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·综述·

# 鱼类胰岛素、胰岛素受体和胰岛素受体底物的生物学特性及其对营养物质代谢的调控

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**摘要:** 为了深入解析胰岛素调控鱼类营养物质代谢的机制, 本文综述了鱼类胰岛素信号系统的3个重要成员(胰岛素、胰岛素受体以及胰岛素受体底物)的结构特征和表达规律, 以及胰岛素对营养物质(糖类、脂肪和蛋白质)代谢调控方面的研究进展。目前, 在鱼类, 虽然胰岛素信号传递系统的研究已取得了一定的进展, 但仍有需要重点加强的研究: ①鱼类不同亚型胰岛素、胰岛素受体和胰岛素受体底物基因的功能研究, 解析鱼类胰岛素信号传递系统的调控机制; ②加强胰岛素对鱼类营养物质代谢调控机制的研究, 揭示不同食性鱼类胰岛素信号传递系统调控功能的异同; ③深入开展鱼类胰岛素信号传导通路和调控机制的研究, 全面解析胰岛素调控鱼类营养物质代谢的分子机制。

**关键词:** 鱼类; 胰岛素; 信号传递系统; 生物学特征; 营养物质代谢调控

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胰岛素(insulin, Ins)是动物体内重要的内分泌激素, 能调控动物的生长、发育和代谢等各个方面, 具有广泛的生物学功能[1-2]。胰岛素信号传导的大致步骤: 胰岛素首先与细胞表面的胰岛素受体(insulin receptor, IR)结合, 激活其ß亚基的酪氨酸蛋白激酶(protein tyrosine kinase, PTK); PTK磷酸化胰岛素受体底物(insulin receptor substrate, IRS)而使之激活, 导致受体本身磷酸化和几种底物蛋白磷酸化; IRS作为一种船坞蛋白(docking protein), 与含肉瘤同源区段2(Src homology 2 domain, SH2)结构域的信号分子结合, 从而激活许多下游信号通路, 包括PI3K/Akt和mTOR等, 导致蛋白激酶和磷酸酶的级联反应, 从而发挥广泛的生物学功能[2-3]。鱼类胰岛素信号传递系统如图1所示。

目前, 在哺乳动物中已有大量关于胰岛素信号传递系统的研究报道。相比于哺乳动物, 有关鱼类胰岛素信号传递系统的研究较少。本文重点从鱼类胰岛素信号传递系统的3个重要成员, 即Ins、IR和IRS的结构特征, 及胰岛素对营养物质代谢的调控入手, 对最近几年的研究进展进行简要综述, 以期为今后深入研究鱼类胰岛素信号传递系统的功能及调控营养物质代谢的分子机制奠定基础。

## 1 胰岛素、胰岛素受体和胰岛素受体底物

胰岛素是胰腺分泌的内分泌激素, 胰岛素受体和胰岛素受体底物存在于靶组织上。胰岛素结合其受体并使之激活后, 胰岛素受体底物分子的酪氨酸残基磷酸化, 磷酸化的胰岛素受体底物通过不同途径激活下游的信号通路。胰岛素信号的有效传导决定了胰岛素功能的正常发挥。不同鱼类胰岛素、胰岛素受体和胰岛素受体底物的基因和蛋白质结构、合成和分泌等具有一定的相似性, 同时也存在差异。

