内分泌调控与代谢疾病 DOI：10.13406/j.cnki.cyxb.003810

胰岛素抵抗状态下胰高糖素对肝脏代谢的调节机制

于静静，姚振宇，周象宁，叶凌希，魏骏彤，薄　涛
（内分泌糖脂代谢与脑老化教育部重点实验室/山东第一医科大学附属省立医院内分泌代谢病科，济南　250021）

【摘　要】胰高糖素和胰岛素是血糖的主要调节因子，共同维持机体能量代谢稳态，但是二者相互调节和影响的内在机制复杂且不明确。肝脏是胰岛素和胰高糖素共同的重要靶器官，在维持葡萄糖和脂质稳态中发挥重要作用。胰岛素抵抗常伴随肝脏糖脂代谢异常，进而可能影响肝脏胰高糖素的功能活性。肝脏和胰腺之间存在胰高糖素调节相关的反馈回路，称为“肝-α细胞轴”，可能对于理解胰高糖素在胰岛素抵抗状态下的代谢作用至关重要。除了调节葡萄糖稳态外，胰高糖素生理作用已扩展至脂质和氨基酸代谢。因此，胰高糖素代谢调节异常可能进一步导致机体糖、脂以及氨基酸代谢稳态的失衡。在本综述，主要概述了在生理以及胰岛素抵抗状态下，胰高糖素在肝脏葡萄糖稳态、脂质代谢和氨基酸代谢中的调节机制。

【关键词】胰岛素抵抗；高胰高糖素血症；肝脏；糖脂代谢；氨基酸
【中图分类号】R335+.6　　【文献标志码】A

Mechanism of glucagon regulating hepatic metabolism in the state of insulin resistance

Yu Jingjing, Yao Zhenyu, Zhou Xiangning, Ye Lingxi, Wei Juntong, Bo Tao
(*Key Laboratory of Endocrine Glucose & Lipids Metabolism and Brain Aging, Ministry of Education, Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong First Medical University*)

【**Abstract**】Glucagon and insulin are the main regulatory factors for blood glucose and jointly maintain the homeostasis of energy metabolism in the body, but the internal mechanism of the mutual regulation and influence between them remains complex and unclear. The liver is one of the key target organs for both insulin and glucagon, playing a crucial role in maintaining the homeostasis of glucose and lipid metabolism. Insulin resistance is often accompanied by abnormal glucose and lipid metabolism in the liver, which may affect the functional activity of glucagon in the liver. There is a glucagon-related feedback loop between the liver and the pancreas, known as the “liver-α-cell axis”, which may play a critical role in understanding the metabolic effect of glucagon in the state of insulin resistance. In addition to the regulation of glucose homeostasis, the physiological action of glucagon has been extended to lipid and amino acid metabolism. Therefore, abnormal regulation of glucagon metabolism may further lead to the imbalance of glucose, lipid, and amino acid metabolism. This article briefly reviews the regulatory mechanism of glucagon in liver glucose homeostasis, lipid metabolism, and amino acid metabolism in physiological condition and the state of insulin resistance.

【**Key words**】insulin resistance; hyperglucagonemia; liver; glucose and lipid metabolism; amino acid

1922年，研究者从胰腺中发现了1种与胰岛素的降血糖作用相反的胰腺因子，并将该因子被命名为“葡萄糖激动剂”，或简称胰高糖素（glucagon，GCG）[1]。GCG是一种由29个氨基酸组成的肽激素，由胰高糖素原在胰腺α细胞中通过激素原转化酶2（prohormone convertase，PC-2）加工而成[2-3]。GCG通过细胞膜上的GCG受体（glucagon receptor，GCGR）发挥作用。GCGR是1个由485个氨基酸组成的7次跨膜蛋白受体，属于G蛋白偶联受体（G-protein coupled receptor，GPCR）家族成员[4]。GCG通过激活其受体调节多种途径[5]，例如减少食物摄入、增加能量消耗、增加心率、肾电解质排泄以及胃排空和蠕动。肝脏是糖、脂、氨基酸代谢的关键枢纽，也是维持体内代谢稳态的重要靶器官。生理条件下，GCG能够在肝脏中调节葡萄糖、脂质和氨基酸代谢。GCG能够通过刺激糖原分解和糖异生，同时抑制糖酵解和糖原合成增加血糖水平，与胰岛素共同维持体内葡萄糖稳态；GCG还能参与肝脏脂质代谢的调节，例如，其可以上调脂肪酸（fatty acid，FA）β氧化和抑制新生FA合成（*de novo* lipogenesis，DNL）等途径[6-8]；此外，大量研究表明，GCG可以刺激尿素生成调节肝细胞中的氨基酸代谢[9]。这表明GCG是体内代谢稳态的重要调节因子。最近，胰腺α细胞和肝细胞中的胰岛

作者介绍：于静静，Email：1480316803@qq.com，
研究方向：代谢功能障碍相关脂肪性肝病的机制研究。
通信作者：薄　涛，Email：botao666666@126.com。
基金项目：国家自然科学基金资助项目（编号：81770788、82470888）。
优先出版：https://link.cnki.net/urlid/50.1046.R.20250319.1614.006
（2025-03-20）

素抵抗（insulin resistance，IR）被认为能够影响GCG的分泌与受体表达，进而影响GCG的稳态和功能。GCG功能失调是糖尿病病理学和代谢疾病的关键因素之一。2012年，Unger RH和Cherrington AD[10]提出“GCG中心假说”，相比胰岛素缺乏，过量的GCG是2型糖尿病（type 2 diabetes mellitus，T2DM）发生的必要条件。这与之前认为的T2DM仅是“以胰岛素为中心的疾病”的观点进行了补充，表明了GCG在T2DM的发病机制中至关重要[10]。在本综述中，将简要介绍在IR状态下，GCG的分泌调节以及其对肝脏葡萄糖、脂质和氨基酸的调节机制。这将有助于理解GCG在健康和疾病中的生物学特性。

