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·综述·

鱼类的葡萄糖感知与糖代谢调节研究进展

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摘要: 为加深对鱼类糖的感知与代谢调控的认识,本文综述了鱼类的葡萄糖感知与摄食调控、糖代谢调控等领域的研究进展。鱼类的下丘脑不仅是中枢葡萄糖感受器所处的主要部位,同时也是食欲调节中枢。leptin、ghrelin、CCK、NPY 等内分泌因子均能调控鱼类对糖的感知与摄食。另一方面,鱼类糖代谢受到胰岛素、GLP-1、ghrelin、CCK、NPY、SS 等内分泌因子和糖、脂、蛋白质等营养素的双重调节。尽管鱼类对糖的利用能力低于陆生动物,但鱼体内亦存在较完善的糖的感知、摄食与代谢调节机制。因此,将来的重点工作应在于研究鱼类中枢神经系统整合营养和内分泌等信号的机制,研究草食性鱼类、杂食性鱼类在糖耐受力及糖异生调控机制上与肉食性鱼类存在的差异。

关键词: 鱼类; 糖代谢; 营养调控; 内分泌调控; 葡萄糖感受器; 摄食

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糖类是自然界中广泛分布的有机物,也是饲料中一种重要的廉价能源物质。长期以来,鱼类对糖类的摄取、利用、代谢及其调控机制一直是研究中的热点。大量研究发现,同哺乳动物相比,鱼类对体内的葡萄糖水平存在“不耐受性”与“耐受性”的特点。其中,前者是指增加糖负荷后,鱼类血糖水平升高,并且高血糖状态持续的时间长,即对高血糖的不耐受性(intolerance to hyperglycemia),也就是临床上所指的葡萄糖不耐症[1];而后者是指鱼类对低血糖的耐受能力强[2],即对低血糖的耐受性(tolerance to hypoglycemia)。

随着研究的深入,发现传统意义上认为鱼类对高血糖的不耐受性并非普遍现象,在一些草食性、杂食性鱼类,甚至一些肉食性鱼类中并非如此[2]。尽管在各种鱼类中进行葡萄糖耐受实验的结果有所差异,但值得重视的是杂食性鱼类由高血糖状态恢复到基础水平的速度比肉食性鱼类快,而杂食性鱼类的基础血糖水平比肉食性鱼类低[3]。此外,虽然鱼体对低血糖具有较高的耐受能力,但是当脑中糖原水平下降后,会导致鱼类低血糖、晕厥甚至死亡,这种现象同哺乳动物较为类似[4]。由此可见,鱼类对糖类的代谢和调控机制与哺乳动物有共同之处,也有明显的区别。并且,鱼类的中枢神经系统在对糖的感知和调控中可能发挥着更为重要的作用。因此,本文将对鱼类的葡萄糖感知与摄食调控以及糖代谢调控等领域的研究进展进行综述。

1　葡萄糖感知与摄食调控

1.1　鱼类对糖的感知

哺乳动物可通过反馈调节机制来保持血糖稳态、维持能量代谢平衡,这种机制能够运行的关键在于体内广泛存在葡萄糖感应器(glucose sensor, glucosensor),它们能够持续监测体内血糖变化,触发激素分泌和激活自主神经系统,使机体对血糖变化做出响应,从而调控葡萄糖的利用、代谢和食物摄取等生理活动[2]。

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哺乳动物的葡萄糖感应器广泛分布于中枢神经系统和外周组织中。其中,中枢葡萄糖感应器主要是位于下丘脑及后脑的葡萄糖兴奋性神经元(glucose-excited neurons,GE neurons)和葡萄糖抑制性神经元(glucose-inhibited neurons,GI neurons);而外周葡萄糖感应器最经典部位是胰腺,它在感应到血糖变化后,会触发胰岛素(insulin)或胰高血糖素(glucagon)的释放。除此之外,在肝脏[5]、肠道[6]、颈动脉[7]等器官或组织中也存在外周葡萄糖感应器。这些葡萄糖感应器的构成要件主要包括葡萄糖转运蛋白2(glucose transporter 2,GLUT2)、葡萄糖激酶(glucokinase,GK)、糖酵解途径(影响血糖水平与胰岛素分泌)、ATP敏感性钾离子通道(ATP-sensitive inward rectified K^+ channel,K_{ATP})及钙离子通道(calcium channel)等[2],它们在葡萄糖感应器监测到血糖变化时能够做出响应进而促使机体作出调节,维持血糖稳态。

