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水体中氟西汀的赋存、累积和生物效应研究进展

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摘要:介绍了水体中氟西汀的来源及归趋,阐述了该物质在不同水环境介质中的赋存状态,以及其在水生生物体内的累积规律和不同的生态毒理效应。最后,基于目前的研究现状提出了未来氟西汀研究中亟待解决的关键问题。

关键词:氟西汀;水生态环境安全;赋存;累积;生物效应

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Advances in studies on occurrence, accumulation and biological effects of Fluoxetine in water

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Abstract: In this study, the sources and fates of Fluoxetine in the aquatic environment were firstly introduced. And then, the occurrence state of this substance in different water environment medium was elaborated. Besides, its accumulation law in aquatic organisms and different ecotoxicological effects were studied as well. Finally, based on the current research status, the key problems to be solved in the future Fluoxetine research were put forward.

Key words: Fluoxetine; water ecological environment security; occurrence; accumulation; biological effect

近年来,随着现代社会生活节奏的加快和竞争的白热化,患有精神抑郁的人群明显增多,目前我国的抑郁症患者预估高达 9 000 万人,导致抗抑郁类药物的使用大量增加[1]。在这些抗抑郁药物中,氟西汀(Fluoxetine,FLX)作为一种选择性 5 -羟色胺再摄取抑制剂,可以通过选择性抑制神经突触细胞对神经系统突触前释放的血清素再吸收,而增加细胞外可以和突触后受体结合的血清素水平来实现抗抑郁效果[2]。FLX 作为目前临床上治疗抑郁症的首选药物之一,已在许多国家和地区得以广泛应用。随着使用量的不断增加,FLX 也不可避免地在其制造和使用过程中通过各种途径进入水体,进而赋存于水体、沉积物以及水生生物体等不同介质中[3-4]。同时,由于 FLX 的特殊生物活性,能够通过作用于水生生物体的中枢神经系统,干扰神经内分泌信号,从而威胁生物体个体的生长和种群的繁衍,给水生态环境安全甚至人类健康带来潜在风险,并因此逐步成为水体最需关注的药物污染物之一[5-6]。

1 来源和归趋

水环境中 FLX 的来源相对广泛,主要为市政污水处理厂尾水。FLX 经患者口服摄入后,有 20% ~30%

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未经人体代谢直接随着尿液或粪便排出体外,进入市政管网,并经污水处理厂处理后随尾水排入天然水体[7]。但是,现有的污水处理工艺很难将 FLX 完全去除,甚至一部分工艺对 FLX 几乎没有处理效果,从而使 FLX 直接进入天然水体[8-10]。例如,MacLeod 等[10]发现采用活性污泥法的污水处理厂对 FLX 的去除率不足 8%,污水处理厂成为受纳水体中 FLX 污染的最主要来源。此外,污水处理厂甚至可以将 FLX 的代谢产物诺氟西汀(Norfluoxetine,NFLX)再次转化为母体 FLX,从而再次增加水体中 FLX 的浓度[11]。医院或医药企业的污水排放也是水体中 FLX 的一大来源,但相较于污水处理厂尾水排放,医药废水对水体中 FLX 的贡献率不足 1%[12-13]。此外,过期或未经使用的 FLX 作为生活垃圾随意丢弃也是其进入水体的可能途径之一[4]。

水环境中的 FLX 一部分在光照、微生物等作用下得以降解,另一部分则能够通过水-沉积物间的迁移转化进入沉积物中,甚至通过沉积物的解吸附过程重新进入水体[4]。此外,FLX 也会累积于水生生物,尤其是高营养级的水生动物体内,如鱼类、无脊椎动物等,通过食物链进行传递,并产生生物放大效应[14-15]。

2 水环境介质中的赋存

自 Weston 等[17]首次报道了污水厂尾水存在 FLX 污染后,世界范围内的研究人员开始高度关注这一精神类药物在水体中的残留。伴随着化学检测技术的不断提高,美国、加拿大、西班牙以及亚洲一些国家和地区的水体环境中相继检测到了 FLX 的存在,其质量浓度水平一般在 ng/L 至 μg/L 级别,见表 1。检出的水体也从污水厂的进、出水发展到地表水和地下水,甚至饮用水。和水体常见的其他药物污染物相比,FLX 的检出率变化较大。美国地质调查局对全美 139 条河流的检测结果显示,FLX 的检出率仅有 1.2%,且大多集中于污水厂受纳水体中[18]。但是,Ferrer 等[19]对美国不同水体的污染物检测显示,有 25% 的水样中检测出 FLX 的存在。我国洞庭湖水域的 FLX 检出率更是高达 55%,尤其是东洞庭湖水域更是 100% 检出[20]。相较于淡水环境,关于 FLX 在海洋水体中赋存的报道较为罕见,仅有 Pait 等[21]在美国切萨皮克海湾的南部检测出 FLX 的存在,质量浓度为 3 ng/L。