1 胰高糖素分泌的调节

哺乳动物的胰岛由α、β、δ、γ和ε等细胞类型组成，其中，GCG由胰腺α细胞分泌，而胰腺β细胞分泌胰岛素，胰腺δ细胞分泌生长抑素（somatostatin）[11]。胰岛的β和δ细胞与α细胞的相互调节可能会影响GCG的释放。生长抑素抑制GCG的分泌作用已明确。生长抑素通过激活分布在α细胞上的生长抑素受体（somatostatin receptor，SSTR）抑制腺苷酸环化酶（adenylyl cyclase，AC）活性，从而引起细胞内环状腺苷一磷酸（cyclic adenosine monophosphate，cAMP）水平降低并抑制蛋白激酶A（protein kinase A，PKA）活性，最终抑制GCG分泌[12]。胰岛素抑制GCG分泌的作用较复杂。这种作用可能直接通过α细胞中的胰岛素受体（insulin receptor，InsR）介导，也可能间接通过胰腺δ细胞分泌生长抑素的增加介导[13]。胰岛素与α细胞的InsR结合，抑制细胞内cAMP-PKA通路，并减少α细胞中的GCG分泌[14]。此外，一些报告显示，磷酸肌醇3-激酶（phosphoinositide 3-kinase，PI3K）的信号转导被激活后，K_{ATP}（ATP敏感的钾通道）活性的减少抑制GCG的分泌[15]。此外，InsR下游蛋白激酶B（protein kinase B，AKT）参与γ-氨基丁酸（gamma-aminobutyric acid，GABA）受体向细胞膜的易位也抑制GCG的分泌[16]。除了旁分泌因子的调节外，营养物质也影响GCG分泌。葡萄糖通过直接调节cAMP来控制GCG的分泌[17]，或者通过间接的生长抑素、胰岛素途径[18,12]。FA对GCG分泌的调节仍存在争议。FA刺激GCG分泌调节似乎取决于FA特性以及FA来源是外源性还是内源性[19]。摄入中长链FA的个体在40 min后血浆GCG浓度增加[20]，而摄入短链FA则没有增加[21]。体内研究发现，在FA浓度增加时会抑制GCG的分泌[22]，而在分离的α细胞水平上，FA刺激能够增加α细胞的GCG分泌[23]。FA可能通过抑制生长抑素从δ细胞中释放，从而可能介导GCG分泌增加[24]。另外，富含蛋白质的膳食刺激血浆GCG水平的增加[25]。研究表明，氨基酸通过氨基酸转运体触发GCG的释放，并在细胞内积累后改变细胞膜电位[26]。据报道α细胞InsR特异性缺失小鼠表现出高血糖和高胰高糖素血症[27]。在T2DM状态下，胰腺α细胞中的IR状态会损伤胰岛素信号活性，导致GCG的分泌增多，进而可能影响肝脏GCG功能失调[28]。

GCG是一种重要的葡萄糖调节激素，其能够调节肝脏葡萄糖的产生，升高的葡萄糖水平能够反馈调节GCG的分泌[10]。除了葡萄糖调节作用外，GCG还能响应氨基酸调节，通过促进氨基酸代谢和尿素生成，从而降低血浆氨基酸水平。这表明在肝脏和胰腺α细胞之间存在1个反馈回路，称为“肝-α细胞轴”[29-30]。此外，肝-α细胞轴可能还调节肝脏脂质代谢[31]。GCG可能也响应高水平的FA调节，通过增加肝脏β氧化，减少DNL，从而降低循环中FA的浓度。肝-α细胞轴反映了GCG对葡萄糖、氨基酸和脂质代谢的重要性。

IR被认为是胰岛素靶器官（主要是肝脏、肌肉和脂肪组织）对胰岛素信号的敏感性降低，导致胰岛素相对分泌过多[32]。IR状态下，GCG的肝脏作用可能部分受损，也是导致糖、脂、氨基酸稳态失衡的重要原因之一。因此，肝脏糖、脂、氨基酸代谢调节的紊乱与IR密切相关。IR是代谢综合征和代谢功能障碍相关脂肪性肝病（metabolic dysfunction-associated steatotic liver disease，MASLD）的发病机制之一。IR与FA增加和脂质的过量沉积（如肝脏）有关，这会进一步促进炎症和内质网应激。另外，这又加重并维持IR状态，构成恶性循环[33]。这表明肝脏脂肪积累与IR之间存在潜在联系。最近报告指出作为肝脂肪变性的危险因素之一，IR可能是肝脏GCG信号转导受损的致病因素[34]。据报道IR与肝脏脂肪变性共同作用，可能导致肝脏GCG信号转导受损[35-36]。Charbonneau A等[37]指出大鼠高脂肪喂养诱导的肝脂质浸润干扰了GCG对脂质和葡萄糖产生的作用。这可能是脂肪变性可能通过蛋白激酶C-α（protein kinase C alpha，PKC alpha）降低GCGR表达[38]。因此，IR可能与肝脂肪变性共同作用，导致GCG对肝脏葡萄糖、脂质和氨基酸的调节机制受损。GCG分泌的调节维持肝脏糖脂、氨基酸代谢稳态。另外，在IR、MASLD等状态下，肝脏糖、脂、氨基酸代谢的稳态失衡又与GCG分泌的调节密切联系。接下来，将要概述GCG对肝脏糖、脂、氨基酸代谢的调节，以及肝脏糖、脂、氨基酸稳态的失衡对GCG的影响。

2 生理及胰岛素抵抗状态胰高糖素对肝脏葡萄糖代谢的调节

GCG在体内葡萄糖代谢中起着关键作用。在生理状态下，GCG的作用是升高血浆葡萄糖，有助于在空腹状态下维持葡萄糖稳态[39]。GCG在低血糖期间分泌增加，在高血糖期间受到抑制[40]。在低血糖情况下，GCG会释放到血液中，通过增加肝糖输出来提高血浆葡萄糖水平[41]。GCG升糖的这一方面已被用于治疗低血糖症[42-43]。在运动期间，GCG是为肌肉提供充足循环葡萄糖的关键因素。因此，GCG是在空腹、运动和低血糖期间的主要调节剂[40]。遗传性GCGR缺乏症和靶向GCG的中和抗体足以降低血糖[44-46]。研究表明，在链脲佐菌素诱导的β细胞破坏的小鼠中，消除GCGR信号转导可以逆转高血糖症[47]。这些结果支持GCG在体内葡萄糖稳态中的重要作用。此外，有报告指出GCG是体内葡萄糖稳态的敏感和及时调节剂。小剂量的GCG，足以诱导葡萄糖明显升高[48]。GCG以脉冲形式从胰岛分泌[49]，导致GCG对肝脏葡萄糖产生的作用在几分钟内发生并迅速失活[50]。这在剧烈运动的低血糖急性发作期间可能特别重要。接下来阐述GCG对肝脏葡萄糖代谢调节机制（图1A）：GCG与肝细