同哺乳动物相似,鱼类的葡萄糖感应器同样存在于中枢神经系统和外周组织中。Polakof等[2]以虹鳟(*Oncorhynchus mykiss*)为模型,对肉食性鱼类的葡萄糖感知机制进行了大量研究,并详细阐述了虹鳟体内葡萄糖感应器的部位及构成分子。这些部位包括脑中的某些神经元及星形胶质细胞、肝胰脏中的布氏体(Brockmann body)以及肠道。其中,脑和布氏体中葡萄糖感应器的构成分子主要是GLUT2、GK、K_{ATP}及糖原;在肠道中则主要是Na^+依赖性葡萄糖转运载体(sodium-dependent glucose co-transporter,SGLT)、GLUT2、GK和K_{ATP}等。然而,在其他鱼类中(尤其是草食性和杂食性鱼类),尚缺乏相关的研究。

目前,在鱼类的脑中尚未鉴定出葡萄糖感应器所在的神经元。鱼类是否同哺乳类一样,脑中也存在GE或GI神经元;或者,在鱼类中是否由其他神经元负责监测血糖的变化,这些问题还有待研究。尽管如此,相关研究已经发现了鱼类脑中也存在葡萄糖感应器的一些构成分子。例如,在斑马鱼(*Danio rerio*)、虹鳟等鱼类的脑中有GLUT2和GK等基因的表达[8-10],在尼罗罗非鱼(*Oreochromis niloticus*)脑中能够检测到GLUT1基因的mRNA表达[11]。此外,鱼类的肝脏也分布着葡萄糖感应器。目前已在虹鳟[12]、欧洲海鲈(*Dicentrarchus labrax*)[13]、斑马鱼[14]、鲤(*Cyprinus carpio*)[9]、金头鲷(*Sparus aurata*)[9]等多种鱼类的肝脏中检测到*GK*等基因的表达。肉食性鱼类的肠道也具有感应单糖的能力。在虹鳟中的研究发现,肠道在糖代谢过程中的作用显著[15],它能够感应葡萄糖、半乳糖和甘露糖等单糖的变化,进而做出响应并改变糖敏感基因的表达水平,如GLUT2、GK、SGLT1,肝X受体α(liver X receptor alpha,LXRα)以及G蛋白偶联味觉受体相关基因等[16],进而启动葡萄糖氧化或糖原转化贮存[15]。

1.2 鱼类葡萄糖感应与摄食调控

哺乳动物下丘脑不仅存在着中枢葡萄糖感应器,能够监测体内血糖水平和能量变化,同时还是整合与发放各种食欲信号的中枢。下丘脑弓状核(arcuate nucleus,ARC)中存在着神经肽Y(neuropeptide Y,NPY)/刺鼠相关蛋白(agouti-related protein,AgRP)促摄食性神经元、原阿片黑皮素(proopiomelanocortin,POMC)/可卡因-苯丙胺调节转录肽(cocaine amphetamine regulated transcript,CART)抑摄食性神经元,它们是中枢神经系统调节摄食的关键性神经元[17]。此外,下丘脑弓状核中的腺苷酸活化蛋白激酶(AMP-activated protein kinase,AMPK)和哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR),通过磷酸化/去磷酸化的方式被激活或抑制,这两种激酶在感知体内能量状态中发挥关键性作用,其中,前者在低能量状态时被激活,而后者在高能量状态时被激活,两者具有协同作用,并且还受到其他内分泌因子(如瘦素,leptin)的调控[18-20]。因此,营养状况或一些内分泌因子可能通过AMPK或mTOR信号通路,作用于下丘脑中促摄食性或抑摄食性神经元,进而调控哺乳动物的摄食。

