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农药类化合物对鱼类脂质代谢的影响及机制研究进展

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摘要: 由于农药的广泛使用,目前许多农药类化学物质在水生生态系统中被检出,造成水环境污染,影响水生非靶生物的健康。脂质在鱼类生长发育中发挥着重要作用,近年来大量研究表明农药暴露能够干扰鱼类脂质代谢,导致脂质水平紊乱。本文在介绍农药污染现状基础上,从干扰脂质消化吸收、合成、分解和转运等过程综述了农药类化合物对鱼类脂质代谢的干扰效应及机制。以期为今后进一步探究农药的脂代谢毒性作用及其安全性评价提供更多的理论参考。

关键词: 农药;鱼类;脂质代谢;作用机制
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Advance on Effect and Mechanism of Pesticide Chemicals on Lipid Metabolism in Fish

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Abstract: Due to the widespread use, residues of many chemical pesticides have been detected in the aquatic ecosystem. Pesticides pollution not only causes great damage to the water environment, but also adversely affects aquatic non-target organisms. In this paper, current pollution status of pesticides was reviewed, and then the adverse effect and its underlying mechanisms of pesticide compounds on lipid metabolism in fish were summarized, especially focusing on the disruption of lipid digestion, absorption, synthesis, decomposition, and transport. It will provide more theoretical references for further exploring the lipid metabolism-disrupting effect of pesticides and also for safety evaluation of emerging pesticide chemicals in the future.

Keywords: pesticides; fish; lipid metabolism; mechanism of action

自 20 世纪 50 年代以来,化学合成农药在全世界农业生产中广泛使用,全球农药产量以每年约 11% 的速度增长[1],目前在土壤、沉积物、地表水、地下水和海水等环境介质和生物体内均有检出农药残留。越来越多的研究表明环境中的农药污染与生物脂代谢紊乱密切相关[2],脂质在鱼类生长发育中发挥着重要作用,涉及机体的能量供应和储存、生物膜组成等重要的生命过程[3],因而农药类污染物对脂

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代谢稳态的干扰作用可能是其影响鱼类生存、生长和繁殖的重要原因。本文综述了近10年农药类化合物对鱼类脂代谢的干扰作用及机制,为揭示农药导致脂代谢紊乱的效应及机制提供依据。

1　农药类化合物污染现状(Pollution status of pesticide compounds)

农药按其防治目标生物不同,可以分为杀虫剂(如滴滴涕、六六六、敌百虫和久效磷等)、除草剂(如草甘膦、阿特拉津和扑草净等)、杀菌剂(如三氯生、苯醚甲环唑和溴代吡咯腈等)、杀螺剂(如螺螨酯、螺甲螨酯和螺虫乙酯等)、杀线虫剂(如霜霉威、毒死蜱等)、杀真菌剂(如多菌灵等)和植物生长调节剂等[4]。一般农药施用后直接作用于目标生物的有效利用率很低,约99%的农药会渗透进入环境中[5]。近年来农药类化合物在地表水、地下水、海水和沉积物等各种环境介质中频繁检出,例如,在中国洞庭湖区域的22个地表水样品中,检出滴滴涕的平均浓度为14.20 ng·L^{-1},六六六的平均浓度为26.70 ng·L^{-1}[6];Sumon等[7]对孟加拉国西北部水体的农药残留调查发现,地表水中毒死蜱的检出浓度高达9.10×10^3 ng·L^{-1}。在我国松嫩平原典型农业区的30个地下水样本中,呋喃丹的检出浓度约为1 972 ng·L^{-1}[8]。调查发现西班牙农村和城市地区地下水中的除草剂残留浓度较高,检出阿特拉津的平均浓度为3.45×10^3 ng·L^{-1},西马嗪的平均浓度为1.69×10^3 ng·L^{-1},扑草净的平均浓度高于0.5×10^3 ng·L^{-1}[9]。此外,通过土地开垦、土壤侵蚀、暴雨径流、河流输入和沉积,农药污染物最终会进入海洋,而沉积物则成为污染物的最终蓄库[10]。在中国北江水系沉积物中,三氯生的平均检出浓度为7.01 ng·g^{-1}[11];Li等[12]对中国珠江三角洲地区城市水道中沉积物的农药残留进行分析发现,珠江三角洲地区氯氰菊酯的检出浓度最高,为1.44~219 ng·g^{-1}。Yang等[13]对中国黄海和渤海的64个监测站采集的样本进行了除草剂浓度测定,其中阿特拉津、扑草净和特丁净,莠灭津是表层海水中含量最高的4种除草剂,其浓度分别高达720、748.88、296.64和132.48 ng·L^{-1}。表1中总结了下文所涉及的主要农药种类在不同环境介质中的检出浓度。