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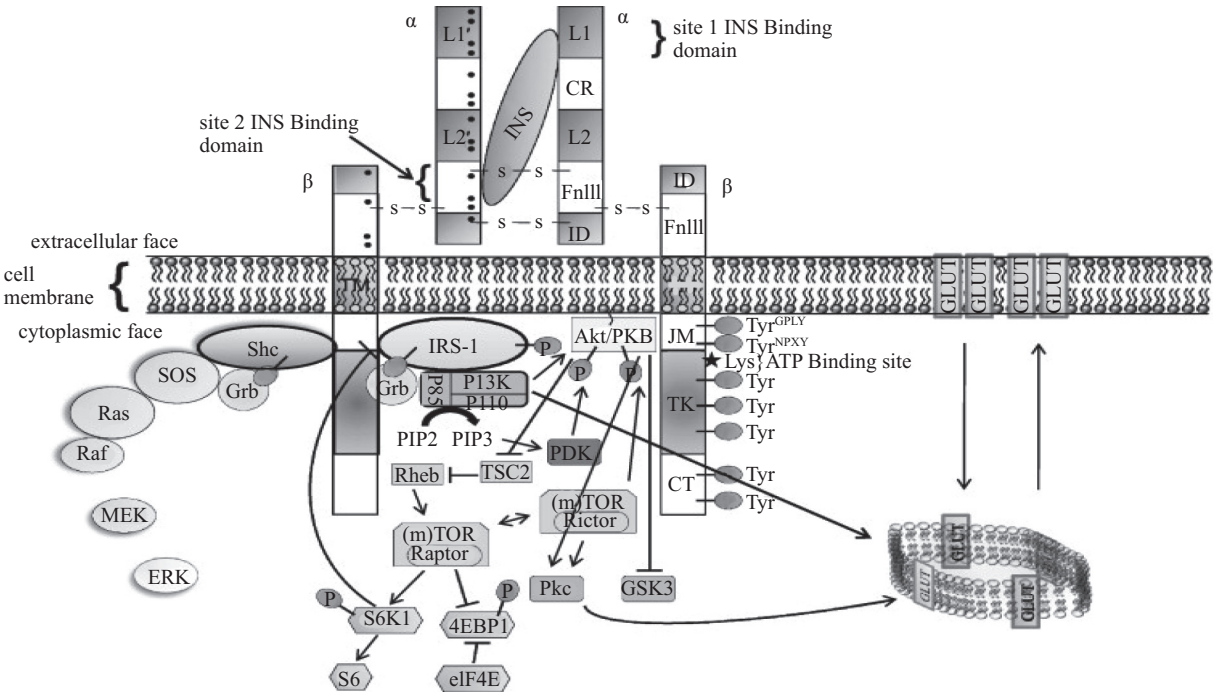


**图 1 鱼类胰岛素信号传递系统[2]**

**Fig. 1 Model of insulin signaling in fish[2]**

### 1.1 胰岛素、胰岛素受体和胰岛素受体底物的基因和蛋白结构

*胰岛素* 目前，大约有30多种鱼类的胰岛素基因被发现[2]。胰岛素基因的结构主要包括3个外显子和2个内含子。大部分鱼类如虹鳟(*Oncorhynchus mykiss*)等存在2种胰岛素基因[2]，而在大口黑鲈(*Micropterus salmoides*)只存在一种[4]。不同鱼类胰岛素的氨基酸序列相对保守，例如靳利娜等[4]指出大口黑鲈胰岛素基因与其它硬骨鱼类的同源性在75%~94%。胰岛素外显子编码的氨基酸个数在105~116，其结构由N端信号肽、B链、C肽和A链组成。前胰岛素原(pre-proinsulin)在胰岛ß细胞的高尔基体中脱去信号肽，形成含86个氨基酸残基的胰岛素原(proinsulin)，再经蛋白酶将C肽水解，得到A链和B链，成为有生物学活性的含51~58个氨基酸的胰岛素[5]。

*胰岛素受体* 胰岛素受体属于细胞膜糖蛋白，是胰岛素和靶细胞结合过程中必不可少的。胰岛素受体基因主要由21~22个外显子和20~21个内含子组成，其中1~12个外显子编码α亚基，13~22个外显子编码β亚基[2]。胰岛素受体在大部分鱼类只有2种亚型[2]，而在虹鳟中有4种IR亚型(IR1、IR2、IR3和IR4)[6]。不同鱼类胰岛素受体的直系同源性非常高，草鱼(*Ctenopharyngodon idella*) IRa与斑马鱼(*Danio rerio)* IRa的氨基酸同源性高达96.6%，与其他鱼类的同源性在80%左右；草鱼IRb与斑马鱼IRb同源性为85.30%，与其他鱼类同源性为70%[7]。与哺乳动物类似，鱼类胰岛素受体的氨基酸结构域包括N端信号肽、3个纤维连接蛋白以及酪氨酸磷酸化结构域[7]。