胞上的GCGR结合，导致已知至少有两类G蛋白（由α、β、γ异源三聚体亚基构成的GTP结合蛋白），Gsα和Gq的转导激活，Gs的α亚基激活AC，引起细胞内cAMP水平升高，进而激活PKA。PKA磷酸化并激活糖异生途径相关酶，包括磷酸烯醇丙酮酸羧激酶（phosphoenolpyruvate carboxykinase，PEPCK）和葡萄糖-6-磷酸酶（glucose-6-phosphatase，G-6-Pase），上调糖异生和糖原分解。此外，活化的PKA导致糖原磷酸化酶激酶（glycogen phosphorylase kinase，GPK）的磷酸化和GP的激活，上调糖原分解。而Gq通路导致磷脂酶C（phospholipase C，PLC）的激活，催化4，5-二磷酸脂酰肌醇（phosphatidy linositol 4，5-biphosphate，PIP2）生成肌醇1，4，5-三磷酸（inositol 1，4，5-trisphosphate，IP3），随后释放细胞内钙离子（Ca^{2+}）[51-52]。细胞内Ca^{2+}的水平通过P38激酶抑制GCG诱导的糖酵解。Gs诱导的PKA激活或Gq对Ca^{2+}/钙调蛋白依赖性蛋白激酶（calmodulin-dependent protein kinase，CAMK）的效应，导致cAMP反应元件结合蛋白（cAMP response element binding protein，CREB）磷酸化，进一步影响PEPCK和G-6-Pase。此外，GCG通过抑制糖原合酶（glycogen synthase，GS）的活性来减少糖原的产生。因此，在肝脏中，GCG通过GCGR信号转导刺激糖原分解和糖异生，同时抑制糖酵解和糖原合成来增加肝脏葡萄糖的生成[53-54]。

传统理论认为，GCG在低葡萄糖条件下分泌最高，而高葡萄糖抑制GCG分泌。然而，IR状态下，尽管存在肝脏葡萄糖生成增加[55]，但仍会出现反常的GCG分泌过多[56-57]。α细胞中葡萄糖调节的GCG分泌，可能部分解释了IR状态下GCG分泌过多的矛盾性。胰腺α细胞通过葡萄糖转运蛋白1（glucose transporter type 1，GLUT1）、钠葡萄糖协同转运蛋白（sodium-glucose cotransporters，SGLT1）摄取葡萄糖，并且三磷酸腺苷（adenosine triphosphate，ATP）/二磷酸腺苷（adenosine diphosphate，ADP）比率伴随糖酵解和TCA循环期间产生的ATP而增加[58-59]。当发生高血糖时，ATP/ADP比率升高，使K_{ATP}通道打开，细胞膜去极化导致钠离子（Na^+）通道失活。这种失活阻碍了电压依赖性P/Q型Ca^{2+}通道，Ca^{2+}内流的减少抑制GCG分泌[60-61]。此外，葡萄糖引发的旁分泌信号，特别是δ细胞分泌的生长抑素以及β细胞分泌的胰岛素，均抑制GCG的分泌[18]。研究指出葡萄糖对GCG分泌的抑制很大一部分是由旁分泌因子间接介导的，而只有一小部分可能是由直接的葡萄糖感应[62]。当低血糖以及细胞内ATP水平较低时，K_{ATP}通道部分打开，细胞膜去极化导致Na^+从Na^+通道流入。随后，Ca^{2+}通过电压依赖性Ca^{2+}通道流入，触发GCG释放[60]。另外，有报道指出低血糖通过直接升高cAMP浓度来刺激GCG的分泌，与Ca^{2+}信号传导无关[17]。另外，有报告称胰腺α细胞特异性敲除InsR的小鼠，餐后葡萄糖和血浆GCG水平升高[63]。这表明胰腺α细胞胰岛素信号受损也可以导致高胰高糖素血症，进而导致高血糖。因此，在T2DM患者中，高胰高糖素血症可能不仅是T2DM的症状之一，也是导致高血糖的原因之一。另外，有报告指出高胰高糖素血症可能反映了肝-α细胞之间的生理反馈回路的紊乱，而不是α细胞对葡萄糖的敏感功能失调[34]。在肥胖或MASLD患者中，高胰高糖素血症的原因是由于IR可能导致GCG信号转导受损，进而产生的高水平氨基酸[64-65]。值得考虑的是，高胰高糖素血症可能会加重肝细胞的GCG抵抗，其中持续升高的肝葡萄糖输出对T2DM的进展起到重要作用[66]。总的来说，IR状态下，α细胞中的IR或高氨基酸血症均导致高胰高糖素血症。高胰高糖素血症又会加重血糖升高，形成恶性循环，从而导致体内葡萄糖稳态失衡。然而，IR状态下，胰高血糖对肝脏葡萄糖代谢涉及的分子调节机制在很大程度上尚未被详细阐述（图1B）。

3 生理及胰岛素抵抗状态胰高糖素对肝脏脂质的调节

GCGR主要在肝脏表达[31,54]，其能够介导GCG调节肝脏脂质代谢的多种途径[67]。GCG刺激FA的β氧化，并减少DNL和极低密度脂蛋白（very-low-density lipoprotein，VLDL）释放，降低肝脏甘油三酯（triglyceride，TG）含量[68]。此外，GCG还可以通过增加肝细胞中的低密度脂蛋白受体（low density lipoprotein receptor，LDLR）活性和胆固醇摄取来增强LDL颗粒从血液中的清除[69-70]。接下来阐述GCG对肝脏脂质代谢调节机制（图1A）：首先，当GCG与其在肝细胞上的GCGR结合时，导致cAMP-PKA-CREB信号转导激活，进而导致肉碱酰基转移酶（carnitine palmitoyltransferase-1，CPT-1）的转录增加，这使得FA能够转化为酰基肉碱，从而激活β氧化。在β氧化过程中，FA降解为乙酰辅酶A（acetyl-coenzyme A，acetyl-CoA），进入三羧酸（tricarboxylic acid，TCA）循环。因此，肝脏GCG信号传导增加FA分解代谢，抑制糖酵解，并促进TCA循环。其次，当GCG与其在肝细胞上的受体结合时，细胞内cAMP的增加会激活PKA，PKA磷酸化导致乙酰辅酶A羧化酶（acetyl-CoA carboxylase，ACC）失活，从而抑制丙二酰辅酶A的形成。丙二酰辅酶A的水平降低会导致FA转移到β氧化，而不是重新酯化为TG。通常，当FA与结合甘油时，它们以TG的形式储存起来，并以VLDL的形式从肝细胞释放到循环中。因此，GCG诱导FA走向β氧化并减少DNL，从而减少VLDL释放。GCG信号转导还可能会增加一磷酸腺苷（adenosine monophosphate，AMP）水平，从而上调AMP活化激酶（AMP-activated protein kinase，AMPK）活性。AMPK依赖性方式激活p38丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase，p38 MAPK），导致过氧化物酶体增殖物激活受体α（peroxisome proliferator activated receptor α，PPARα）与热休克蛋白90（heat shock protein-90，HSP90）解离并转位至细胞核以激活靶基因的转录[71]，从而诱导β氧化相关基因的转录，如CPT-1和乙酰辅酶A氧化酶。总之，GCG作为脂质稳态的有效调节剂，主要通过刺激FA的β氧化，减少DNL和VLDL释放来发挥作用。