在鱼类下丘脑中,已证实存在有调节摄食的神经肽类,如NPY、AgRP、POMC、CART[21],但尚未有直接证据表明鱼类是否也存在NPY/AgRP神经元、POMC/CART神经元或者其他类似的促摄食性和抑摄食性神经元。此外,已有研究成果发现了能量状态或一些内分泌因子与鱼类AMPK或mTOR磷酸化水平的相关性。例如多耙牙鲆(*Paralichthys adspersus*)在饥饿的状态下,其血清中leptin含量下降,肌肉中AMPK磷酸化水平升高、mTOR磷酸化水平降低;再投喂后则血清中

leptin 含量升高,肌肉中 AMPK 磷酸化水平降低、mTOR 磷酸化水平升高[22]。因此,推测鱼类中可能也存在与哺乳动物类似的摄食调控机制。

2　糖代谢的调节

2.1　内分泌调节

在哺乳动物中,胰岛素/胰高血糖素是一对拮抗调节血糖变化的激素,可进行降血糖或升血糖调节。目前研究证实,肉食性鱼类中也存在胰岛素/胰高血糖素拮抗调节机制[23]。此外,一些脑肠肽、神经肽等激素或内分泌因子,如 ghrelin、胆囊收缩素(cholecystokinin,CCK)、NPY、生长抑素(somatostatin,SS)等在鱼类中可能通过调节胰岛素/胰高血糖素促使血糖下调或上调。leptin、ghrelin、CCK、NPY 等对中枢葡萄糖感应器也有调节作用。

胰岛素是一种多功能肽类激素,可加强糖的利用、转化,抑制糖异生,起到降血糖作用。肉食性鱼类摄食后,血液中胰岛素水平也会上升。胰岛素可促进外周组织摄取葡萄糖,促进肝脏、肌肉组织合成糖原[24]。鱼类在体和离体实验均验证了胰岛素具有激活糖原合成酶(glycogen synthase,GSase)和抑制糖原磷酸化酶(glycogen phosphorylase,GPase)活性的功能,从而加强了糖原合成[25],缓解机体高血糖症状。胰岛素对糖酵解和糖异生途径的作用受到鱼类营养状况、种类的影响。当用胰岛素灌喂处理禁食虹鳟 4 d 后,发现糖异生相关酶类 mRNA 表达水平下降[25];而若用胰岛素灌喂高碳水化合物饲喂的虹鳟,其糖代谢基因的表达则不受影响,显示灌注胰岛素对血糖调节作用不明显,血糖维持在较高水平。在鲤、红鲷(*Pagrus major*)、鲆鱼(*Seriola quinqueradiata*)中,胰岛素可促进糖酵解途径[26],但在虹鳟中,胰岛素处理实验鱼后,GK 活性下降,己糖激酶(hexokinase,HK)活性升高[25]。

GLP(glucagon-like peptide)是由肠道分泌的肠促胰岛素激素,它是胰高血糖素原基因的表达产物,存在 GLP-1 和 GLP-2 两种形式。在哺乳动物中,GLP-1 能够促进胰岛素的分泌、抑制胰高血糖素的释放,从而具有降血糖的功能[27]。但是,同在哺乳动物体内的功能正好相反,GLP-1 在鱼类中具有类似胰高血糖素的功能,即促进糖质新生和肝糖原分解、具有升高血糖水平的作用,而对胰岛素的分泌没有影响[27-28]。在虹鳟的研究中发现,腹腔注射和脑室注射 GLP-1 均能够引起血糖水平和肝糖原水平升高,并影响肝脏、下丘脑或后脑中 GK、丙酮酸激酶(pyruvic kinase,PK)、GSase、GLUT2 等的活性或 mRNA 表达水平[29]。因此,推测 GLP-1 可通过脑-肠轴双重调控鱼类的糖代谢。在虹鳟、鸡和蜥蜴中存在选择性剪切 RNA 转录本编码的 GLP-2[30-31],但 GLP-2 在鱼类中的作用尚未见报道。