*胰岛素受体底物* 胰岛素受体底物是胰岛素信号通路中受体后水平的重要信号蛋白。IRS作为一种船坞蛋白，与含肉瘤同源区段2结构域的信号分子结合，激活下游的磷酯酰肌醇-3-激酶(PI3K)等信号通路。IRS能通过磷酸化、与其它蛋白发生相互作用和蛋白质修饰等在胰岛素信号传导过程中发挥重要作用[8]。

最近，Al-Salam等[9]综述了脊椎动物IRS基因家族的起源和分子进化。目前在脊椎动物中已发现胰岛素受体底物的4个亚型，即IRS1、IRS2、IRS3和IRS4。这四个成员具有相似的蛋白质结构特征，即保守的N-端pleckstrin homology (PH)和近N-端的phosphotyrosine binding (PTB) 结构域。PH和PTB结构域帮助胰岛素受体底物在细胞膜上进行定位并能和胰岛素受体结合[10-11]。胰岛素受体底物蛋白的C-端保守型较低[12-13]。Zhuo

等[14]指出黄颡鱼(*Pelteobagrus fulvidraco*) IRS1与人类和鼠的同源性为35%，与其他硬骨鱼类同源性在65%~75%；黄颡鱼IRS2与人类和鼠的同源性为57%，与其他硬骨鱼类同源性在60%~79%。然而，不同物种C端都有一些保守的酪氨酸激酶磷酸化位点，以便能和其它信号蛋白发生相互作用，但其磷酸化位点的个数和位置并不完全相同[12-14]。已有研究指出，IRS1上的Y99、Y1150、Y1151和Ser265、Ser302、Ser325和Ser358位点的磷酸化能增强胰岛素下游通路，而Ser307、Ser636和Ser639 位点磷酸化抑制胰岛素下游通路[15]。

### 1.2　胰岛素、胰岛素受体和胰岛素受体底物的表达和分泌

*胰岛素*　　与哺乳动物类似，胰腺也是鱼类胰岛素的主要合成和分泌部位，合成胰岛素的其他部位包括脑和脂肪组织等[2]。一般来说，鱼类血浆胰岛素的浓度为1~30 ng/mL，同时胰岛素的合成和分泌受饲料营养组成、鱼体的营养状态、激素和相关转录因子等的调控，并且呈现亚型和组织特异性[16-18]。

在饲料营养组成方面，许多研究表明，与摄食低水平碳水化合物的饲料相比，高碳水化合物饲料上调了血浆胰岛素的水平[19-22]，然而，饲料碳水化合物水平和血浆胰岛素这种一致性的变化趋势并非总是如此[23-24]。Enes等[22]推测这可能是由于饲料氨基酸掩盖了碳水化合物的促胰岛素分泌的效果，因为一些氨基酸，特别是精氨酸和赖氨酸，被认为是比碳水化合物更有效的促进胰岛素分泌的营养素[25]。

鱼体的营养状态被认为是影响胰岛素表达和分泌的重要因素之一。Caruso等[26]报道虹鳟禁食4周，胰腺Ins1、大脑Ins1和Ins2表达量降低；禁食6周，胰腺Ins1和Ins2以及大脑Ins1的表达量降低，而再投喂只能增加胰腺Ins2的表达。禁食也降低了鱼类血浆胰岛素的水平[27-28]，与这种激素促进合成代谢的特性相适应[29-30]。

鱼体胰岛素的合成和分泌也受到生长激素(growth hormone, GH)和生长激素抑制素(somatostatin，SS)的影响。Caruso等[18]发现注射SS抑制虹鳟胰腺Ins1和Ins2的表达，但上调脂肪组织Ins1和Ins2以及脑组织中Ins1的表达。此外，鱼类Ins的表达受其启动子区相关元件和转录因子的调控，C/EBP、IEF-1、PDX-1等转录因子会激活尼罗罗非鱼(*Oreochromis niloticus*)、虹鳟和斑马鱼胰岛素的转录[2]。运动[31]和应激[32]等因素也会影响鱼类胰岛素的分泌；运动降低了血浆胰岛素的水平[31]。