IR引起肝脏DNL增加，FA氧化降低，以及VLDL的过量产生[72-73]，导致肝细胞脂质过量沉积。研究表明肝脂质浸润能够损伤GCG敏感性，从而导致肝内GCG抵抗[74]。GCG在肝脏不同区域的差异调节可能部分解释了肝脏脂代谢对GCG调节的抵抗。在肝小叶中，靠近门静脉和肝动脉分支的区域称为门静脉周围（periportal，PP）区域，而围绕中央静脉的区域称为中央静脉周围（perivenous，PV）区域。PP区域氧浓度、营养物质浓度较高，而PV区域暴露于富含二氧化碳

的血液以及新陈代谢的其他产物中（氧浓度低）[75]。肝脏代谢的功能分区意味着不同区域的肝实质细胞代谢途径的活跃程度不同。研究表明FA β氧化和胆固醇代谢在PP区域更为活跃，而PV区域肝细胞的DNL相对活跃[76-77]。除脂代谢相关途径外，PP区域还主要发生糖异生、尿素生成，而PV区域还主要介导糖原分解、糖酵解等过程[78-79]。循环中的FA可能主要由PP区域摄取[80]。FA代谢物的积累可能导致PP区域的IR，而PV区域可能摄取较少FA，保持相对的胰岛素敏感性[81]。研究表明GCG可能与Wnt/β-catenin信号通路相互作用，调节肝脏相关代谢基因表达的分区模式[82]。此外，据报道，MASLD患者存在GCG对肝脏脂质代谢抵抗的迹象[83]。因此，GCG对肝脏脂质代谢可能受IR和GCG抵抗的协同作用，最终导致肝脏β氧化降低，DNL增加，从而导致肝脏脂质沉积增加，循环中FA水平增加[84]。因此，肝脏脂肪含量的增加可能不仅是肝细胞中GCG抵抗的原因，也是肝细胞中GCG抵抗的结果。肝脏GCGR敲除的小鼠观察到脂肪生成相关基因如甾醇调节元件结合转录因1（sterol regulatory elements bind transcription factor 1，Srebf1）、脂肪酸合酶（fatty acid synthase，FASN）、苹果酸酶（malic enzyme 1，Me1）的上调和β-氧化相关酶的下调，如CPT-1[85]。因此，GCG对肝脏脂质的代谢调节可能受IR和GCG抵抗的共同作用，涉及的分子机制可能如上文所述（图1B）。