除水体环境外,FLX 也能够通过水-沉积物界面迁移到沉积物中,然而,目前关于 FLX 在沉积物中赋存的报道相对较少。Schultz 等[7]在美国科罗拉多博尔德河底泥中检测出 FLX 的质量浓度范围为 0.39 ~ 19.37 ng/g。Bringolf 等[37]检测了美国纽斯河支流某污水处理厂出水口、出水口下游 50 m、100 m 处河流底泥中 FLX 的浓度,结果显示 3 个采样点采集的底泥中的检出浓度分别为 17.4 ng/g、5.3 ng/g、1.3 ng/g,表现为 FLX 沿河流流向不断衰减。这表明河流底泥中的 FLX 主要来源于污水处理厂的尾水排放,且其浓度与距污水处理厂排污口的河流长度存在负相关性。但相较于河流底泥,污水处理厂污泥中 FLX 的检出浓度更高,最高达到了 μg/g 级别,这主要归因于 FLX 在污水中的浓度远大于天然水体,沉积物中的 FLX 主要来源于水体污染物的迁移和蓄积。如

表 1 不同地区水体中 FLX 的检出浓度

水体类型	水体来源	质量浓度/(ng·L^{-1})
地表水	加拿大汉密尔顿港小河流	13 ~ 46[22]
	加拿大圣劳伦斯河	0.422 ~ 1.300[23]
	加拿大格兰德河	4 ~ 141[24]
	西班牙埃布罗河	0.2 ~ 3.0[9]
	西班牙埃布罗河流域	106[25]
	西班牙马德里市区 5 条河流	8 ~ 44[26]
	韩国汉江及支流	0.5 ~ 6.5[27]
	中国上海黄浦江	0.1 ~ 1.3[28]
	中国洞庭湖	0 ~ 40.2[20]
地下水	美国某地区地下水	56[29]
	葡萄牙 5 座墓地周边地下水	0 ~ 1.97[30]
污水处理厂进水	葡萄牙塞沙尔污水处理厂	17 ~ 3 645[31]
	加拿大埃德蒙顿污水处理厂	18[10]
	加拿大蒙特利尔污水处理厂	3.1 ~ 3.5[23]
	加拿大安大略省南部污水处理厂	20 ~ 91[24]
	加拿大某 5 家污水处理厂	9 ~ 26[32]
	美国纽约牙买加湾污水处理厂	600[8]
	挪威朗格内斯等 3 家污水处理厂	0.4 ~ 2.4[33]
	挪威朗伊尔城多家污水处理厂	1.1 ~ 18.7[34]
	西班牙埃布罗河沿岸污水处理厂	2 ~ 26[9]
	上海黄浦江沿岸污水处理厂	0.7 ~ 4.7[28]
污水处理厂出水	西班牙某 5 家污水处理厂	19 ~ 929[35]
	西班牙埃布罗河沿岸污水处理厂	1 ~ 16[9]
	美国某 7 家污水处理厂	40 ~ 73[36]
	美国纽斯河支流某污水处理厂	104 ~ 119[37]
	美国纽约牙买加湾污水处理厂	560[8]
	韩国胶州岛和南三省某污水处理厂	1.7[38]
	瑞典克里斯蒂安斯塔德污水处理厂	225[16]
	挪威朗格内斯等 3 家污水处理厂	0.12 ~ 1.3[33]
	挪威朗伊尔城多家污水处理厂	0.6 ~ 8.4[34]
	加拿大卡尔加里污水处理厂	509[39]
	加拿大汉密尔顿港和温莎污水厂	50 ~ 99[22]
	加拿大埃德蒙顿污水处理厂	14[10]
	加拿大蒙特利尔污水处理厂	2.0 ~ 3.7[23]
	加拿大某 5 家污水处理厂	6.6 ~ 20.0[32]
	上海黄浦江沿岸污水处理厂	0.8 ~ 2.2[28]
医疗卫生废水	西班牙某医院废水出口	4 ~ 100[40]
	美国医院、护理等方面医疗设备	42 ~ 180[12]
	北京某医院废水	10 ~ 17[41]
饮用水	美国某地区成品水	0.5[42]
	美国某地区水源水、自来水、成品水	0.64 ~ 0.80[43]