*胰岛素受体*　　与胰岛素的合成主要是在胰腺、脑和脂肪组织相比，胰岛素受体在各种组织中均有表达，表明胰岛素在体内起着广泛的作用。而且，胰岛素受体各种亚型在不同组织中呈现差异性表达，表明胰岛素在体内所起的作用具有组织特异性[2]。在虹鳟，IR1的表达主要在脾脏、肝脏、肾脏、肌肉和心脏，IR3的表达主要在肝脏、肾脏、脾脏和胰腺，而IR2和IR4在除脾脏外的所有组织中都高度表达[6]。在草鱼，IRa和IRb在脑、肝脏、脂肪组织、肾脏、肌肉、肠道和心脏中都有表达，其中IRa在后肠、心脏和肝脏中表达最高，IRb在后肠、肝脏和脑中表达较高[7]。

胰岛素受体的表达也受营养状态和激素等多种因素影响。Cai等[7]发现高碳水化合物饲料投喂显著增加草鱼肝脏IRb的表达。禁食上调了虹鳟肝脏IR3的表达，以及脂肪组织IR4的表达，但对肌肉胰岛素受体的表达没有显著影响[26]。而激素能影响胰岛素受体的表达，并且具有构型和组织特异性[18]。

*胰岛素受体底物*　　在鱼类，关于IRS表达和分泌的研究并不多。我们的研究指出黄颡鱼IRS1在肝脏、肌肉和脂肪组织中表达量较高，其次是肠道，而在卵巢、脾脏、肾脏、鳃和心脏中表达量相对较低；IRS2主要在肝脏、大脑、肌肉和卵巢中表达，其次在鳃、脂肪组织、脾脏、心脏和肾脏中表达[14]。胰岛素受体底物在各组织中的广泛表达表明这些组织均是胰岛素作用的潜在靶组织。胰岛素受体底物表达量的降低及磷酸化障碍都会影响胰岛素信号的有效传递而导致胰岛素抵抗[2]。

## 2　胰岛素对营养代谢的调控

胰岛素分泌及信号传导途径受鱼体营养状态的影响，反过来胰岛素信号传递系统又调控体内营养物质的代谢，包括糖、脂肪和蛋白质代谢。胰岛素被认为是最有力的促进合成代谢的重要激素，能促进糖类、脂肪和蛋白质的合成和储存，抑制它们降解[33]。因而，胰岛素对这些营养物质的代谢具有重要的调控作用(图2)。

