为污水处理厂污水;[c]暴露浓度为地表水的浓度;[d]在同一条河流中,从未被污染的河流点位中捕捉的鱼类被标记并放养到被污染的点位进行暴露;[e]暴露浓度范围取文中给出的河流点位所检测到的化合物浓度的范围。

Note: BCF stands for bioconcentration factor; BAF stands for bioaccumulation factor; LOD stands for limits of detection, and <LOD stands for not detected; “–” indicates not given; [a] fish were exposed to fluoxetine at a nominal concentration of 0.64 μg·L^{-1} for 7 d and then purified in clear water for 21 d; [b] the exposed solution is the sewage treatment plant effluent; [c] the exposure concentration is the surface water concentration; [d] in the same river, fish caught in uncontaminated river points are tagged and released to the contaminated points for exposure; [e] the exposure concentration range is taken from the range of compounds detected at the river point.

可以看出,除肝脏和肾脏外,脑很可能是 SSRIs 对鱼类作用的主要靶组织。鱼类的行为由中枢神经系统和骨骼肌共同控制[30-31],脑内神经递质系统的改变能够影响鱼类的发育和行为[14,32-33]。另外,神经内分泌系统通过下丘脑-垂体-性腺轴调节脊椎动物的生殖。下丘脑是脊椎动物产生神经肽、促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)的主要部位,在控制脊椎动物的生殖方面发挥着重要作用[15]。因此,SSRIs 在鱼类体内中的积累可能对鱼类产生潜在的生长发育、生殖和神经行为毒性效应。

2　SSRIs 对鱼类的毒性作用(Toxic effects of SSRIs on fish)

2.1　SSRIs 对鱼类的急性毒性

SSRIs 对鱼类的急性毒性相对较低,半数致死浓度(median lethal concentration, LC_{50})通常在 μg·L^{-1} ~ mg·L^{-1}水平(表 2),环境浓度剂量的 SSRIs 污染(ng·L^{-1})一般不会对鱼类造成急性致死效应。目前关于 SSRIs 对鱼类的急性毒性效应研究主要集中在氟西汀、舍曲林和西酞普兰。根据不同 SSRIs 对青鳉仔鱼的 72 h-LC_{50} 值,氟西汀和舍曲林的毒性相当(LC_{50} = 0.84 mg·L^{-1}),高于西酞普兰(LC_{50} = 9.14 mg·L^{-1})(表 2)。另外,不同的氢离子浓度指数(hydrogen ion concentration, pH)条件下,SSRIs 对鱼类的急性毒性有很大差异,越接近药物解离常数(dissociation constant, pK_a)的 pH 条件下药物的毒性越强[34-35]。

2.2　SSRIs 对鱼类生长发育的影响

迄今为止,已有多篇文献报道了 SSRIs 对鱼类生长发育的影响。例如,SSRIs 可以导致鱼类的畸形率增加、心率异常和孵化率异常等。其中,氟西汀的暴露不仅能够引起斑马鱼胚胎的累积畸形率增加(0.52 ~ 276.63 μg·L^{-1})[43],还会导致斑马鱼胚胎/仔鱼的孵化时间提前、存活率降低、心率降低和体长减少(0.009 ~ 99 μg·L^{-1})[44]。不仅如此,氟西汀的暴露(0.03 ~ 0.50 μg·L^{-1},35 d)还会导致孔雀鱼(*Poecilia reticulata*)幼鱼的脊索长度、腹部宽度和湿体质量显著减少[45]。帕罗西汀(10 μg·L^{-1})的暴露能够显著加速斑马鱼的孵化[46]。舍曲林暴露不但能够显著抑制斑马鱼胚胎的孵化(10 μg·L^{-1})[46],还能够引起斑马鱼胚胎的畸形率显著增加(100 μg·L^{-1})[47]。此外,SSRIs 还能够干扰调控鱼类发育相关基因的表达。Sehonova 等[48]将斑马鱼胚胎暴露在 0.1 μg·L^{-1} 和 10 μg·L^{-1}的舍曲林下约 144 h 后,利用实时荧光定