由于其化学稳定性和亲脂性,农药类化合物往往会在生物组织中积累,并在食物链中逐级放大。据报道,在埃塞俄比亚科卡湖的4种鱼类体内检出滴滴涕、硫丹和毒死蜱等农药,其中滴滴涕的检出浓度最高,为0.05~72.53 ng·g^{-1}[14]。我国学者在一些海洋动物中也检出了三嗪类除草剂,如青岛胶州湾海域无脊椎动物中阿特拉津的平均浓度为0.31 ng·g^{-1},鱼类中阿特拉津的平均浓度为0.3 ng·g^{-1}[15]。在印度托尔萨河流域的鱼类样本中检测到三氯生的残留,其检出范围为91.1~589 ng·g^{-1},其中厚唇新条鳅(*Neonemacheilus*)样本中的检出浓度最低,为91.1 ng·g^{-1},印度大帆鲫(*Oreichthys cosuatis*)的检出浓度最高,为589 ng·g^{-1}[16]。Riaz等[17]检测了巴基斯坦奇纳布河中美洲鳗鲡(*Anguilla rostrata*)体内拟除虫菊酯类杀虫剂的浓度,检出氯氰菊酯、溴氰菊酯、氯菊酯和联苯菊酯的平均浓度分别为472、459、278和251 ng·g^{-1}。

2　农药类化合物对鱼类的脂代谢影响及作用机制(Effects and mechanism of pesticide chemicals on lipid metabolism in fish)

脂质作为重要的营养、能源和结构物质,在生物体内的代谢具有重要意义。脂质是脂肪和类脂的总称,其中脂肪也称甘油三酯(triglyceride, TG),而类脂主要包括磷脂和胆固醇等多种脂质。鱼类的脂代谢稳态是一个复杂的调控过程,源自食物的脂质进入鱼体内,经消化后被肠吸收,在血液中以脂蛋白的形式运输,进而在肝脏等组织中进行代谢,而脂肪组织是脂质蓄积和储存的主要场所[46]。研究发现,很多农药类化合物能够通过干扰鱼体内脂质的消化吸收、合成、分解和转运等一个或多个脂代谢调控过程,进而导致鱼体内脂代谢紊乱、TG等脂质水平异常。表2中总结了下文所涉及的农药类污染物干扰鱼类脂质代谢的机制。

2.1　干扰鱼类脂质的消化吸收(Disruption of the lipid digestion and absorption in fish)

鱼类消化和吸收脂质的主要场所为肠道。首先,膳食脂质在肠腔内经胰脂肪酶等消化酶水解为游离脂肪酸、单酰甘油和二酰甘油等,然后被胆汁酸盐溶解、乳化形成微胶团(micelle),再被肠上皮细胞吸收。肠道摄取后,长链脂肪酸被重新酯化,然后在脂蛋白的作用下形成乳糜微粒(chylomicron, CM),经由淋巴进入血液循环系统并用于脂质的储存、β氧化或其他机体代谢过程。中短链脂肪酸直接通过门静脉进入血液并参与β氧化,或被转运至其他组织或细胞中发挥相应生理功能。

肠道消化与吸收脂质主要是依靠肠道内的各种分泌物、消化酶等,尤其是肠道消化酶的活性能够直

表1　不同环境介质中农药类化合物的残留水平

Table 1　Residual levels of pesticides in different environmental media

农药类别 Pesticide category	名称 Name	检出区域 Detection area	环境介质 Environmental media	检出浓度 Detection concentration	参考文献 References
杀虫剂 Insecticide	滴滴涕 Clofenotane	中国洞庭湖 Dongting Lake, China	地表水 Surface water	14.20 ng·L^{-1}	[6]
	六六六 Hexachlorocyclohexane	中国洞庭湖 Dongting Lake, China	地表水 Surface water	26.70 ng·L^{-1}	[6]
	六六六 Hexachlorocyclohexane	摩洛哥库洛伊尔-南里凡 Couloir Sud Rifain, Morocco	地下水 Groundwater	22.30 ng·L^{-1}	[18]
	敌百虫 Trichlorfon	中国东江 Dongjiang River, China	地表水 Surface water	44.33 ng·L^{-1}	[19]
	久效磷 Monocrotophos	印度工业区 Indian Industrial zone	地下水 Groundwater	8.30×10^{3} ng·L^{-1}	[20]
	呋喃丹 Carbofuran	中国松嫩平原 Songnen Plain, China	地下水 Groundwater	1 970.00 ng·L^{-1}	[8]
	呋喃丹 Carbofuran	印度河流域 Indus River	沉积物 Sediment	69.00 ~ 81.00 ng·g^{-1}	[21]
	氯氰菊酯 Cypermethrin	中国珠江三角洲城市水道 Water channel in the Pearl River Delta, China	沉积物 Sediment	1.44 ~ 219.00 ng·g^{-1}	[12]
	氯氰菊酯 Cypermethrin	西班牙埃布罗河 Ebro River in Spain	地表水 Surface water	5.00 ~ 58.00 ng·L^{-1}	[22]
	联苯菊酯 Bifenthrin	中国浙江省农田 Farmland in Zhejiang Province, China	地表水 Surface water	3 360.00 ng·L^{-1}	[23]
	溴氰菊酯 Deltamethrin	巴基斯坦奇纳布河 The River Chenab, Pakistan	地表水 Surface water	44.00 ~ 71.00 ng·L^{-1}	[24]
	敌敌畏 Dichlorvos	印度奇利卡湖 Chilika Lake, India	地表水 Surface water	0.65 μg·L^{-1}	[25]
	残杀威 Propoxur	乌拉圭河 Uruguay River	地表水 Surface water	40.00 ~ 2 910.00 ng·L^{-1}	[26]
	吡虫啉 Imidacloprid	五大湖 The Great Lakes	地表水 Surface water	1.33×10^{3} ng·L^{-1}	[27]
除草剂 Herbicide	草甘膦 Glyphosate	波罗的海(德国沿岸区域) Baltic Sea (German coastal area)	海水 Seawater	28.00 ~ 1 690.00 ng·L^{-1}	[28]
	草甘膦 Glyphosate	潘帕斯(阿根廷境内区域) Pampas (The part area in Argentina)	沉积物 Sediment	8.28 ~ 32.00 ng·g^{-1}	[29]
	阿特拉津 Atrazine	西班牙农村 Spanish countryside	地下水 Groundwater	3.45 ng·L^{-1}	[9]
	阿特拉津 Atrazine	中国黄渤海海域 Yellow Sea and Bohai Sea, China	海水 Seawater	7.20×10^{8} ng·L^{-1}	[13]
	扑草净 Prometryne	西班牙农村 Spanish countryside	地下水 Groundwater	0.50 ng·L^{-1}	[9]
	恶唑酰草胺 Metamifop	印度西孟加拉邦农田水 Farmland water in West Bengal, India	地表水 Surface water	20.00 ng·L^{-1}	[30]
	百草枯 Paraquat	泰国地下水 Groundwater in Thailand	地下水 Groundwater	$(1.50 \sim 18.90)\times10^{6}$ ng·L^{-1}	[31]