Vasskog 等[44]报道了挪威两家污水处理厂污泥中 FLX 的赋存状况,检出其浓度在 30 ~ 40 ng/g;Radjenovic 等[45]在某污水处理厂的处理污泥中检出的 FLX 浓度为 174.1 ng/g;而 Lajeunesse 等[32]报道了加拿大某 5 家污水处理厂处理污泥中不同抗抑郁药的含量,其中 FLX 的最高检出浓度甚至达到了 1 033 ng/g。

3 代谢转化和生物累积

FLX 被人体摄入后,其代谢路径为肝脏代谢,并以 N -去甲基和葡萄酸盐的形式排出体外,但代谢程度存在个体差异性[46]。与之相类似,FLX 被水生生物体摄入后,主要的代谢产物为 NFLX,其生物活性甚至比母体化合物 FLX 更强效[47]。由于 FLX 和 NFLX 都具有较高的辛醇水分配系数,两者在被水生生物体摄取后都极易蓄积于体内,尤其是在高营养级的硬骨鱼类体内。Brooks 等[14]首先报道了美国野生鱼类组织中 FLX 和 NFLX 的赋存和累积,并发现两者在肝脏和脑组织中的水平最高,肌肉最低。这一发现和 Ramirez 等[48]的研究结果相类似,这可能和肝脏是 FLX 在鱼体内的主要代谢器官,而脑组织则是 FLX 的主要靶标器官有关。其后,大量关于野生鱼类组织内 FLX 和 NFLX 的累积也相继被报道出来,具体情况见表 2。

相较于野外检测,实验室内关于 FLX 的生物累积和代谢研究开展相对较晚,但内容更为系统和具体。Paterson 等[49]发现日本青鳉在暴露于 0.64 μg/L 的 FLX 溶液 7 d 后就累积了大量的 FLX 及其代谢产物 NFLX,质量比分别为 40.8 μg/kg 和 64.3 μg/kg,这表明 FLX 在 7 d 内就可以大量代谢为 NFLX,且 NFLX 呈现出更高的累积潜能。这一结果也得到 Gelsleichter 等[50]的证实,他们认为与 FLX 相比,NFLX 具有更小的极性,因此更易于富集在鱼体组织内,进而造成相同甚至更坏的生态影响。Chu 等[51]同样发现,随着暴露时间的增加,代谢物 NFLX 在鱼体组织的累积水平会逐步和 FLX 相持平甚至更高。但需要特别关注的是,FLX 作为一种弱碱性药物化合物,其在较高 pH 值环境下主要以中性分子形态存在,在低 pH 环境下则以离子形态为主要存在形式,而化合物的离子化会显著影响其在生物膜上的转运过程,并最终影响其在水生生物的累积水平[52]。可见,水体不同 pH 值环境可能会显著影响 FLX 在生物体内的累积。基于此,Nakamura 等[52]研究了不同的 pH 暴露条件下 FLX 在日本青鳉体内的富集情况,结果显示在 pH 值为 7、8 和 9 的条件下,FLX 及其代谢产物 NFLX 的生物累积系数(bioconcentration factor,BCF)分别为 13、37 和 330 以及 100、170 和 720,水体 pH 值越靠近 FLX 的离子平衡常数,其越容易富集于生物体中。因此,水体的 pH 值会影响 FLX 在鱼体内的累积水平,进而改变其组织分布和毒性大小,所以仅仅从辛醇水分配系数来评估药物等活性化合物在生物体的累积还存在一定的不足,需要更多的研究加以论证。

除鱼类外,FLX 在其他水生生物体内的累积也时有报道。Bringolf 等[37]发现美国纽斯河支流中的贻贝(*Elliptiocomplanata*)体内即有 FLX 的累积,生物累积因子(bioaccumulation factor, BAF)达到 125 ~ 1 347。在实验室研究中,Farrzellitti 等[15]将紫贻贝(*Mytilusgalloprovincialis*)暴露于 FLX 溶液 7 d 后发现,FLX 在紫贻贝的 BCF 介于 200 ~ 800;Silva 等[47]则发现紫贻贝暴露于 75 ng/L 的 FLX 溶液 3 d 后,70% 的样品中都检测出了 FLX 的存在,10% 的样品中检测出 NFLX,当暴露达到 15 d 后,FLX 和 NFLX