表 2　SSRIs 对鱼类的急性毒性

Table 2　Acute toxity of SSRIs on fish

药物 Pharmaceutical	受试生物 Organisms	暴露时间/h Expose time/h	LC_{50}/(mg·L^{-1})	参考文献 References
氟西汀 Fluoxetine	斑马鱼胚胎 *Danio rerio* embryo	168	1.18	[36]
	斑马鱼仔鱼 *Danio rerio* larva	96	0.25	[37]
	食蚊鱼仔鱼 *Gambusia affinis* larva	168	0.55	[38]
	麦穗鱼幼鱼 Juvenile *Pseudorasbora parva*	96	2.89	[39]
	黑头软口鲦幼鱼 Juvenile *Pimephales promelas*	48	0.71	[40]
	青鳉仔鱼 *Oryzias latipes* larva	72	0.84	[41]
	青鳉仔鱼 *Oryzias latipes* larva	96	5.5 (pH=7) 1.3 (pH=8) 0.2 (pH=9)	[34]
舍曲林 Sertraline	青鳉仔鱼 *Oryzias latipes* larva	72	0.84	[41]
	虹鳟幼鱼 Juvenile *Oncorhynchus mykiss*	96	0.38	[42]
	黑头软口鲦幼鱼 *Pimephales promelas* larva	48	0.65 (pH=6.5) 0.21 (pH=7.5) 0.07 (pH=8.5)	[35]
西酞普兰 Citalopram	青鳉仔鱼 *Oryzias latipes* larva	72	9.14	[41]

注:LC_{50} 表示半数致死浓度;pH 表示氢离子浓度指数。

Note: LC_{50} stands for median lethal concentration; pH represents hydrogen ion concentration.

量多聚核苷酸链式反应(real-time quantitative polymerase chain reaction, qPCR)技术对其心脏发育相关基因(*nkx2.5*)、眼睛和脑发育相关基因(*otx2* 和 *pax6*)、骨发育相关基因(*bmp4*)的 mRNA 水平进行测定,结果显示,*otx2* 在 0.1 μg·L^{-1}舍曲林暴露后显著上调,*pax6* 和 *bmp4* 在 0.1 μg·L^{-1}舍曲林暴露后显著下调,而所有基因在 10 μg·L^{-1}舍曲林暴露后均显著下调。Wu 等[49]将斑马鱼胚胎暴露在 0.1 ~ 10 μg·L^{-1}氟西汀中 120 h 后,利用 qPCR 技术分析了斑马鱼胚胎的基因表达水平,发现氟西汀暴露能够显著下调调节细胞生长和分化的早期生长反应因子基因(*egr1* 和 *egr4*),其中 *egr1* 在 0.1 μg·L^{-1}和 10 μg·L^{-1}的氟西汀暴露组中显著下调,而 *egr4* 在所有暴露组中显著下调。Park 等[50]将斑马鱼仔鱼分别暴露于 25 μg·L^{-1}和 250 μg·L^{-1}的氟西汀和舍曲林中 96 h 后,利用转录组学技术进行斑马鱼的全基因表达分析,结果显示,调控细胞生长相关基因(insulin-like growth factor binding protein 1b)和肌肉发育的相关基因(myogenin)在 25 μg·L^{-1}和 250 μg·L^{-1}的氟西汀暴露后显著上调,调控视网膜发育的相关基因(MCM2 minichromosome maintenance deficient 2, mitotin (*S. cerevisiae*))和眼睛感光细胞发育的相关基因(ornithine decarboxylase 1)在 25 μg·L^{-1}和 250 μg·L^{-1}的氟西汀暴露后显著下调,同时,在 25 μg·L^{-1}和 250 μg·L^{-1}舍曲林暴露后,myogenin 基因显著上调。可以看出,环境浓度下的 SSRIs 即可引起鱼类的生长发育异常。一方面,5-HT 能系统在脊椎动物的胚胎发育中发挥着重要的作用[51-52]。另一方面,鱼类和哺乳动物的 5-HT 能系统具有很大的相似性[14,53],而药物对鱼类的毒性效应可能与其作为人类药物的作用模式有关。因此,SSRIs 可能通过作用于鱼类的 5-HT 能系统影响鱼类的生长发育。此外,除 5-HT 能系统外,SSRIs 也能通过干扰其他的调控系统[36,54-55],如多巴胺能系统、胆碱能系统等,影响鱼类的发育,因此,关于 SSRIs 影响鱼类发育的相关机制仍需进一步的探索。