续表1

农药类别 Pesticide category	名称 Name	检出区域 Detection area	环境介质 Environmental media	检出浓度 Detection concentration	参考文献 References
除草剂 Herbicide	乙草胺 Acetochlor	中国广西甘蔗产区 Guangxi Sugarcane Production Area, China	地表水 Surface water	88.00 ng·L^{-1}	[32]
	敌草隆 Diuron	日本獭户内海 Seto Inland Sea, Japan	海水 Seawater	65.00 ng·L^{-1}	[33]
	西马津 Simazine	中国辽东半岛海域 Liaodong Peninsula Sea Area, China	海水 Seawater	1.40 ~ 5.30 ng·L^{-1}	[34]
杀菌剂 Bactericide	三氯生 Triclosan	中国北江 Beijiang River, China	沉积物 Sediment	7.01 ng·g^{-1}	[11]
	苯醚甲环唑 Difenoconazole	中国九龙河流域 Jiulong River, China	地表水 Surface water	3 904.00 ng·L^{-1}	[35]
	溴代吡咯腈 Tralopyril	葡萄牙阿维罗港 Porto Avero, Portugal	海水 Seawater	0.70 ng·L^{-1}	[36]
	丙环唑 Propiconazole	哥斯达黎加 Costa Rica	地表水 Surface water	125.00 ng·L^{-1}	[37]
	三环唑 Tricyclazole	中国武汉 Wuhan, China	地表水 Surface water	4.21 ~ 67.90 ng·L^{-1}	[38]
	腐霉利 Procymidone	中国九龙河流域 Jiulong River, China	地表水 Surface water	(0.15 ~ 13.00)×10^{3} ng·L^{-1}	[39]
	氟酰胺 Flutolanil	日本南部区域 Southern Japan	地表水 Surface water	30.00 ~ 1 640.00 ng·L^{-1}	[40]
	啶酰菌胺 Boscalid	美国加利福尼亚沿海河口 Estuaries off the coast of California, USA	沉积物 Sediment	0.70 ~ 88.80 ng·g^{-1}	[41]
	三唑醇 Triadimenol	中国辽东半岛海域 Liaodong Peninsula Sea Area, China	海水 Seawater	4.30 ~ 20.80 ng·g^{-1}	[34]
杀螺剂 Molluscide	螺螨酯 Spirodiclofen	萨瓦河沉积物 Sava River sediments	沉积物 Sediment	881.00 ng·g^{-1}	[42]
	螺甲螨酯 Spiromesifen	萨瓦河沉积物 Sava River sediments	沉积物 Sediment	1 750.00 ng·g^{-1}	[42]
	螺虫乙酯 Spirotetramat	萨瓦河沉积物 Sava River sediments	沉积物 Sediment	431.00 ng·g^{-1}	[42]
	氯柳硝胺 Chlorosalanide	中国鄱阳湖地区南鹿山岛 Nanjishan Island, Poyang Lake Region, China	地表水 Surface water	(1.00 ~ 38.00)×10^{3} ng·L^{-1}	[43]
杀线虫剂 Nematicide	霜霉威 Propamocarb	西班牙阿尔梅里亚 Almeria, Spain	地表水 Surface water	3.80×10^{6} ng·L^{-1}	[44]
	毒死蜱 Chlorpyrifos	孟加拉国西北部地区 Northwest Bangladesh	地表水 Surface water	9.10×10^{3} ng·L^{-1}	[7]
杀真菌剂 Fungicide	多菌灵 Carbendazim	略布列加河 Llobregat River	地表水 Surface water	10.82 ~ 697.39 ng·L^{-1}	[45]