SS(somatostatin)是一类环状多肽类激素,在硬骨鱼类中存在两种形式,SS-14 和 SS-25,分别由 14 和 25 个氨基酸组成,参与机体的生长、发育、代谢、生殖以及免疫等生理过程。中枢系统及多数外周组织均可分泌该激素。虹鳟空腹 2 d 后注射 SS-14 和 SS-25,均能够引起血糖水平升高,胰高血糖素水平降低,但 SS-14 对肝糖原水平和胰岛素水平无影响,而 SS-25 可导致肝糖原含量下降,胰岛素水平下降[32]。虹鳟中 SS 升血糖作用是其对高血糖不耐受的重要原因之一[22],在哺乳动物中,SS 具有降低血糖的作用。SS 对血糖调节的效果在鱼类与哺乳类之间存在差异,具体机制尚未见报道。

瘦素是由肥胖基因(*ob*)编码的一种细胞因子或激素,它在调控鱼类摄食和能量代谢过程中发挥着重要作用[33]。在虹鳟的研究中发现,用 leptin 处理体外培养的下丘脑、后脑组织后,能够直接激活下丘脑和后脑的葡萄糖感应器,提高这些组织中的葡萄糖水平、糖原水平、GK 的活性及 mRNA 表达水平、GSase 的活性[34]。在体实验也得出了类似的结果,如虹鳟脑室中注射 leptin 后,其下丘脑和后脑的糖原水平及 GK 活性升高、葡萄糖感应相关基因的表达水平上升[35]。在哺乳动物中,leptin 能够抑制胰岛素的分泌,进而调控糖类的利用和代谢[36];而在鱼类中,leptin 是否参与调控胰岛素的合成与分泌,目前尚未见报道。

ghrelin 是生长激素促分泌物的内源性配体,是由胃肠道合成与分泌并能够作用于中枢神经系统的一种脑肠肽。在体实验(腹腔注射和脑室注射)表明,ghrelin 对虹鳟的血糖水平没有影响,但能够激活虹鳟下丘脑和后脑中的葡萄糖感应器,提高 GLUT2 的 mRNA 表达水平、增强 GK 活性以及激活 K_{ATP}[37]。某些鱼类如斑马鱼[38]、尼罗罗非鱼[39]等的脑中能够合成和分泌胰岛素。有

研究表明,ghrelin 还能够参与鱼类脑中胰岛素合成与分泌的调控。斑马鱼腹腔注射 ghrelin 后,脑中胰岛素及其受体基因的表达水平下降,GPase、胰高血糖素及其受体基因表达水平上升,说明 ghrelin 能够通过胰岛素和胰高血糖素两种途径,降低鱼类的血糖水平,提高其对葡萄糖的摄取和利用[40]。同时,葡萄糖也能够通过反馈机制调节鱼类 ghrelin 的表达和分泌。在莫桑比克罗非鱼(*O. mossambicus*)中的研究发现,葡萄糖能够提高胃中 ghrelin mRNA 的表达水平和血浆中 ghrelin 的水平[41]。这些研究结果均表明,ghrelin 在鱼类葡萄糖感应以及糖类代谢过程中也发挥着重要作用。

CCK 同样是一种典型的脑肠肽,它广泛分布于中枢神经系统和胃肠道,具有双重调节神经系统和消化系统的功能(如摄食与消化等),同时还可对中枢葡萄糖感应器、肝脏糖代谢发挥调节作用。如在虹鳟中的研究发现,腹腔注射 CCK-8 后,能够引起血糖水平和肝糖原含量升高,肝脏 GK、葡萄糖-6-磷酸酶(glucose-6-phosphatase,G6Pase)、GSase 的活性增强,GPase 的活性降低,下丘脑 PK 活性增强、后脑糖原水平升高[12]。而脑室注射 CCK-8 同样能够提高虹鳟的血糖水平,并增强其肝脏的 GPase 活性、降低肝糖原水平、增强下丘脑和后脑 GK 的活性[12]。在哺乳动物中,CCK 具有促进胰岛素合成与分泌的作用[42];在鱼类中,CCK 对胰岛素合成与分泌的影响,目前尚未见报道。