2.3 SSRIs 对鱼类的生殖毒性

神经内分泌系统通过下丘脑-垂体-性腺轴(hypothalamic-pituitary-gonadal axis, HPG 轴)调节脊椎动物的生殖,同时 HPG 轴受多种因素的调节,如性腺类固醇、神经递质等[15]。下丘脑分泌的 GnRH 在控制脊椎动物的生殖和性功能方面发挥着重要作用[56-57]。多数硬骨鱼至少有 2 ~ 3 种类型的 GnRH (GnRH1、GnRH2 和 GnRH3)[58-59]。GnRH 与位于垂体的受体结合,调节促黄体生成素(luteinizing hormone, LH)和促卵泡激素(follicle-stimulating hormone, FSH)2 种促性腺激素(gonadotropin, GTH)的合成和释放[57,60]。GTH 能够控制性腺的发育和成熟,刺激雄性睾丸的类固醇生成和精子生成,以及雌性卵巢的卵泡生成和卵子生成[57,61-62]。一方面,5-HT 能够通过影响 HPG 轴调节硬骨鱼的多种生殖功能,如性腺成熟和生殖行为(图 3)[15,63]。另一方面,硬骨鱼的 5-HT 能系统也受性腺类固醇的调节[15,63]。因此,硬骨鱼的 5-HT 能系统与生殖内分泌的信号通路密切相关。

SSRIs 已被发现能够对鱼类的生殖产生影响,如改变性腺形态,干扰雌激素的内分泌和生殖相关基因的表达等。其中,环境浓度的氟西汀暴露能够增加雄性黑头软口鰕虎[64]的睾丸间质细胞突起(28 ng·L^{-1},21 d),诱导雄性黑头软口鰕虎[64](28 ng·L^{-1},21 d)和雄性金鱼[65](*Carassius auratus*) (0.54 μg·L^{-1},14 d)血浆卵黄蛋白原的生成,增加雌性青鳉[66](0.1 μg·L^{-1},4 周)血浆和雄性金鱼[67](0.54 μg·L^{-1},14 d)血清中的雌二醇的含量,改变雄性孔雀鱼[68](350 ng·L^{-1},28 d)的交配策略,增加雄性东部食蚊鱼(*Gambusia holbrooki*)的交配行为(479 ng·L^{-1},30 d)和精子数量(30 μg·L^{-1}和 380 ng·L^{-1},30 d)[69]。另外,高于环境浓度的氟西汀暴露还能够改变黑头软口鰕虎的交配行为(1 μg·L^{-1}和 100 μg·L^{-1},4 周)[70],降低斑马鱼卵巢内芳香酶基因(*Arom-A*) (3.2 μg·L^{-1}和 32 μg·L^{-1},7 d)、LH 受体基因(*LHr*) (32 μg·L^{-1},7 d)和 FSH 受体基因(*FSHr*) (32 μg·L^{-1},7 d)的 mRNA 水平以及卵巢内雌二醇的水平(32 μg·L^{-1},7 d)[71]。环境浓度的舍曲林暴露(1.6 ng·L^{-1},21 d)能够显著减少雄性黑头软口鰕虎的睾丸间质细胞突起[64]。此外,雄性斑马鱼在 4、40 和 100 μg·L^{-1}西酞普兰中暴露 2 周或 1 个月,其脑中 GnRH 基因(*gnrh2* 和 *gnrh3*)和垂体中 GTH 基因(*lhβ* 和 *fshβ*)的 mRNA 水平显著改变,其中,*gnrh3*、*lhβ* 和 *fshβ* 在 4 μg·L^{-1}和 40 μg·L^{-1}西酞普兰中暴露 2 周和在 40 μg·L^{-1}和 100 μg·L^{-1}西酞普兰中暴露 1 个月后均显著下调,而在 100 μg·L^{-1}西酞普兰中暴露 2 周后,*gnrh2*、*gnrh3* 和 *lhβ* 均显著上调,*fshβ* 显著下调,同时,雄鱼睾丸内的精原细胞、次级精母细胞和精子的细胞密度在 40 μg·L^{-1}和 100 μg·L^{-1}西酞普兰中暴露 1 个月后均显著减少[57]。综上所述,环境浓度的 SSRIs 即可对鱼类产