接反映鱼类对脂质的消化吸收水平及利用能力。许多研究表明农药类化合物可以通过影响肠道内消化酶的活性干扰脂质的消化吸收。非洲鲶鱼(*Clarias gariepinus*)和斑马鱼(*Danio rerio*)分别暴露于氯氰菊酯(50 μg·L^{-1} 和 100 μg·L^{-1})和亚致死浓度(0.025、0.10 和 0.40 mg·L^{-1})的恶唑酰草胺后,其肠道内脂肪酶的活性均显著降低,使得脂肪吸收能力受损[47–48]。亚致死浓度(0.75 μg·L^{-1} 和 7.5 μg·L^{-1})的三丁基锡暴露幼年鲤鱼(*Cyprinus carpio*)60 d 后,也显著抑制其肠道内的消化酶(胰蛋白酶、脂肪酶)活

性[49]。由此可知多种农药类化合物可以通过抑制肠道内消化酶的活性，从而阻碍脂质的消化与吸收过程，进而降低机体内脂质含量。

此外，农药也可以通过影响鱼类的肠道菌群丰度及组成来干扰脂质吸收。有研究表明肠道微生物群与脂质代谢之间存在密切关系，厚壁菌等微生物群可增加肠上皮中的脂质，并影响脂肪吸收[50]。例如，Semova 等[51]通过在无菌斑马鱼肠道内定植菌群，发现肠道细菌能够增加宿主肠上皮细胞对脂肪酸的吸收和脂滴数量。肠道菌群的组成受饮食、外部环境以及肠道内环境的影响，肠道菌群组成变化会影响脂肪分布、胰岛素敏感度、能量与脂质代谢等生理功能。Jiang 等[52]研究发现，苯醚甲环唑(0.4 mg·L^{-1})暴露斑马鱼 21 d 后，斑马鱼肠道微生物群的组成显著改变，西杆菌的相对丰度降低，厚壁菌、肠杆菌和拟杆菌的丰度增加，肝脏内脂质蓄积明显。雄性成年斑马鱼暴露于霜霉威(1 000 μg·L^{-1})7 d 后，其肝脏 TG 含量显著降低，同时肠道微生物种群的组成和丰度发生了显著变化，在门水平上，α-变形菌、γ-变形菌、拟杆菌和厚壁菌的丰度显著增加，在属水平上，鲸杆菌和希瓦氏菌显著减少，黄杆菌、不动杆菌、巨单胞菌和沉积物杆状菌的丰度显著增加。这些分类群的变化可以减少短链脂肪酸和抗菌肽的产生，从而间接影响肝脏功能和脂质代谢[53]。三苯基锡(100 ng·L^{-1})暴露海水青鳉(*Oryzias melastigma*) 21 d 后，显著改变海水青鳉的肠道微生物群丰度，从而使其肠道微生物多样性显著下降。对暴露组海水青鳉肠道进行代谢组学分析发现其代谢谱发生显著变化，并且差异代谢物主要集中在脂质代谢途径中[54]。因而，农药类化合物可以通过干扰鱼类肠道内菌群的种类与含量进而影响肝脏内中性脂质与脂肪酸的含量。

2.2　干扰鱼类的脂质合成代谢(Disruption of the lipid anabolism in fish)

鱼体内的脂肪来源主要分为 2 种，一是从食物中摄入的外源性途径，二是在肝脏、脂肪组织中进行的从头合成，也就是内源性合成。脂质合成的主要途径是脂肪酸合成。脂肪酸合成的前体是乙酰辅酶A，首先在乙酰辅酶 A 羧化酶(acetyl-CoA carboxylase, ACC)的催化作用下羧化生成丙二酰辅酶 A，然后乙酰辅酶 A 和丙二酰辅酶在脂肪酸合成酶(fatty acid synthase, FAS)的多次催化下生成十六碳的饱和脂肪酸——棕榈酸。棕榈酸可在动物肝细胞中的内质网和线粒体内在脂肪酸去饱和酶的作用下进行碳链延长与脂肪酸的脱饱和，从而得到更长碳链的脂肪酸或不饱和脂肪酸。

鱼类的脂质合成过程由多个酶促反应组成，因而研究发现农药类污染物干扰脂质合成过程中 *FAS*、*ACC* 等关键酶或基因的表达是其导致 TG 等脂质含量异常的重要原因。*FAS* 在长链脂肪酸的从头合成中发挥关键作用，是脂肪合成的关键基因之一，其表达量的升高会促进生物体内脂肪的合成[55]。而 *ACC* 主要在脂肪组织中表达，是催化长链脂肪酸合成过程中的限速酶[56]。除草剂恶唑酰草胺(0.40 mg·L^{-1})暴露成年斑马鱼 21 d 后，脂质合成相关基因 *FAS* 和 ACC1 的转录水平上调，促进脂质合成，使得肝脏内 TG 和游离脂肪酸水平显著增加[57]。幼年奇努克鲑鱼(*Oncorhynchus tshawytscha*)暴露于氯氰菊酯 21 d 后，通过上调肝脏中 *FAS* 和 ATP 柠檬酸裂解酶(ATP-citrate lyase, ACL)的表达水平，促进脂质合成，进而导致鲑鱼体内脂质蓄积[58]。