此外,褪黑色素(melatonin)[43]、促肾上腺皮质激素释放因子(corticotropin-releasing factor,CRF)[44]、NPY[45]和甘丙肽[45]等,也对鱼类糖的感知与代谢调控有着显著影响。褪黑色素能够在虹鳟下丘脑中激活葡萄糖感应器,而 CRF 则对虹鳟下丘脑和后脑中的葡萄糖感应器则均有影响,两者在脑中不同的部位调控中枢葡萄糖感应器,目前尚不清楚这种区别的意义和机制。NPY 和甘丙肽体外孵育虹鳟布氏体,可促进 SS 释放,进而通过 SS 参与糖代谢调节[45]。其他胃肠激素,如肠促胰液素(secretin)、YY 肽(peptide-YY)、肠胰高血糖素(enteroglucagon)、肠血管活性肽(vasoactive intestinal peptide)、胃泌酸调节素(oxyntomodulin)等已被证实存在于鱼类肠道内,这些因子对鱼类糖代谢有何作用还有待阐明[46]。

2.2 营养素的调节

糖类、脂类和蛋白质是鱼类饲料中的主要供能物质,这些营养成分也对糖代谢具有重要调节作用。葡萄糖稳态调节依赖于参与糖酵解,糖质新生,糖原合成与分解,脂肪生成等相关关键酶的表达调控及活性调节。常用的限速酶包括糖酵解过程的葡萄糖激酶(GK);糖质新生关键酶磷酸烯醇式丙酮酸羧激酶(phosphoenolpyruvate carboxykinase,PEPCK)、果糖 1,6-二磷酸酶(fructose 1,6-bisphosphatase,FBPase)和葡萄糖-6-磷酸酶(G6Pase)以及糖原合成酶(GSase)等。鱼类摄食后,机体营养感知系统与激素水平产生变化,通过调节糖代谢关键酶的活性或 mRNA 表达变化维持血糖稳定。

糖类 肉食性鱼类对碳水化合物利用率相对较低,其添加量一般低于 20%,而在杂食性或草食性鱼类中可添加至 30%~50%,若添加过高,能量蛋白比失衡会引起鱼类膳食后高血糖,导致生长受抑制、鱼体肝指数和肝糖原含量增高,诱发肝细胞肿大或空泡化[47]。

摄食含糖饲料后,鱼类肝脏糖酵解途径被上调,GK 活性和 mRNA 表达水平均升高。在虹鳟中,GK 活性可达到与哺乳动物接近的水平[9],摄食不同淀粉含量的饲料后,GK 分子水平表达量和活性随饲料糖含量(20% 和 40%)的升高而按比例增加[48]。在金头鲷饲料中添加碳水化合物(12%、16%、22% 和 28%)并减少脂类,饲喂 15 周后,GK mRNA 表达量随糖类添加量的增多而逐渐升高,但在 28% 处理组出现下降[49]。在肉食性鱼类大菱鲆(*Scophthalmus maximus*)中,GK 活性也随着糖类浓度的升高而增强[50]。在杂食性鱼类如鲤[9]、斑马鱼[51]中,当饲料中糖类/蛋白比例上升后,GK 活性及表达量均上升。但用含糖饲料饲喂后发现,糖类对鲤鱼 GK 活性的诱导作用低于虹鳟和金头鲷[9],这与预期结果相悖,具体机制有待深入研究。此外,在鱼类发育早期,碳水化合物也可诱导 GK 的表达。幼鱼开口期的营养调节研究发现,饲喂含有或不含糖的饲料后均可诱导 GK 的表达[52]。但是,当饲料含有碳水化合物时,GK 的表达量显著升高[52-53]。近期研究验证了上述结论,GK 在斑马鱼受精 0.2~1 d 后即出现低水平表达,从 4 d 开始,GK 显著增加[14]。