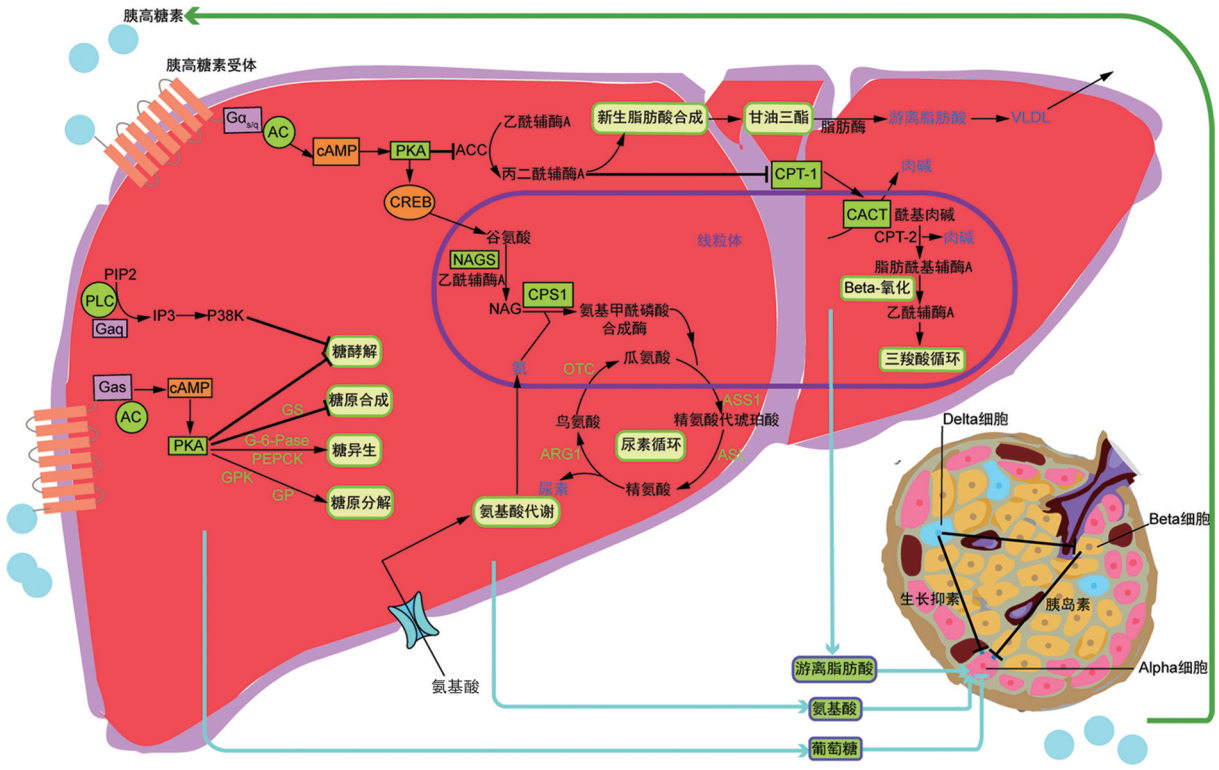
4 生理及胰岛素抵抗状态胰高糖素对肝脏氨基酸代谢的调节

GCG能够调节肝脏氨基酸的摄取和代谢，包括氨基酸转运和尿素生成增加[86]，降低循环中的氨基酸浓度，有助于清除体内有毒氨积累[87]。在富含蛋白质的膳食中，血浆GCG水平增加，促进了氨基酸在肝脏中的分解代谢[25]。GCG是肝脏尿素生成的强大调节剂，而尿素生成的调控很复杂，除了底物可用性（例如氨基酸）和葡萄糖水平外[88]，还包括GCGR通过转录或翻译后修饰机制调节尿素循环所需的必需酶[89-91]。由于肝脏氨基酸代谢依赖于完整的GCG信号通路，体内GCG信号通路的抑制导致肝脏氨基酸转运蛋白和参与氨基酸代谢的基因表达降低，即尿素生成受损和高氨基酸血症。GCG对肝脏氨基酸代谢调节机制如下（图1A）：在生理条件下，GCG与肝脏GCGR结合后，通过cAMP-PKA-CREB信号转导增加尿素循环中必需转运蛋白和酶的活性，从而调节肝脏氨基酸代谢。尿素循环从*N*-乙酰基-L-谷氨酸（acetyl-L-glutamic acid，NAG）形成开始，由*N*-乙酰谷氨酸合成酶（*N*-acetylglutamate synthase，NAGS）催化。NAGS是参与尿素形成的酶之一，CREB可能调节NAGS的转录。NAG激活氨基甲酰磷酸合酶1（carbamoyl phosphate synthetase 1，CPS-1），这是催化尿素循环第一步的酶，以上过程均在线粒体发生。CPS-1催化氨形成氨基甲酰磷酸盐，随后启动尿素循环。尿素循环中精氨酸酶（arginase-1，ARG1）、精氨琥珀酸裂解酶（argininosuccinate lyase，ASL）以及精氨琥珀酸合成酶1（argininosuccinate synthase 1，ASS1）可能在转录水平上受到GCG的调节。另外，GCG还可以通过PKA介导的磷酸化变构激活尿素循环。GCG除了对尿素生成具有转录和翻译后修饰作用，并且还通过激活位于肝细胞膜上的氨基酸转运蛋白的转录上调来增加氨基酸摄取和尿素生成的底物可用性[92]。GCG直接控制氨基酸进入肝细胞的通量，最后可能通过增加TCA循环间接促进尿素生成。

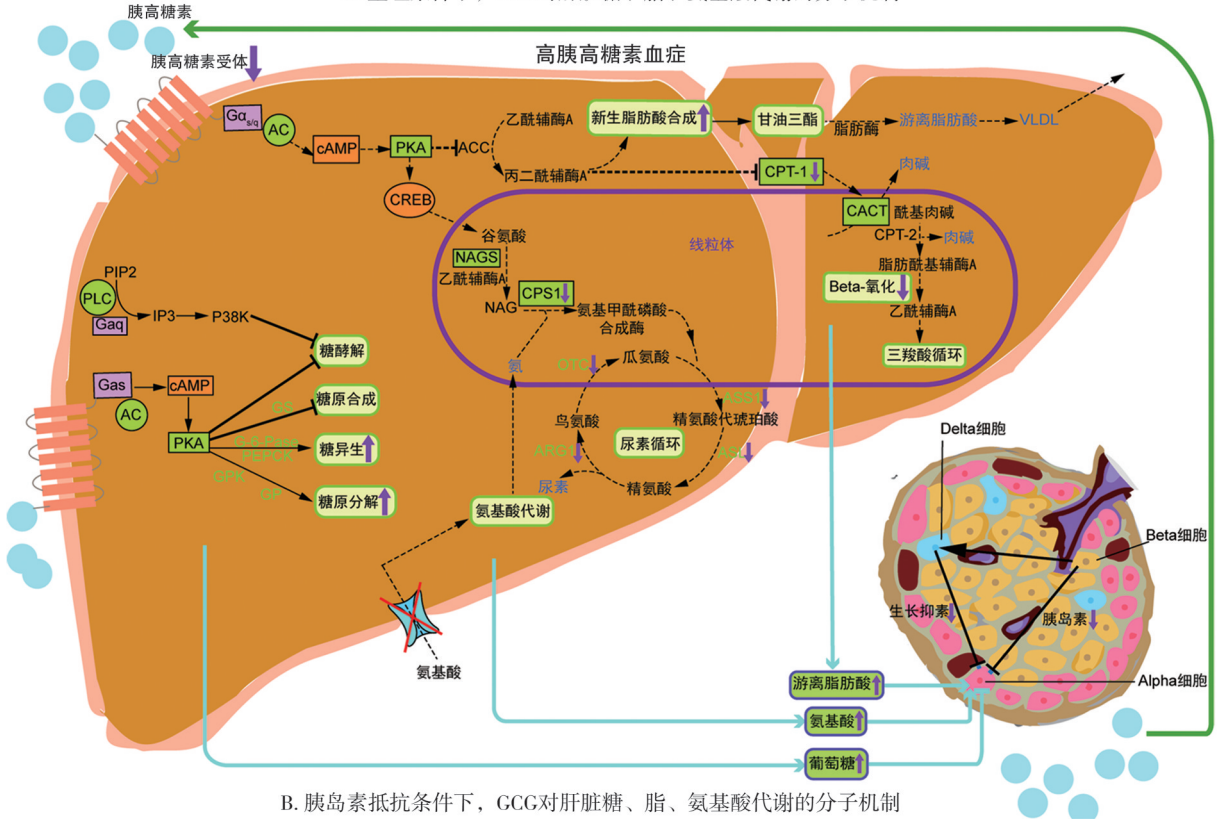
IR可能通过影响肝脏脂质沉积，导致GCG在肝脏中对氨基酸的调节能力受损，进而导致高氨基酸血症和高胰高糖素血症[93]。由高氨基酸血症诱导的高胰高糖素血症可能被视为一种代偿反应，在一定程度上恢复氨基酸转换和尿素生成，从而维持氨基酸稳态。然而，肝脏葡萄糖代谢仍保持较高敏感性，持续升高的GCG会导致高血糖。因此，从GCG角度来讲，氨基酸稳态的维持伴随的是高血糖症[1]。在一些胰高糖素瘤综合征的患者中，会出现严重的低氨基酸血症[94-95]。GCG通过将肝脏摄取的氨基酸转化为尿素，从而导致严重的低氨基酸血症[96]。这表明肝脏和胰腺α细胞之间的生理反馈对维持氨基酸稳态至关重要。IR可能减弱GCG诱导的氨基酸转换（GCG抵抗），导致尿素生成受损以及高氨基酸血症[34]。这可能涉及氨基酸转运蛋白和代谢相关基因的表达下调[97]。另外，研究表明在MASLD患者中发现鸟氨酸转氨甲酰酶（ornithine transcarbamylase，OTC）、CPS1的基因和蛋白质表达以及OTC的活性可逆地降低[98-99]。此外，在GCGR敲除小鼠中，许多氨基酸转运体和尿素循环基因被下调，在GCGR拮抗剂治疗的小鼠中也观察到类似的结果[100-101]。因此，IR可能抑制GCG信号传导，诱导调节尿素循环中关键中间体鸟氨酸水平的OTC、尿素循环酶（CPS1、ASS1、ASL、ARG1）以及氨基酸转运蛋白下调，导致体内氨基酸分解代谢减少（图1B）。