同时，农药类污染物还可以通过干扰调控鱼类脂代谢过程的转录因子的表达而干扰脂质的合成代谢。已知固醇调节元件结合蛋白(sterol regulatory element binding protein, SREBP)是维持细胞内脂肪稳态的重要核转录因子，SREBP1 参与调节生物体内大多数脂肪生成相关基因的转录，与脂质合成密切相关[59]。研究报道，吡噻菌胺(1.20 mg·L^{-1})暴露斑马鱼胚胎以及霜霉威(1 000 μg·L^{-1})暴露成年斑马鱼 7 d 后，均会影响鱼类体内 SREBP1 的表达，进而调控 *FAS*、ACC1 的活性从而引起其 TG 含量改变[60,53]。过氧化物酶体增殖物激活受体家族(peroxisome proliferators-activated receptors, PPARs)是一类由配体激活的转录因子，在脂肪细胞分化及脂肪代谢方面发挥关键作用。*PPARγ* 能够调控脂肪细胞的分化与成熟，诱导脂肪细胞相关基因的表达。其表达升高会促进机体对脂质的吸收和脂肪的沉积[61]。转录组分析表明，三苯基锡(1、10 和 100 ng·L^{-1})暴露海水青鳉 21 d 后能够激活 *PPAR* 信号通路，其中 *PPARγ* 基因表达量显著上调，刺激脂肪细胞分化，导致机体肥胖[54]。研究发现，苯醚甲环唑(1 000 ng·L^{-1})暴露海水青鳉 6 个月以及亚致死剂量的三氯生(200 μg·L^{-1})急性暴露斑马鱼仔鱼后均会上调其 *PPARγ* 的表达，从而刺激脂肪细胞分化，诱导其脂质积聚[62-63]。*PPAR* 基因表达水平的改变可能与农药类化合物干扰了其转录调控机制有关，例

如,双(2-乙基己基)-2,3,4,5-四溴邻苯二甲酸酯(1 412 μg·L^{-1})暴露斑马鱼胚胎 14 d 后,通过显著上调 DNA 羟化酶(ten-eleven translocation, TET)表达量,促进了 *PPARγ* 启动子的去甲基化,进而导致该基因转录上调,最终使得斑马鱼幼鱼体内 TG 水平发生改变[64]。

2.3　干扰鱼类的脂质分解代谢(Disruption of the lipid catabolism in fish)

脂质的分解主要分为两部分即 TG 的水解和脂肪酸的 β 氧化。与脂质合成相似,脂质分解过程中也有许多催化酶起到重要的调控作用。激素敏感脂肪酶(hormone-sensitive triglyceride lipase, HSL)可以将 TG 分解为脂肪酸和甘油并释放进入血液供其他组织氧化利用,是 TG 分解过程中的限速酶。此外肉碱棕榈酰转移酶 1(carnitine palmitoyl transterase-1, CPT-1)将脂肪酸的活化产物脂酰辅酶 A 转移进入线粒体从而进行 β 氧化过程,是脂肪酸 β 氧化过程的主要限速酶。农药类化合物可以通过影响 TG 水解和/或脂肪酸氧化过程中这些关键酶的表达、活性而干扰鱼类的脂质代谢。研究报道,草甘膦(5 mg·L^{-1}和 50 mg·L^{-1})暴露幼年鲤鱼 45 d、敌百虫(2.0 mg·L^{-1})暴露异育银鲫(*Carassius auratus gibelio*)30 d 后,均能显著降低肝脏内 HSL 活性,抑制脂质分解,从而导致其体内脂质含量增加[65-66]。斑马鱼暴露于噻呋酰胺(0.19 mg·L^{-1}和 1.90 mg·L^{-1})28 d 后,其体内脂质分解相关基因 CPT-1 活性显著升高,促进脂肪酸的 β 氧化,进而导致 TG 和总胆固醇(total cholesterol, TC)含量显著降低[67]。

另外,农药化合物也可以通过干扰脂质分解代谢相关转录因子的表达干扰鱼类的脂质代谢过程。PPARs 家族中的 *PPARα* 通过调控酰基辅酶 A 中脂肪酸转化、脂肪酸进入线粒体和线粒体脂肪酸分解代谢酶的表达,在脂质分解代谢中发挥重要作用[68]。研究表明,*PPARα* 的激活能够显著提升其肝脏脂肪酸的 β 氧化效率及 CPT-1 活性,并降低草鱼血浆中 TG 和 TC 水平[69]。而杀菌剂啶酰菌胺(1.0 mg·L^{-1})能够通过提高斑马鱼肝脏内 *PPARα* 的表达水平上调 CPT-1 的表达,进而促进脂肪酸 β 氧化,最终促使斑马鱼肝脏中 TG、TC 含量显著降低[70]。

2.4　干扰鱼类的脂质转运过程(Disruption of the lipid transport in fish)