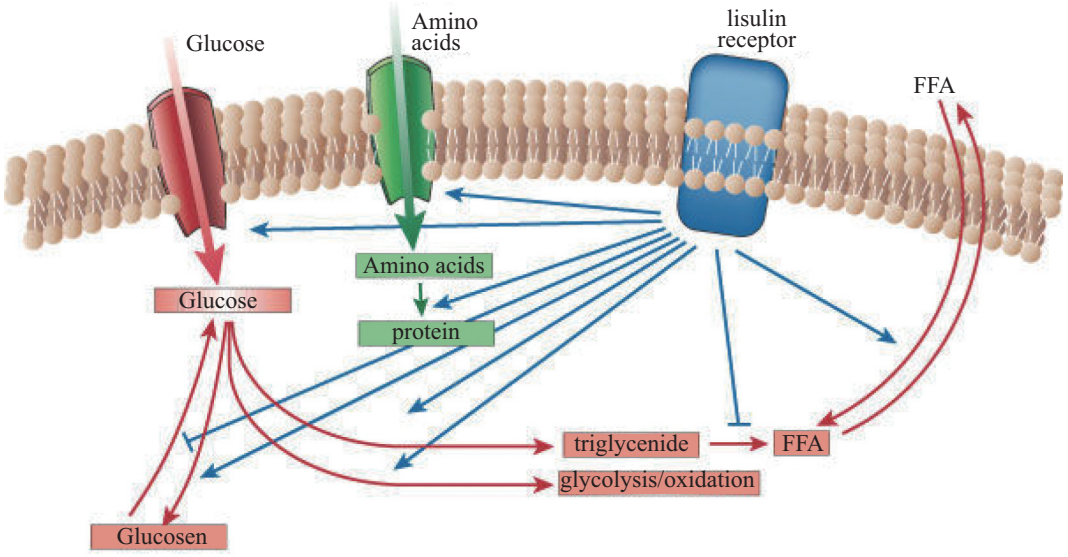


**图 2 胰岛素对营养物质代谢的调控[33]**

**Fig. 2 The regulation of metabolism by insulin[33]**

## 2.1 对糖代谢的调节

对血糖水平的调节 在哺乳动物，胰岛素是调控血糖稳态的主要激素。胰岛素能刺激餐后外周组织如肝脏、骨骼肌和脂肪组织对血糖的吸收，促进肝脏糖原的合成，抑制糖异生，因而维持机体血糖的稳态[34]。唐伟等[35]指出血糖的调节主要受胰岛素受体/IRS-1/PI3K/磷酸肌醇依赖的蛋白激酶/蛋白激酶B/葡萄糖转移因子4信号途径的影响。

与哺乳动物相比，鱼类对葡萄糖的耐受能力较低，胰岛素分泌对血糖的反应也较哺乳动物缓慢。鱼类血浆胰岛素含量在葡萄糖摄取后2~3 h才达到最高水平[36-37]。鱼类胰岛素的分泌滞后于鱼类对糖类的吸收速度，被认为是鱼类吸收的葡萄糖不能被很好利用的关键因素[38]。进一步的研究指出，鱼类胰岛素对血糖反应的滞后性与胰岛生长抑素分泌细胞对血液葡萄糖的变化比胰岛素分泌细胞更敏感有关[39-40]。此外，在鱼类，虽然葡萄糖可以刺激胰岛素的释放，但是氨基酸被认为是比葡萄糖更有力的刺激胰岛素分泌的物质[16]。尽管如此，一些研究指出，注射外源胰岛素后，会降低鱼类血浆葡萄糖浓度[41-42]。

对糖代谢的调节 鱼类的糖代谢主要包括糖酵解、糖异生和糖转运等过程。为了探讨胰岛素对鱼类糖代谢的调控机制，很多糖酵解、糖异生和转运途径的关键酶和蛋白被广泛研究，但是研究的结果往往不一致。例如，在虹鳟，研究指出胰岛素能通过调控蛋白激酶(protein kinase, PKB)的表达抑制糖分解相关酶如糖原磷酸化酶(glycogen phosphorylase, GP)、PEPCK和G6Pase的活性和mRNA的表达[43-44]。然而，Polakof等[45]发现胰岛素处理对虹鳟肝脏G6Pase的mRNA表达和活性影响不显著，但是上调了PEPCK的表达和活性。进一步的研究指出，胰岛素对糖代谢的影响具有组织特异性。Polakof等[45]指出胰岛素处理对虹鳟肌肉HK活性及其基因表达，以及GLUT4基因表达水平的影响都不显著，也没有显著影响脂肪组织中GLUT4和HK的表达，以及HK酶的活性，对肌肉和脂肪组织中的糖原水平影响不显著，但是增加了虹鳟肝脏糖原的水平。Deck等[42]发现胰岛素上调太平洋白斑角鲨(*Squalus suckleyi*)肌肉糖原合成酶激酶(glycogen synthase kinase, GSK)的表达，而不影响肝脏中的表达。此外，胰岛素对鱼类糖代谢调节作用还受其他因素的影响。例如，饲料中过高的氨基酸会降低胰岛素对虹鳟肝细胞糖代谢的调节作用[46]。

## 2.2 对脂肪代谢的调控

鱼类的脂肪代谢 脂肪是鱼类的重要能量来源。机体内脂肪代谢过程包括脂肪合成、分解和转运。脂肪的合成与分解代谢受机体内一系列酶促反应的调控，例如与脂肪合成有关的酶有脂肪酸合成酶(fatty acid synthase, FAS)、乙酰辅酶A羧化酶(acetyl-CoA carboxylase, ACC)、6-