5 基于胰高糖素的药物治疗

由于GCG通过刺激肝糖输出引起高血糖，其通常用于治疗低血糖症[43]。GCGR拮抗作用正成为T2DM患者潜在的治疗策略。临床研究发现GCGR拮抗剂可降低T2DM患者的空腹、餐后血糖浓度以及糖化血红蛋白（hemoglobin A1c，HbA1c）水平[102-103]。这表明抑制GCG的信号传导对T2DM患者的葡萄糖代谢会产生有益影响。然而，有报道称GCGR拮抗剂增加了肝脏脂肪含量和血浆LDL浓度[70]，这些副作用阻碍了这类药物的临床使用。除了对葡萄糖代谢的影响外，GCG还具有降低血脂[104]、刺激能量消耗[105-106]和增加饱腹感的作用[107-108]，这使其成为治疗血脂异常和肥胖有前景的药物。研究表明静脉注射GCG可以改善血脂异常、增加耗氧量以及产热，但伴随而来的是高血糖风险[12]。为了安全地利用GCG的分解代谢和产热作用来治疗代谢性疾病，需要选择性地对抗GCG诱导的高血糖风险。其中，胰高糖素样肽-1（glucagon-like peptide-1，GLP-1）作为一种肠促胰酶素，其最重要的功能之一是通过刺激胰岛素分泌来降低血糖水平[109]，同时抑制GCG释放。GLP-1还具有延迟胃排空[110]和通过中枢神经系统增加饱腹感[111]等作用。目前已经开发了用于治疗肥胖和T2DM的新型双重受体激动剂，其概念是GLP-1抑制GCG升高血糖，同时允许其对体质量调节、食物摄入和脂质代谢发挥有益作用[112-113]。临床试验表明，能够激活GCGR和胰高糖素样肽-1受体（GLP-1 rceptor，GLP-



A. 生理条件下，GCG对肝脏糖、脂、氨基酸代谢的分子机制



B. 胰岛素抵抗条件下，GCG对肝脏糖、脂、氨基酸代谢的分子机制

注：图 1A 在生理条件下，GCG 促进糖异生、糖原分解并抑制糖酵解，同时通过 cAMP-PKA-CREB 途径调控尿素循环及氨基酸摄取，并通过 PKA-AMPK 途径增强β氧化，抑制脂质合成。图 1B 在 IR 状态下，GCG 信号转导受损，分泌增加，导致氨基酸代谢异常、尿素循环受损及β氧化降低，促进肝脂沉积并加重 GCG 水平升高，形成恶性循环。虚线代表 GCG 信号转导受损。AC，腺苷酸环化酶；ACC，乙酰辅酶 A 羧化酶；ARG1，精氨酸酶；ASL，精氨琥珀酸裂解酶；ASS1，精氨琥珀酸合成酶 1；cAMP，环状腺苷一磷酸；CREB，cAMP 负责结合元件；CPT-1，肉碱酰基转移酶-1；CACT，肉碱-酰基肉碱转位酶；CPT-2，肉碱酰基转移酶-2；CPS-1，氨基甲酰磷酸合酶 1；GS，糖原合酶；G-6-Pase，葡萄糖-6-磷酸酶；GPK，糖原磷酸化酶激酶；GP，糖原磷酸化酶；IP3，1，4，5-三磷酸；NAGS，N-乙酰谷氨酸合成酶；NAG，N-乙酰基-L-谷氨酸；OTC，鸟氨酸转氨甲酰酶；PKA，蛋白激酶 A；PIP2，4，5-二磷酸脂酰肌醇；PLC，磷脂酶 C；P38K，P38 激酶；PEPCK，磷酸烯醇丙酮酸羧激酶；VLDL，极低密度脂蛋白

图 1　IR 状态下，GCG 对肝脏代谢可能的分子机制

1R）的双重激动剂可改善葡萄糖耐量、血脂异常以及减少肝脏脂肪变性[114-115]。因此，双重受体激动剂协同作用可能是治疗代谢综合征方面的潜在途径[116]。另外，为了更有效地改善血糖和控制体重，一系列的三联受体激动剂已进入临床开发阶段[117]。葡萄糖依赖性促胰岛素多肽（glucose-dependent insulinotropic polypeptide，GIP）是一种肠促胰岛素激素，其可增强膳食刺激胰岛素分泌的能力，并已被证明能够以葡萄糖依赖性方式调节 GCG 的分泌[118-119]。在健康人中，GIP 在高血糖条件下抑制 GCG 分泌[120]，但在低血糖或正常血糖期间增加 GCG 分泌[121]。这表明三联受体激动剂可以进一步降低空腹血糖并改善葡萄糖耐量，而不会引起低血糖。作为一种肠促胰岛素激素，GIP 还具有促进餐后脂质清除和调节食物摄入量的作用[122]。到目前为止，三联受体激动剂在减轻体重、改善血糖和逆转肝脂肪变性方面更具有优势，并在临床研究中显示出一定的安全性[123-124]。因此，GCG 和肠促胰岛素激素的多重受体激动作用已显示出巨大的治疗潜力，这为治疗代谢综合征方面提供了新的视角。