在鱼体中,脂质的运输由内源性运输和外源性运输组成。在外源性途径中,从食物中摄取的脂肪经消化后分解为长链脂肪酸和一酰甘油,再由肠上皮细胞吸收后转化成 TG,然后与载脂蛋白(apolipoprotein, APO)、胆固醇等结合形成 CM 释放到血液中。在内源性转运系统中,肝脏中合成的长链脂肪酸酯化成 TG 后与载脂蛋白、胆固醇等形成极低密度脂蛋白(very low-density lipoprotein, VLDL)运输到肝外组织中储存或利用。脂蛋白脂肪酶(lipoproteinlipase, LPL)是控制脂质运输的关键酶,它的作用是从 CM 和 VLDL 中水解 TG,将 TG 衍生的脂肪酸输送到外周组织以供利用和储存[71]。研究表明,机体内脂肪酸跨膜运输是被动扩散或由蛋白介导的过程,脂肪酸被组织摄取涉及多种蛋白的参与,包括脂肪酸转运蛋白(fatty acid transport protein, FATP)、脂肪酸结合蛋白(fatty acid binding protein, FABP)等。

农药类化合物可以通过影响载脂蛋白、VLDL、LPL 和脂肪酸结合蛋白的活性从而破坏鱼类的脂代谢稳态。例如,敌百虫(2.0 mg·L^{-1})暴露异育银鲫 30 d 导致其肝脏内 VLDL 和载脂蛋白 Apob100 的含量显著下降,从而不能将肝脏内的脂质转运至外周组织,致使肝脏内脂肪沉积[66]。Zhang 等[72]发现 3 种杀螨剂螺螨酯、螺甲螨酯和螺虫乙酯暴露斑马鱼胚胎 8 d 后,显著抑制了 FABP2 和 LPL 的活性,胚胎内总胆固醇含量显著降低。苯醚甲环唑(2.0 mg·L^{-1})暴露斑马鱼幼鱼 120 h 后,脂肪酸含量和 FABP 的表达水平降低,阻碍脂质转运,使得幼鱼体内 TG 水平升高[52]。

除了影响上述的脂代谢过程之外,农药类化合物还可以通过其他的途径干扰鱼类的脂质代谢,比如,通过诱导线粒体的功能障碍从而影响鱼类的脂代谢,线粒体在以三磷酸腺苷(adenosine triphosphate, ATP)的形式从营养物质中产生能量方面起着核心作用,通过线粒体的脂质氧化增加可能会减少脂质积累[73]。有研究报道,氯硝柳胺暴露会增加生物体内二磷酸腺苷(adenosine diphosphate, ADP)/ATP 比率,随后增加脂质和葡萄糖氧化,最终抑制肝脏中 TG 的合成和糖异生[74]。Zhu 等[75]发现斑马鱼暴露于氯硝柳胺(40 mg·L^{-1})120 h 后,其 ATP 含量显著下降,从而抑制 TG 和 TC 合成。此外,农药类化合物还可以通过干扰鱼类的糖代谢从而间接影响鱼类的脂代谢,甲基硫菌灵(12.5 mg·L^{-1}和 25 mg·L^{-1})暴露斑马鱼 28 d 后,斑马鱼肝脏中糖原和多糖物质的积累减少,参与糖酵解的关键酶乳酸脱氢酶以及戊糖磷酸途径的限速酶 6-磷酸葡萄糖酸脱氢酶

表2 农药类污染物干扰鱼类脂质代谢的机制

Table 2 Mechanisms underlying the disruption of lipid metabolism induced by pesticides in fish