磷酸葡萄糖脱氢酶(6-Phosphogluconate dehydrogenase, 6PGD)、葡萄糖6磷酸脱氢酶(glucose 6-phosphate dehydrogenase, G6PD)、苹果酸酶(ME)和异柠檬酸脱氢酶(ICDH)；调控脂肪分解的关键酶主要有激素敏感脂酶(hormone-sensitive triglyceride lipase, HSL)、脂肪甘油三酯脂肪酶(ATGL)、肉碱棕榈酰转移酶I(CPT I)和3-羟酰辅酶A脱氢酶(3-hydroxyacyl-CoA dehydrogenase, HOAD)[47-51]。脂肪转运相关蛋白有脂蛋白脂酶(lipoprtein lipase, LPL)、脂肪酸转运蛋白(fatty acid transport protein, FATP)、脂肪酸结合蛋白(fatty acid binding protein, FBP)和脂肪酸移位酶(fatty acid translocase, CD36)[50, 52]。脂肪的合成与分解也受体内很多关键转录因子的调控，如胆固醇结合蛋白调节元件(sterol regulatory element binding protein 1, SREBP1)、过氧化物酶增殖体(peroxisome proliferators-activated receptors PPARα、PPARß和PPARγ)、肝核X受体(liver X receptor, LXR)和肝脏维甲酸X受体(retinoid X receptor, RXR)[47-49, 53-55]。此外，内质网应激[56-57]、自噬[58]和凋亡[59]也参与了鱼类脂肪代谢的调控。

胰岛素对鱼类脂肪代谢的调控　　在哺乳动物的研究表明，胰岛素能刺激脂肪酸和甘油三酯的合成，提高肝脏甘油三酯的沉积，同时伴随着脂肪酸ß-氧化的抑制[60]。然而，在鱼类，有关胰岛素对鱼类脂肪代谢的调控研究十分缺乏，有限的研究指出，胰岛素能通过调控脂肪代谢关键酶、转运蛋白和转录因子的活性和表达来调控鱼类脂肪代谢[45, 54-55, 61]。Polakof等[62]发现，在摄食高碳水化合物的虹鳟，胰岛素能刺激肝脏的生脂能力，这种生脂能力的上调与ACC和FAS的活性、蛋白和mRNA表达的增加是一致的。Polakof等[45]指出，胰岛素处理对虹鳟肝脏FAS和G6PD的基因表达以及G6PD的酶活性影响不显著，但是上调了FAS酶的活性，以及SREBP-1c的表达水平；在脂肪组织，胰岛素处理上调了脂肪组织FAS的基因表达和酶活，降低了G6PD和SREBP-1c的表达，但是对G6PD酶活性没有显著影响。胰岛素促进鱼类外周组织游离脂肪酸和胆固醇的摄取，伴随着血浆游离脂肪酸含量降低，肝脏和肌肉脂肪合成增加、脂肪分解降低等特征，而且胰岛素对脂类代谢相关基因和酶表达的影响具有时间、浓度、组织和种类特异性[63]。本研究表明，不同胰岛素水平对黄颡鱼肝细胞脂代谢相关酶的活性和基因的表达存在差异。离体条件下，胰岛素显著增加黄颡鱼肝细胞FAS、G6PD和6PGD的酶活和mRNA的表达，并且100 nmol/L胰岛素孵育48 h变化最为显著；但对CPT1的活性没有影响[64-65]。Sanchez-Gurmaches等[66]报道胰岛素注射降低大西洋鲑(*Salmo salar*)红肌和白肌FATP1和CD36的表达，增加脂肪组织中FATP1和CD36的表达。

此外，胰岛素对一些脂肪代谢关键酶和转录因子的调控具有亚型特异性。Sun等[67]研究发现胰岛素降低草鱼肝细胞HSLb的表达，但是对HSLa的表达没有显著影响。在我们实验室，Wu等[68]报道胰岛素孵育矛尾复虾虎鱼(*Synechogobius hasta*)肝细胞24 h，抑制CPT 1α1a和CPT 1α2a的表达，而不影响CPT 1b和CPT 1α2b1a的表达；在黄颡鱼，胰岛素下调肝脏PPARα的表达，上调PPARγ的表达[69-70]；胰岛素促进黄颡鱼肝细胞LXRa1的表达、降低RXRgb的表达，而不影响LXRa2和RXRga的表达[54-55]。胰岛素对脂肪代谢的调控被一些核受体介导，如PPARs、LXR和RXR等；胰岛素通过调节这些转录因子的表达进而调控LPL、HSL等酶的活性和表达[53]。