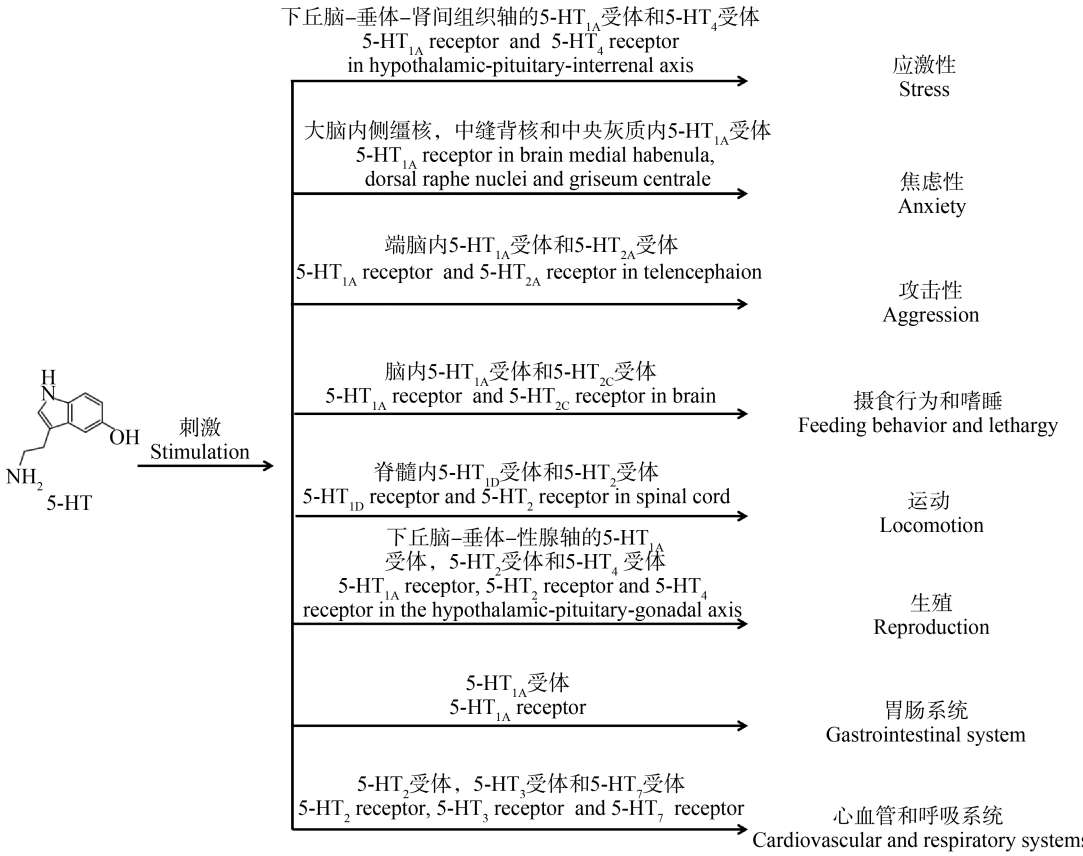

图 3　5-HT 对硬骨鱼的功能示意图(参考文献[15]和[63])

Fig. 3　Schematic diagram of 5-HT function on teleost (reference from literature [15] and [63])

生生殖毒性。由于 5-HT 能系统在鱼类的生殖调控中发挥着重要作用,SSRIs 可能通过影响鱼类的 5-HT 能系统,干扰鱼类的生殖功能。然而目前关于 SSRIs 对鱼类生殖毒性相关机制的研究较为缺乏,今后的研究应加强这方面的工作,以进一步阐明该类化合物对鱼类生殖系统和生殖行为的影响及其作用规律。