农药类别 Pesticide category	名称 Name	暴露物种 Exposed species	干扰机制 Mechanism of action	参考文献 Reference
杀虫剂 Insecticide	滴滴涕 Clofenotane	斑马鱼 (*Danio rerio*)	抑制脂肪酸β氧化 Inhibit β oxidation of fatty acids	[77]
	滴滴涕 Clofenotane	蓝鳍金枪鱼 (*Thunnus thynnus*)	脂质合成相关转录因子 *PPARγ* 的表达显著上调 The expression of *PPARγ*, a transcription factor related to lipid synthesis, was significantly up-regulated	[78]
	敌百虫 Trichlorfon	异育银鲫 (*Carassius auratus gibelio*)	脂质分解过程中的 HSL 活性降低，载脂蛋白 Apob100 和 VLDL 的含量下降 The activity of HSL and the content of apolipoprotein Apob100 and VLDL decreased during lipid decomposition	[66]
	敌敌畏 Dichlorvos	斑马鱼 (*Danio rerio*)	CPT-1 表达显著降低，抑制脂肪酸β氧化 The expression of CPT-1 is significantly reduced, inhibiting β oxidation of fatty acids	[79]
	氯氰菊酯 Cypermethrine	非洲鲶鱼 (*Clarias gariepinus*)	CPT-1 的表达显著降低，阻碍脂质吸收 The expression of CPT-1 is significantly reduced, inhibiting lipid absorption	[47]
	氯氰菊酯 Cypermethrine	奇努克鲑鱼 (*Oncorhynchus tshawytscha*)	脂肪酸合成过程中的 *FAS* 和 *ACL* 的表达水平显著上升 The expression level of *FAS* and *ACL* increased significantly during fatty acid synthesis	[58]
除草剂 Herbicide	草甘膦 Glyphosate	鲤鱼 (*Cyprinus carpio*)	脂质分解过程中的 HSL 活性显著降低 HSL activity decreased significantly during lipid decomposition	[80]
	恶唑酰草胺 Metamifop	斑马鱼 (*Danio rerio*)	脂肪酸合成过程中的 *FAS*、ACC1 的表达水平上升 The expression level of *FAS* and ACC1 increased during fatty acid synthesis	[57]
杀菌剂 Bactericide	三氯生 Triclosan	斑马鱼 (*Danio rerio*)	脂质合成过程中的转录因子 *PPARγ* 的表达上调 The expression of *PPARγ*, a transcription factor, was up-regulated during lipid synthesis	[63]
	苯醚甲环唑 Difenoconazole	斑马鱼 (*Danio rerio*)	肠道微生物群的组成显著改变，影响脂质吸收；FABP 的表达水平降低，阻碍脂质转运 The composition of intestinal microbiota changed significantly, affecting lipid absorption; the expression level of FABP decreased, which hindered lipid transport	[52]
	苯醚甲环唑 Difenoconazole	海水青鳉 (*Oryzias melastigma*)	肌肉中的 *PPARγ* 表达显著上调，刺激脂肪细胞分化 The expression in of *PPARγ* in muscle was significantly up-regulated, stimulating adipocyte differentiation	[62]
	多效唑 Paclobutrazol	褐菖鲉 (*Sebastiscus marmoratus*)	*PPARs*、ACC1 、*FAS* 和 FABP4 的表达水平上调，促进脂质合成 The expression levels of *PPARs*, ACC1, *FAS* and FABP4 were up-regulated to promote lipid synthesis	[81]
	噻呋酰胺 Thiofuramide	斑马鱼 (*Danio rerio*)	CPT-1 mRNA 水平显著升高，促进脂肪酸β氧化 The level of CPT-1 mRNA increased significantly, promoting β oxidation of fatty acids	[67]
	氟环唑 Epoxiconazole	斑马鱼 (*Danio rerio*)	*FAS* 的 mRNA 水平显著升高，SREBP1α、Apo 和 CPT-1 的 mRNA 水平下降，促进脂质合成 The mRNA level of *FAS* was significantly increased, and the mRNA levels of SREBP1α, Apo and CPT-1 decreased, promoting lipid synthesis	[82]

续表2

农药类别 Pesticide category	名称 Name	暴露物种 Exposed species	干扰机制 Mechanism of action	参考文献 Reference
杀菌剂 Bactericide	丙硫菌唑 Prothioconazole	斑马鱼 (*Danio rerio*)	CPT-1 的 mRNA 水平上调,胆固醇合成有关基因 *Cyp51* 的 mRNA 水平下降 The mRNA level of CPT-1 was up-regulated, and the mRNA level of *Cyp51*, a gene related to cholesterol synthesis, was decreased	[83]
	丙环唑 Propiconazole	斑马鱼 (*Danio rerio*)	*FAS* 和 LPL 的表达水平显著降低,阻碍脂质合成 The expression level of *FAS* and LPL decreased significantly, which hindered lipid synthesis	[84]
	啶酰菌胺 Boscalid	斑马鱼 (*Danio rerio*)	*PPARα* 的表达水平显著增加,促进脂肪酸 β 氧化 The expression level of *PPARα* increased significantly, promoting β oxidation of fatty acids	[70]
杀螺剂 Molluscide	螺螨酯 Spirodiclofen	斑马鱼 (*Danio rerio*)	ACC1 、*FAS*、FABP2 和 LPL 表达水平降低,抑制脂质积累 The expression levels of ACC1, *FAS*, FABP2 and LPL were decreased, which inhibited lipid accumulation	[42]
	螺甲螨酯 Spiromesifen	斑马鱼 (*Danio rerio*)	ACC1 、*FAS*、FABP2 和 LPL 表达水平降低,抑制脂质积累 The expression levels of ACC1, *FAS*, FABP2 and LPL were decreased, which inhibited lipid accumulation	[42]
	螺虫乙酯 Spirotetramat	斑马鱼 (*Danio rerio*)	ACC1 、*FAS*、FABP2 和 LPL 表达水平降低,抑制脂质积累 The expression levels of ACC1,*FAS*, FABP2 and LPL were decreased, which inhibited lipid accumulation	[42]
	氯柳硝胺 Chlorosalanide	斑马鱼 (*Danio rerio*)	LPL 和 CPT-1 的活性显著增加,*FAS* 的活性显著降低 The activities of LPL and CPT-1 were significantly increased, while the activity of *FAS* was significantly decreased	[75]
杀线虫剂 Nematicide	霜霉威 Propamocarb	斑马鱼 (*Danio rerio*)	肠道微生物种群的组成和丰度发生了显著变化,影响脂质吸收 The composition and abundance of intestinal microbial population changed significantly, affecting lipid absorption	[53]
	霜霉威 Propamocarb	斑马鱼 (*Danio rerio*)	*PPARγ* 、*FAS*、ACC1 、SREBP1 和 DGAT 的 mRNA 水平显著降低,抑制脂质合成 The mRNA levels of *PPAR γ*, *FAS*, ACC1, SREBP1 and DGAT were significantly decreased, which inhibited lipid synthesis	[53]
	毒死蜱 Chlorpyrifos	大西洋鲑 (*Salmo salar*)	*PPARα* 的 mRNA 水平上调,促进脂肪酸 β 氧化 The mRNA level of *PPARα* was up regulated, promoting β oxidation of fatty acids	[85]
	毒死蜱 Chlorpyrifos	斑马鱼 (*Danio rerio*)	*FAS*、ACC1 和 *PPARγ* 的 mRNA 水平显著降低,抑制脂质合成 The mRNA levels of *FAS*, ACC1, *PPARγ* were significantly decreased, which inhibited lipid synthesis	[86]
杀真菌剂 Fungicide	多菌灵 Carbendazim	斑马鱼 (*Danio rerio*)	*PPARγ* 和 *FAS* 的 mRNA 水平显著增加,ACC1 和 Apo 的 mRNA 水平显著降低 The mRNA levels of *PPARγ* and *FAS* were significantly increased, while the mRNA levels of ACC1 and Apo were significantly decreased	[87]