表 2 FLX 和 NFLX 在野生鱼类体内的富集浓度

鱼类名称	样品来源	组织	FLX 质量比/(ng·g^{-1})	NFLX 质量比/(ng·g^{-1})
蓝鳃太阳鱼(*Lepomismacrochirus*)、斑点叉尾鮰(*Ictaluruspunctatus*)、鲤鱼(*Cyprinuscarpio*)、黑莓鲈(*Pomoxisnigromaculatus*)	美国德克萨斯州核桃溪市[14]	脑	1.58	8.86
		肝	1.34	10.27
		肌肉	0.11	1.07
云斑鮰(*Ameiurusnebulosus*)、美洲真鳐(*Dorosomacepedianum*)、美洲狼鲈(*Moroneamericana*)	加拿大安大略省汉密尔顿港口[51]	组织匀浆	0.37	0.27
鱼(未标明种类)	美国德克萨斯州核桃溪市[54]	肌肉	—	4.37
大嘴鲈鱼(*Micropterussalmoides*)、鲤鱼(Cyprinuscarpio)、弓鳍鱼(*Amiacalva*)、白亚口鱼(*Catostomuscommerson*)、小口胭脂鱼(*Ictiobusbubalus*)	美国芝加哥、达拉斯、奥兰多、菲尼克斯、西赤斯特等地[48]	肝	19 ~ 70	37 ~ 73
		肌肉	—	3.2 ~ 4.0
白亚口鱼(*Catostomuscommerson*)	美国科罗拉多州博尔德溪[7]	脑	0.02 ~ 0.6	0.07 ~ 0.9
黑头呆鱼(*Pimephalespromelas*)	加拿大安大略省某大河[24]	全鱼匀浆	小于最低定量限	1.22
公牛鲨(*Carcharhinusleucas*)	美国佛罗里达克卢萨哈奇河[50]	血浆	小于最低定量限	4.08

的检出率全部达到100%，平均累积质量比也分别达到9.31 ng/g和11.65 ng/g，这表明随着暴露时间的增加，生物体内富集的FLX可能逐渐代谢为NFLX。Gust等[53]也发现FLX可以在田螺(*Potamopyrgusantipodarum*)和盘螺(*Valvatapiscinalis*)体内产生累积并逐渐代谢为NFLX，但NFLX的BCF远小于FLX。

4 生态毒理效应

随着FLX使用量的不断增加，其对人体的副作用也不断被披露，包括胃肠道功能紊乱、厌食、精神异常、性功能障碍、精子活性降低等。当这类物质进入水体和生物体后，其也可能通过调控和模仿神经递质5-羟色胺的作用，激活暴露生物体内转运蛋白和受体的调节机制，最终对各类水生非靶标生物产生较为严重的负面效应[55-56]。自Brooks等[57]首先报道了赋存于水体和沉积物中的FLX可能会对鱼类产生多种不良影响以后，大量研究人员开始关注水体中FLX的生态毒理效应。其后《Science》发表了《Fish on Prozac》的报道，环境中残留的FLX对生物体的潜在危害性开始进入公众视野。作为一种精神类药物，FLX对水生生物的影响主要体现在神经功能和行为学损伤。已有研究发现，水体FLX污染明显阻碍了鱼类的游动，表现出行动障碍，觅食和逃避天敌行为迟缓，求偶和交配行为受抑制等[58-62]。Abreu等[63]发现环境相关浓度的FLX可以直接抑制斑马鱼体内皮质醇激素的合成，从而引起鱼体应急响应行为迟缓。同时，FLX还可以通过下调斑马鱼脑内神经叶激素、尿皮素和泌乳素等相关神经肽的表达而减缓鱼体的焦虑行为[64]。Dzieweczynski等[65]进一步研究发现FLX还可以显著降低雄性暹罗斗鱼(*Bettasplendens*)的冒险行为，呈现浓度相关性且极有可能影响个体的生存。除了抑制逃避捕食行为外，Pelli等[66]还证实环境相当浓度的FLX可能会干扰生物体能量代谢过程而抑制古比鱼(*Poeciliareticulata*)的生长发育。已有研究证实，FLX的存在可以引起鱼体厌食等症状，并通过磷酸腺苷活化的蛋白激酶路径促进生物体内葡萄糖、脂肪和氨基酸的代谢，进而减缓鱼体内的能量存储，干扰其正常的生长发育[67-69]。除鱼体外，水体FLX暴露也会显著降低小龙虾(*Orconectesrusticus*)[70]和蝌蚪(*Anax imperator*)[71]的移动能力和逃避天敌能力，从而削弱它们的生存能力。