6 总 结

虽然对胰岛素的作用已深入研究，但对 GCG 的研究仍相对较少。在这里，本研究主要回顾了 IR 状态下，GCG 对肝脏葡萄糖稳态、脂质和氨基酸代谢的作用。α 细胞的 IR，可能引起 GCG 分泌量的异常，进而导致 GCG 分泌病理性增加。此外，由于肝脏葡萄糖代谢的敏感性在 GCG 抵抗中没有明显受损，这也是导致 IR 状态下血糖升高的原因之一。生理条件下，GCG 对脂质代谢的调节主要包括刺激 FA 的 β 氧化，减少 DNL 和 VLDL 释放。然而，IR 状态下伴随的脂质沉积，对 GCG 在肝脏中的功能活性有较大的影响，因此形成恶性循环。**GCG** 主要通过调节肝脏氨基酸的摄取和代谢，包括氨基酸转运和尿素生成来维持体内氨基酸稳态。IR 状态下，由于肝脏氨基酸代谢存在 GCG 抵抗，这引起 GCG 诱导的尿素生成受损，进而导致高氨基酸血症。因此，调节 GCG 的分泌或作用是改善代谢疾病潜在的靶点。然而，这些观点还存在争论和未知的机制。本文分析 IR 状态下，GCG 对肝脏糖脂的代谢机制，这有助于理解糖尿病和其他代谢疾病的复杂病理生理学。同时，这对于了解 GCGR 激动剂和拮抗剂的影响和并发症是有意义的。

参 考 文 献

[1] Müller TD, Finan B, Clemmensen C, et al. The new biology and pharmacology of glucagon[J]. Physiol Rev, 2017, 97(2): 721-766.

[2] Rouillé Y, Bianchi M, Irminger JC, et al. Role of the prohormone convertase PC2 in the processing of proglucagon to glucagon[J]. FEBS Lett, 1997, 413(1): 119-123.

[3] Rouillé Y, Westermark G, Martin SK, et al. Proglucagon is processed to glucagon by prohormone convertase PC2 in alpha TC1-6 cells [J]. Proc Natl Acad Sci USA, 1994, 91(8): 3242-3246.

[4] Jelinek LJ, Lok S, Rosenberg GB, et al. Expression cloning and signaling properties of the rat glucagon receptor[J]. Science, 1993, 259 (5101): 1614-1616.

[5] Campbell JE, Drucker DJ. Islet α cells and glucagon: critical regulators of energy homeostasis[J]. Nat Rev Endocrinol, 2015, 11(6): 329-338.

[6] Berthet J. Influence of glucagon and Adrenalin on the *in vitro* synthesis of cholesterol by hepatic tissue[J]. Prog Nucl Energy 6 Biol Sci, 1958, 2(3): 179-184.

[7] Berthet J. Some aspects of the glucagon problem[J]. Am J Med, 1959, 26(5): 703-714.

[8] Lipsett MB, Engel HR, Bergenstal DM. Effects of glucagon on plasma unesterified fatty acids and in nitrogen metabolism[J]. J Lab Clin Med, 1960, 56: 342-354.

[9] Boden G, Rezvani I, Owen OE. Effects of glucagon on plasma amino acids[J]. J Clin Invest, 1984, 73(3): 785-793.

[10] Unger RH, Cherrington AD. Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover[J]. J Clin Invest, 2012, 122(1): 4-12.

[11] Wewer Albrechtsen NJ, Holst JJ, Cherrington AD, et al. 100 years of glucagon and 100 more[J]. Diabetologia, 2023, 66(8): 1378-1394.

[12] Rorsman P, Huising MO. The somatostatin-secreting pancreatic δ-cell in health and disease[J]. Nat Rev Endocrinol, 2018, 14(7): 404-414.

[13] Briant LB, Reinbothe TM, Spiliotis I, et al. δ-cells and β-cells are electrically coupled and regulate α-cell activity *via* somatostatin[J]. 2018, 596(2): 197-215.

[14] Elliott AD, Ustione A, Piston DW. Somatostatin and insulin mediate glucose-inhibited glucagon secretion in the pancreatic α-cell by lowering cAMP[J]. Am J Physiol Endocrinol Metab, 2015, 308(2): 130-143.

[15] Leung YM, Ahmed I, Sheu L, et al. Insulin regulates islet alpha-cell function by reducing KATP channel sensitivity to adenosine 5′-triphosphate inhibition[J]. Endocrinology, 2006, 147(5): 2155-2162.

[16] Xu E, Kumar M, Zhang Y, et al. Intra-islet insulin suppresses glucagon release *via* GABA-GABAA receptor system[J]. Cell Metab, 2006, 3(1): 47-58.

[17] Yu Q, Shuai HY, Ahooghalandari P, et al. Glucose controls glucagon secretion by directly modulating cAMP in alpha cells[J]. Diabetologia, 2019, 62(7): 1212-1224.

[18] Vergari E, Knudsen JG, Ramracheya R, et al. Insulin inhibits glucagon release by SGLT2-induced stimulation of somatostatin secretion [J]. Nat Commun, 2019, 10(1): 139.

[19] Zeigerer A, Sekar R, Kleinert M, et al. Glucagon's metabolic action in health and disease[J]. Compr Physiol, 2021, 11(2): 1759-1783.

[20] Kristinsson H, Sargsyan E, Manell H, et al. Basal hypersecretion of glucagon and insulin from palmitate-exposed human islets depends on FFAR1 but not decreased somatostatin secretion[J]. Sci Rep, 2017, 7(1): 4657.

[21] Mandøe MJ, Hansen KB, Hartmann B, et al. The 2-monoacylglycerol moiety of dietary fat appears to be responsible for the fat-induced release of GLP-1 in humans[J]. Am J Clin Nutr, 2015, 102(3): 548-555.

[22] Luyckx AS, Lefebvre PJ. Arguments for a regulation of pancreatic glucagon secretion by circulating plasma free fatty acids[J]. Proc Soc Exp Biol Med, 1970, 133(2): 524-528.

[23] Collins SC, Salehi A, Eliasson L, et al. Long-term exposure of

mouse pancreatic islets to oleate or palmitate results in reduced glucose-induced somatostatin and oversecretion of glucagon[J]. Diabetologia, 2008,51(9):1689-1693.

[24] Gremlich S, Bonny C, Waeber G, et al. Fatty acids decrease IDX-1 expression in rat pancreatic islets and reduce GLUT2, glucokinase, insulin, and somatostatin levels[J]. J Biol Chem, 1997, 272(48): 30261-30269.

[25] Kraft G, Coate KC, Winnick JJ, et al. Glucagon's effect on liver protein metabolism *in vivo*[J]. Am J Physiol Endocrinol Metab, 2017, 313(3): 263-272.

[26] Danielle Dean E. A primary role for α-cells as amino acid sensors [J]. Diabetes, 2020, 69(4): 542-549.