### 2.3　对蛋白质代谢的调节

胰岛素也在鱼体蛋白质代谢方面起着重要的调控作用，一方面促进细胞对氨基酸的摄取和蛋白质的合成，另一方面抑制蛋白质的分解，因而有利于鱼类的生长[71]，相关研究报道已见于虹鳟[72-73]、金头鲷(*Sparus aurata*)[74]、斑马鱼[75]和黄颡鱼[76]等鱼类，但其调控的分子机制不清楚。Cleveland等[72]的研究表明，1 μmol/L胰岛素处理虹鳟肌细胞，导致蛋白质合成增加了13%，蛋白质分解下降了17%；胰岛素处理也刺激了转录因子FOXO1和FOXO4的磷酸化，而这种磷酸化能够被PI3K激酶抑制剂Wortmannin阻断，表明PI3K/Akt通路介导了胰岛素抑制蛋白质分解的途径。胰岛素和IGF-1处理虹鳟骨骼肌细胞，导致MAPK/ERK、Akt/PKB和PI3K通路的激活[77]，静脉注射胰岛素也刺激了虹鳟肝脏Akt/PKB通路的激活，因而对蛋白质代谢起着调控作用[43]。

在哺乳动物的研究表明，mTOR途径是参与调控细胞蛋白质代谢的主要途径[78]。胰岛素与靶器官胰岛素受体结合，活化的胰岛素受体与胰岛素受体底物结合，从而激活磷脂酰肌醇3-激酶

(PI3K)，进一步激活的蛋白激酶B (PKB/AKT)通过抑制TSC1/2复合物激活mTOR的上游因子Rheb，从而激活mTOR通路[79]。另外，JAK/STAT信号通路也在胰岛素调控蛋白质代谢中起着重要作用。我们的研究表明胰岛素能通过PI3K信号通路刺激黄颡鱼肝脏蛋白质的合成和肝脏蛋白含量的增加；在7种PI3K构型中，PI3KCb和PI3KC2a是对胰岛素最敏感的2种构型[76]。Seiliez等[73]指出，胰岛素注射6 h后导致虹鳟肌肉与蛋白质合成有关的关键基因IRS1、TOR和4E-BP1的磷酸化，这部分解释了胰岛素有利于蛋白质合成的分子机制。

## 3 总结与展望

胰岛素调控鱼类的生长、发育和营养代谢等功能。目前，虽然在鱼类中，胰岛素的研究已取得了一定的进展[2, 80]，但仍有很多重要的科学问题尚未解决，重点需要加强以下几方面的研究：①鱼类不同亚型胰岛素、胰岛素受体和胰岛素受体底物基因的功能研究，解析鱼类胰岛素信号传递系统的调控机制；②加强胰岛素对鱼类营养物质代谢调控机制的研究，揭示不同食性鱼类胰岛素信号传递系统调控功能的异同；③深入开展鱼类胰岛素信号传导通路和调控机制的研究，全面解析胰岛素调控鱼类营养物质代谢的分子机制。

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# Biological characteristics of three key members of insulin signaling systems and their functions in regulation of nutrient metabolism in fish: A review

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**Abstract**: Insulin is a member of peptide family and plays important roles in the regulation of nutrition metabolism in fish. To decipher the mechanism of insulin regulating nutrient metabolism, the present paper reviewed the progress involved in the structure and expression of three members (insulin, insulin receptor and insulin receptor substrate) of insulin signaling pathways, and the regulation of insulin in carbohydrate, lipid and protein metabolism. At present, although some progress has been made in study of the insulin signaling pathway, many basic questions remain unknown and further investigations are needed: (1) studies involved in the functions of different isoforms of insulin, insulin receptor and insulin receptor substrate; (2) molecular mechanism of insulin regulating nutrient metabolism; (3) investigation into insulin signaling pathway and regulatory mechanism.

**Key words**: fish; insulin; signaling pathway; biological characteristics; nutrient metabolism

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