糖异生途径在肉食性鱼类中并未随着摄食糖类物质增加而被抑制。Enas 等[54]用含有 20% 普通玉米淀粉和 20% 蜡质玉米淀粉作为高碳水化合物组饲料饲喂欧洲海鲈,对糖异生关键酶 FBPase 活性无显著影响。进一步使用糖类梯度饲料(10%、20% 和 30%)饲喂欧洲海鲈,测定 FBPase 活性,3 个梯度组酶活分别为 10.8、11.4 和 11.8 mU/mg,差异不显著,不存在剂量依存效应[55]。大菱鲆中的研究结果也验证了该结论,即 FBPase 活性不随饲料中糖类含量的变化而变化[50]。此外,糖异生第一个限速酶 G6Pase 同样不受饲料糖含量影响。在金头鲷[56]、虹鳟[57]中,G6Pase 活性均未受到抑制,转录水平仍维持在较高数值。而在杂食性鱼类鲤鱼中,糖类饲料饲喂后,G6Pase 表达受到强烈抑制,部分肉食性鱼类,如黄锡鲷(*Sparus sarba*)[58] G6Pase 的 mRNA 表达受到高碳水化物的抑制。饲喂含糖饲料无法抑制糖异生,可能是部分肉食性鱼类不能有效利用碳水化合物的原因之一[23]。糖异生作用对鱼类高血糖的贡献力,以及不同食性鱼类之间糖异生代谢的差异机制有待阐明。

饲料中碳水化合物的含量对不同鱼类的糖原合成酶调节效果存在差异,碳水化合物可诱导欧洲海鲈和金头鲷 GSase 活性增加,糖原合成加强[47]。摄食后鱼类糖原含量变化也可间接反映糖原合成酶活力,Ekmann 等[59]采用同位素示踪法,用 4 组不同碳水化合物饲料饲喂金头鲷,在养殖 10 d、20 d 和 30 d 时取样,结果发现,肝糖原含量随碳水化合物添加量的增多及饲喂时间的延长而逐渐增高。但在黄锡鲷 20% 高糖处理组中,GSase 的 mRNA 表达水平并未升高[60]。在杂食性鱼类斑马鱼中,经 0%、15%、25% 和 35% 等 4 个糖梯度组饲喂 12 周后取样,发现 Gsase 的 1 和 2 型基因表达无显著差异[51],显示在部分杂食性和肉食性鱼类中碳水化合物未能诱导 Gsase mRNA 高表达。

脂类　　饲料脂肪含量对糖酵解关键酶的影响在不同鱼类、不同学者的研究中存在差异。Pansera 等[61]最早报道了脂肪对糖代谢关键酶的影响,发现高脂(26% 脂肪/ 11% 糖)和低脂(11% 脂肪/ 16% 糖)饲料饲喂虹鳟 8 周后,高脂组在摄食后 3 h 时 GK mRNA 表达量显著高于低脂组,GK 活性在 3 h、12 h 时高于低脂组。但是,用鱼油高脂(25% 脂肪/14% 淀粉)与未加鱼油的低脂(10% 脂肪/17% 淀粉)饲料饲喂虹鳟 7 周,并在摄食 8 h 后取样,结果发现这两组虹鳟的肝脏 GK 活性无显著差异[62]。该结果与 Pansera 等[61]的报道迥异,这可能是由于两者的养殖时间和取样时间存在差异造成的。翘嘴红鲌(*Erythroculter ilishaeformis*)的饲养时间与取样时间与 Pansera 等[61]所用条件相同,高脂组(19.93% 脂肪/14.45% 糖)GK mRNA 表达显著高于低脂组(9.92% 脂肪/12.38% 糖),与 Pansera 等[61]报道结果一致,但高脂组 GK 活性与低脂组接近[63]。可见高脂未能促使 GK 活性增强,这一现象在塞内加尔鳎(*Solea senegalensis*)内也存在,高脂(17% 脂肪/14% 淀粉)、低脂(4% 脂肪/23% 淀粉)饲料饲喂后,GK 活性变化不大[64]。