考虑到水生生物，特别是鱼类的生殖行为(性腺成熟、求偶等)受到其体内血清素的调节，水体中FLX这一血清素抑制剂的存在很可能会影响到水生生物的繁殖过程[72-73]。Mennigen等[74]发现FLX可以通过减缓雄鱼精子释放、降低睾丸素水平以及抑制性信息素合成等多个路径干扰雄性金鱼的生殖轴线，进而降低其生殖能力。Bringolf等[37]也认为FLX会促使雌性贻贝分娩出无法生存的幼虫并诱导雄性贻贝释放精子，从而对淡水贻贝的种群繁殖产生消极影响。即使痕量水平的FLX在长时间暴露后同样会导致贻贝出现个体生长受阻和性腺指数降低等情况，从而影响到种群的繁衍[75]。与之相反，Campos等[76]证实FLX的加入可以激活大型蚤脑内血清素的免疫活性，从而改变实际环境中低食物量导致的大型蚤繁殖效率低下等状况，明显增加了子代的数量，但其个体相对较小。这表明FLX对生物体繁殖的影响并不是一成不变的，生物种类和环境条件都可能会改变这些影响。

此外，水生生物体的代谢功能、抗氧化体系和内分泌系统等方面也受FLX的影响。相关体外实验表明，FLX能够明显抑制鱼类肝脏内I相代谢酶系细胞色素P450的活性(如CYP1s、CYP2K和CYP3A等)[77-80]，表现为广谱CYP系列酶系抑制剂，从而影响鱼体对外源性污染物的清除效率。而这一代谢抑制效应可能会促进共存污染物罗红霉素、普罗奈尔、炔雌醇等在生物体内的蓄积，并导致了更为明显的生物损伤[81-83]。此外，Zhang等[84]认为FLX还可以通过抑制P糖蛋白(P-glycoprotein，Pgp，0相代谢)和谷胱甘肽转化酶(Glutathione S-Transferase，GST，II相代谢)等路径削弱生物体的代谢功能，进而增加共存污染物对生物体内的危害。除了代谢功能外，FLX也会显著破坏水生生物的抗氧化酶体系，引发氧化应激反应，增加生物体氧化损伤的风险[85-86]。例如，Ding等[81]研究发现FLX暴露会显著抑制鲫鱼(*Carassiusaurassius*)肝脏内超氧化物歧化酶(superoxide dismutase，SOD)活性以及增加鲫鱼肝脏丙二醛(malonaldehyde，MDA)浓度，且呈现明显的浓度效应关系。Cunha等[87]也证实FLX可以明显降低斑马鱼幼鱼体内的SOD活性，进而减弱体内氧化自由基(如过氧化氢)的代谢和清除，干扰其正常的发育过程。Abreu等[2]甚至发现这一增加的氧化损伤可能会导致斑马鱼体内渗透压调节功能的失调。与氧化代谢功能相比较，FLX对生物体内分泌功能干扰的报道更为少见，主要集中在对内循环物质的影响上。例如，Hazelton等[88]发现200 ng/L的FLX明显诱导了斑马贝(*Dreissenapolymorpha*)内循环雌二醇的水平，而Schultz等[89]甚至发现了FLX可以诱导雄性黑头呆鱼体内合成卵黄蛋白原，表现出强烈的雌激素效应。总之，水体FLX污染可能会

对水生生物产生神经毒性并干扰其氧化代谢和内分泌功能,从而对其应激性、觅食和行为产生影响,最终威胁到个体的生长繁殖和种群的延续。

5 展 望

a. 需要考察 FLX 在不同水环境介质中的迁移转化规律,知晓 FLX 在水-沉积物-生物体之间的分配行为以及在不同介质中的降解过程。

b. 加强 FLX 代谢产物理化性质和生态毒性的研究,并考察水质因素(pH、溶解性有机质、离子强度、温度等)及水动力变化对 FLX 及代谢产物生物累积和生物效应的影响,从而建立水质和水动力学模型综合分析不同水环境 FLX 污染的生态风险。

c. 结合水生态系统的食物链结构,研究水环境中 FLX 在食物链不同营养级生物间的传递和代谢转化过程。建立从种群、个体、器官组织、细胞到基因的不同水平的毒理学指标体系,全面掌握 FLX 对生态系统及人体健康的潜在危害,最终建立起 FLX 污染的生态风险评价体系。

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