的活性升高,肝脏转化或储存糖原的能力降低致使糖代谢不能提供足够的能量来支撑机体,因此 TG 被转化以满足机体的能量需求,从而斑马鱼肝脏内 TG 含量降低[76]。

3　总结与展望(Summary and prospect)

综上所述,目前农药类化合物的使用已经对水生环境造成严重污染,并且诱导鱼类脂代谢紊乱的发生。农药可以通过干扰脂质消化吸收、合成、分解

和转运等过程中关键酶、基因和转录因子的表达及线粒体功能受损和干扰糖代谢等脂质代谢过程，导致脂肪酸、TG 等脂质生化指标的异常。目前关于农药的应用及污染现状已经得到较为深入的研究，但是关于农药对鱼类等水生生物脂代谢毒性机制的研究还存在许多有待解决的问题。

首先，目前关于农药类化合物对鱼类脂质代谢的影响研究大多关注中性脂质与胆固醇代谢，对磷脂的研究较少。磷脂是一种极性脂质，具有两亲性，常与胆固醇、糖脂和蛋白质等大分子共同构成生物体的细胞膜，不仅有助于膳食脂质在肠道内的消化吸收[88]，同时也是鱼类体内参与脂质转运的载脂蛋白的重要组成部分[89]。现有的相关研究主要报道了农药化合物暴露对鱼体内磷脂含量的影响，例如，Sarma 等[90]将蓝点石斑(*Channa punctatus*)暴露于亚致死浓度的硫丹($8.1\ \mu g\cdot L^{-1}$)96 h 后，发现蓝点石斑肝脏和肌肉内的总脂质、胆固醇和脂肪酸含量显著降低，肝脏内的磷脂水平也显著下降；在胡鲶(*Clarias batrachus*)生殖周期的卵黄形成阶段，将其暴露于亚致死浓度的杀虫剂马拉硫磷($4\ mg\cdot L^{-1}$)和六六六($8\ mg\cdot L^{-1}$)4 周后，发现马拉硫磷能够抑制其肝脏磷脂向性腺的转运，而六六六不仅阻碍肝脏磷脂向性腺的转运，而且减少其在肝脏中的合成[91]。磷脂作为鱼类生殖前期的必需营养素，可作为底物参与卵黄蛋白原的合成，并能加速肝脏中的脂质经血液转运至卵巢中，促进卵巢卵黄形成[92]。而卵黄积累不仅可以促进卵母细胞的发育，同时也为胚胎的生长发育提供必需的营养物质和能量。因此农药类化合物对鱼类肝脏和/或性腺内磷脂的影响可能会进而干扰鱼类的繁殖及子代的生长发育，但目前鲜有研究关注这一方面，因此今后可以深入研究农药类污染物对鱼类中磷脂代谢的干扰作用机制，尤其是在不同生殖周期探究农药对磷脂的影响可为解析其对鱼类卵巢功能及子代生长发育的干扰机制提供新的视角。

其次，目前已有的研究大多是关于单一农药对水生生物的脂代谢毒性效应，但是在实际应用过程中，常常是多种农药或者农药与其他污染物联合使用从而达到更好的防治效果，这些污染物彼此之间可能存在拮抗或者协同等多种作用关系。因此在今后的研究中应该更加重视农药与其他污染物联合暴露对鱼类及其他水生生物脂代谢的影响，例如，有文献研究三氯生与双酚 A 共同暴露诱导斑马鱼脂质代谢紊乱的差异机制[93]，从而为农药的水生生态毒性和环境风险评估提供更加充分的科学依据。

此外，目前用于农药脂代谢毒性作用研究的水生生物种类较为局限，但是不同种类的水生生物对农药的敏感性存在较大的差异，因此今后可以进一步加强农药对多种水生生物或者不同营养级水生生物的脂代谢毒性效应研究。而且农药对鱼类脂质代谢的影响并非仅仅影响脂质代谢本身，而更有可能由脂质代谢异常进一步影响鱼体的生殖、发育以及抗病免疫过程等。然而，这些相关生理过程的关键连接点、作用靶位点以及作用机制均尚未阐明。因此，在今后的研究中，应加强利用现代生物学技术，深入研究农药影响脂质代谢及其关联生理过程的分子机制，这不仅有利于更深入地阐明鱼类代谢性疾病的发生原因，也为保障水产品的绿色安全提供重要的参考依据。

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