高脂饲料可促进鱼类糖质新生。膳食高脂饲料(26% 脂肪/11% 糖)的虹鳟葡萄糖利用率下降,出现葡萄糖不耐受性现象,并且肝脏糖质新生关键酶 G6Pase 活性及基因的表达均增强[61]。同样现象在翘嘴红鲌[63]和塞内加尔鳎中也存在。高脂组翘嘴红鲌在摄食 3 ~ 24 h 后,G6Pase 的 mRNA 水平显著升高,酶活性在 24 h 后增强。塞内加尔鳎高脂/低糖处理组肝脏 G6Pase 活性也出现升高[64]。结合前文所述碳水化合物对肉食性鱼类糖异生的作用,当饲料中添加糖和脂肪后,肉食性鱼类的糖异生作用可能得到加强,从而降低肉食性鱼类的糖耐量。这一假设得到后续研究的证实,饲喂高水平脂肪,会损害虹鳟体内葡萄糖稳态,即高脂诱导下糖耐量下降,改喂低脂饲料后可迅速扭转这一现象[65]。

高脂饲料可促进鱼类糖质新生,在部分物种中对糖酵解具有促进作用。脂肪对不同鱼类糖酵解的作用机制还不明确。目前研究所用饲料通常是高脂伴随低糖或低脂伴随高糖,为准确评估饲料脂肪对糖代谢的作用,有必要排除糖类物质的间接影响。

蛋白质　　鱼类饲料蛋白质含量可达到 30% ~ 50%。当饲料蛋白含量增加时,糖酵解途径关键酶受到抑制。在虹鳟中,GK 活性随蛋白含量的逐渐升高(26.7%、35.7%、48.7% 和 55.4%)而下降,但是各处理组间的 mRNA 表达水平则无显著差异[66]。Kirchner 等[67]的后续研究结果也验证了这一结论,使用高蛋白 P40

(56.3% 蛋白/17.2% 糖)和低蛋白 P10(27.1% 蛋白/29.8% 糖)饲料饲喂虹鳟 14 d 后,高蛋白组 GK 活性显著下降,而 mRNA 表达水平则无差异。在其他肉食性鱼,如黑点鲷(*Pagellus bogaraveo*)[68]中也存在此现象,饲喂 4 h 和 24 h 后,高蛋白组的 GK 活性显著低于低蛋白组。在杂食性鱼类尼罗罗非鱼中,高蛋白饲料饲喂后,同样导致 GK 活性下降[69]。

饲料中蛋白质含量增加对糖异生途径的影响主要是促进 FBPase 或 G6Pase 的表达。Kirchner 等[66]使用 4 个蛋白梯度饲料(26.7%、35.7%、48.7% 和 55.4%)饲喂虹鳟,结果表明 FBPase、G6Pase 活性及蛋白表达水平均随饲料蛋白浓度的增加而增加。Kirchner 等[67]后续针对虹鳟的实验,以及在其他鱼类如细点牙鲷(*Dentex dentex*)[70]、欧洲海鲈[54]的研究结果均表明 FBPase 的活性或表达水平与饲料中蛋白含量呈正相关。然而,饲料中蛋白含量对虹鳟[67]和欧洲海鲈[54]中的另一个糖异生关键酶 G6Pase 的活性或表达水平无显著影响。但在杂食性鱼类尼罗罗非鱼[69]及肉食性鱼类黑点鲷[68]中,高蛋白处理组 G6Pase 活性增强。

蛋白质与碳水化合物的比值对糖代谢的调节作用可能是通过 kinase B(Akt)/TOR 信号通路介导的。低蛋白饲料饲喂虹鳟,能够显著抑制这一信号通路[71]。高糖低蛋白饲料(35% 糖类/35% 蛋白质)饲喂虹鳟,膳食后肝脏 Akt 磷酸化减弱,验证了上述结论,但肌肉 Akt 含量与高蛋白组相比变化不大[72]。