2.4　SSRIs 对鱼类的神经行为毒性

在生态系统中,动物行为对其个体生存和种族繁衍具有重要作用[72]。SSRIs 作为一类精神类药物,旨在改变人类的行为,即使在低浓度下也能显示出生物活性。SSRIs 的分子靶标存在于鱼类,且 5-HT 对于调控鱼类运动、攻击和焦虑在内的行为至关重要[14]。因此,神经行为毒性被认为是 SSRIs 对鱼类产生的主要毒性作用[73−74]。近年来,有不少研究报道了 SSRIs 对鱼类行为的影响。例如,SSRIs 能够影响鱼类的运动、攻击行为、焦虑行为和社交行为等。环境浓度的氟西汀暴露能够抑制斑马鱼仔鱼[36](0.88 μg·L^{-1},120 h)和孔雀鱼[75](16 ng·L^{-1},28 d)的活动,降低斗鱼[76](*Betta splendens*)(0.54 μg·L^{-1},6 d)的攻击性和雌性食蚊鱼[77]的焦虑性(61 ng·L^{-1},28 d),增加雄性食蚊鱼[77]的焦虑性(352 ng·L^{-1},28 d)。另外,高于环境浓度的氟西汀暴露不仅能够引起青鳉社交焦虑的降低和社交互动的减少(100 μg·L^{-1},10 d)[78],还能够导致黑头软口鲦的摄食速率的降低(10 μg·L^{-1},4 周)和躲避捕食者行为的减少(1 μg·L^{-1},4 周)[70]。舍曲林的暴露能够抑制青鳉仔鱼[41]的活动(10 μg·L^{-1},72 h),降低黑头软口鲦[79]的焦虑性(3 ~ 30 μg·L^{-1},28 d)。不仅如此,舍曲林的暴露(4.36 ~ 116 μg·L^{-1},7 d)还能够导致鲫的活动增加,集群倾向和摄食速率降低,摄食量减少[28]。艾司西酞普兰的暴露不但能够抑制雄性斑马鱼的摄食行为(0.1 μg·L^{-1},3 周)[80],还能够增加雌性斑马鱼的勇敢性(1.5 μg·L^{-1},3 周)[81]。可见,环境浓度的 SSRIs 即可显著改变鱼类的行为,产生神经行为毒性。然而,尽管 SSRIs 的作用通路存在于鱼类,但是 SSRIs 是否能够通过类似通路对鱼类造成神经行为毒性尚不明确,今后的研究有必要针对鱼类的神经行为毒

性效应和作用机制进行深入研究。

3 总结与展望(Summary and prospect)

近些年,随着地表水中 SSRIs 的不断被检出,SSRIs 对水生生物尤其是鱼类的影响引起了国内外学者的广泛关注。已有不少学者开展了 SSRIs 对鱼类的毒性研究,笔者对上述报道中 SSRIs 对鱼类的生态毒性效应研究进展做了简单的归纳,主要分为以下 4 点:(1) SSRIs 在鱼类和哺乳动物体内的代谢酶、代谢产物和代谢速率存在差异,且其在鱼类和哺乳动物体内的代谢途径可能存在差异;(2) SSRIs 能够在不同种类的鱼体内积累,且肝脏、肾脏和脑是 SSRIs 积累的主要靶器官;(3) SSRIs 对鱼类的急性毒性在 $\mu g \cdot L^{-1} \sim mg \cdot L^{-1}$ 水平,而水环境中的 SSRIs 一般不会对鱼类造成急性致死效应;(4) SSRIs 不仅能够引起鱼类生长发育异常,还能够干扰鱼类的生殖系统,改变鱼类的行为。然而,目前 SSRIs 对鱼类的毒性效应与作用机制的研究仍不系统,大多数的研究局限于表型研究,且关于其毒性作用机制及其生态风险仍不明确。因此,针对目前的研究现状不足,提出以下几点展望和建议。

(1)近些年,SSRIs 持久痕量地存在于水环境中,具有“伪持久性”现象,而环境浓度下 SSRIs 长期暴露对鱼类的毒性效应在很大程度上是未知的,有待继续深入研究。

(2) 目前,关于 SSRIs 在鱼类体内的降解转化过程仍不清晰,未来的研究应加强探明鱼类对 SSRIs 的代谢机制,以进一步阐明 SSRIs 对鱼类的毒性效应及其作用机制。

(3)建立 SSRIs 对鱼类神经系统的作用靶及其行为间的调控关系,明确该类物质对鱼类的神经毒性机制,以进一步阐明 SSRIs 对水生态系统的影响。

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