蛋白质营养素在鱼类体内是以氨基酸的形式被吸收的,氨基酸对胰岛素分泌的刺激作用比葡萄糖更为强大。因此,鱼类摄食高蛋白饲料后,氨基酸可能在糖代谢调节中发挥关键作用。在哺乳动物中,亮氨酸具有调节糖代谢的作用。近期研究发现,用 L-亮氨酸处理虹鳟肝细胞,可使 G6Pase、PEPCK 和 GK 的表达水平升高,促进糖异生和糖酵解过程[73]。然而,L-亮氨酸与胰岛素共同处理虹鳟肝细胞后,G6Pase 表达量则下降[73]。精氨酸在哺乳动物中可通过激活多胺转换加强葡萄糖和脂质的氧化,Andersen 等[74]验证了精氨酸在虹鳟中同样具有这一功能,显示精氨酸在虹鳟能量代谢调节中发挥重要作用。

3 展望

关于肉食性鱼类糖代谢研究的资料非常丰富,而对杂食性、草食性鱼类的报道则相对较少。杂食性鱼类与肉食性鱼类在糖耐受力以及高糖对其糖异生和 GK 活性的作用等方面存在差异,这种差异的调控机制有待进一步阐明。另外,糖异生作用对鱼类外周高血糖的贡献力以及饲料脂肪对不同鱼类糖酵解代谢的作用机制尚不明确。针对营养素改变,机体胃肠激素作出何种调节,中枢神经系统作出怎样的响应?中枢葡萄糖感应器位于哪些神经元中,它们监测到葡萄糖水平的变化后,通过什么方式整合营养、内分泌等信号进而调节鱼类摄食,发放摄食调节信号?这些问题都有待深入研究。

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Progress in research on the regulation of glucose sensing and carbohydrate metabolism in fish

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Abstract: The utilization of carbohydrate in fish seems low compared with terrestrial animals, with intolerance to hyperglycemia, but the glucose regulation mechanism does exist in fish. In order to update the studies on glucosensing and carbohydrate metabolism in fish, and provide basic information for getting a better understanding about these physiological mechanisms, this review briefly introduced the progress of research on glucose sensing and its relationship with appetite, and the regulation of glucose metabolism in fish. The piscine glucose sensors were located in the different parts of the body, including central nervous system (CNS) and peripheral tissues. It is worth noting that both the glucose sensors and appestat are located in the hypothalamus, and they are also both regulated by some endocrine factors, such as leptin, ghrelin, cholecystokinin (CCK), neuropeptide Y (NPY), and so on. In mammals, the glucose sensing and appetite regulation were linked by AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signaling pathways. Although this link has not been identified yet in fish, it was found that the energy state or some endocrine factors of fish were highly related with AMPK or mTOR phosphorylation levels. Probably this link was presumably similar to that in mammalian. In addition, the blood glucose levels of fish were regulated by some endocrine factors such as insulin, glucagon-like peptide-1 (GLP-1), ghrelin, CCK, NPY, somatostatin (SS), etc. Besides, the glycometabolism and utilization in fish was aslo regulated by dietary nutrients including carbohydrate, lipid and protein. High-carbohydrate diet increased the activity and mRNA expression of glucose kinase (GK) in the liver of fish, and the glycolysis were also strengthened, even in the early development. Moreover, the hepatic gluconeogenesis in omnivorous species was inhibited by high-carbohydrate diet, but unaffected in carnivorous. Furthermore, High-fat diet promoted the glycolysis in some species, and the gluconeogenesis was also promoted both by high-fat and high-protein diets. However, there are still some questions that need further research. Finally, the development tendency and research hotspot in the carbohydrate metabolism of fish were discussed. For example, how the CNS integrate the nutritional, endocrine and other signals to regulate food intake in fish? what is the mechanism behind the differences between herbivorous, omnivorous and carnivorous species in glucose tolerance and the regulation of hepatic gluconeogenesis, etc.

Key words: fish; glycometabolism; nutritional regulation; endocrine regulation; glucose sensor; food intake

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