[27] Kawamori D, Kulkarni RN. Insulin modulation of glucagon secretion: the role of insulin and other factors in the regulation of glucagon secretion[J]. Islets, 2009, 1(3): 276-279.

[28] Honzawa N, Fujimoto K, Kitamura T. Cell autonomous dysfunction and insulin resistance in pancreatic α cells[J]. Int J Mol Sci, 2019, 20(15): 3699.

[29] Solloway MJ, Madjidi A, Gu CY, et al. Glucagon couples hepatic amino acid catabolism to mTOR-dependent regulation of α-cell mass [J]. Cell Rep, 2015, 12(3): 495-510.

[30] Holst JJ, Wewer Albrechtsen NJ, Pedersen J, et al. Glucagon and amino acids are linked in a mutual feedback cycle: the liver-α-cell axis [J]. Diabetes, 2017, 66(2): 235-240.

[31] Galsgaard KD, Pedersen J, Knop FK, et al. Glucagon receptor signaling and lipid metabolism[J]. Front Physiol, 2019, 10: 413.

[32] Stumvoll M, Häring H. Insulin resistance and insulin sensitizers [J]. Horm Res, 2001, 55(Suppl 2): S3-S13.

[33] Asrih M, Jornayvaz FR. Metabolic syndrome and nonalcoholic fatty liver disease: Is insulin resistance the link?[J]. Mol Cell Endocrinol, 2015, 418 Pt 1: 55-65.

[34] Wewer Albrechtsen NJ, Færch K, Jensen TM, et al. Evidence of a liver-alpha cell axis in humans: hepatic insulin resistance attenuates relationship between fasting plasma glucagon and glucagonotropic amino acids[J]. Diabetologia, 2018, 61(3): 671-680.

[35] Gar C, Haschka SJ, Kern-Matschilles S, et al. The liver-alpha cell axis associates with liver fat and insulin resistance: a validation study in women with non-steatotic liver fat levels[J]. Diabetologia, 2021, 64(3): 512-520.

[36] Galsgaard KD. The vicious circle of hepatic glucagon resistance in non-alcoholic fatty liver disease[J]. J Clin Med, 2020, 9(12): 4049.

[37] Charbonneau A, Couturier K, Gauthier MS, et al. Evidence of hepatic glucagon resistance associated with hepatic steatosis: reversal effect of training[J]. Int J Sports Med, 2005, 26(6): 432-441.

[38] Charbonneau A, Unson CG, Lavoie JM. High-fat diet-induced hepatic steatosis reduces glucagon receptor content in rat hepatocytes: potential interaction with acute exercise[J]. J Physiol, 2007, 579(Pt 1): 255-267.

[39] Jia YB, Liu Y, Feng LL, et al. Role of glucagon and its receptor in the pathogenesis of diabetes[J]. Front Endocrinol, 2022, 13: 928016.

[40] Habegger KM. Cross talk between insulin and glucagon receptor signaling in the hepatocyte[J]. Diabetes, 2022, 71(9): 1842-1851.

[41] Freychet L, Rizkalla SW, Desplanque N, et al. Effect of intranasal glucagon on blood glucose levels in healthy subjects and hypoglycaemic patients with insulin-dependent diabetes[J]. Lancet, 1988, 1(8599): 1364-1366.

[42] Seaquist ER, Dulude H, Zhang XM, et al. Prospective study evaluating the use of nasal glucagon for the treatment of moderate to severe hypoglycaemia in adults with type 1 diabetes in a real-world setting [J]. Diabetes Obes Metab, 2018, 20(5): 1316-1320.

[43] Pontiroli AE. Intranasal glucagon: a promising approach for treatment of severe hypoglycemia[J]. J Diabetes Sci Technol, 2015, 9(1): 38-43.

[44] Sørensen H, Winzell MS, Brand CL, et al. Glucagon receptor knockout mice display increased insulin sensitivity and impaired beta-cell function[J]. Diabetes, 2006, 55(12): 3463-3469.

[45] Guan HP, Yang XD, Lu K, et al. Glucagon receptor antagonism induces increased cholesterol absorption[J]. J Lipid Res, 2015, 56(11): 2183-2195.

[46] Longuet C, Sinclair EM, Maida A, et al. The glucagon receptor is required for the adaptive metabolic response to fasting[J]. Cell Metab, 2008, 8(5): 359-371.

[47] Webb GC, Akbar MS, Zhao CJ, et al. Glucagon replacement *via* micro-osmotic pump corrects hypoglycemia and alpha-cell hyperplasia in prohormone convertase 2 knockout mice[J]. Diabetes, 2002, 51(2): 398-405.

[48] Myers SR, Diamond MP, Adkins-Marshall BA, et al. Effects of small changes in glucagon on glucose production during a euglycemic, hyperinsulinemic clamp[J]. Metabolism, 1991, 40(1): 66-71.

[49] Opara EC, Atwater I, Go VL. Characterization and control of pulsatile secretion of insulin and glucagon[J]. Pancreas, 1988, 3(4): 484-487.

[50] Dobbins RL, Davis SN, Neal D, et al. Rates of glucagon activation and deactivation of hepatic glucose production in conscious dogs[J]. Metabolism, 1998, 47(2): 135-142.

[51] Burcelin R, Katz EB, Charron MJ. Molecular and cellular aspects of the glucagon receptor: role in diabetes and metabolism[J]. Diabetes Metab, 1996, 22(6): 373-396.

[52] Christophe J. Glucagon receptors: from genetic structure and expression to effector coupling and biological responses[J]. Biochim Biophys Acta, 1995, 1241(1): 45-57.

[53] Jiang GQ, Zhang BB. Glucagon and regulation of glucose metabolism[J]. Am J Physiol Endocrinol Metab, 2003, 284(4): 671-678.

[54] Janah L, Kjeldsen S, Galsgaard KD, et al. Glucagon receptor signaling and glucagon resistance[J]. Int J Mol Sci, 2019, 20(13): 3314.

[55] Pivovarova O, Bernigau W, Bobbert T, et al. Hepatic insulin clearance is closely related to metabolic syndrome components[J]. Diabetes Care, 2013, 36(11): 3779-3785.

[56] Bagger JI, Knop FK, Lund A, et al. Glucagon responses to increasing oral loads of glucose and corresponding isoglycaemic intravenous glucose infusions in patients with type 2 diabetes and healthy individuals [J]. Diabetologia, 2014, 57(8): 1720-1725.

[57] Baron AD, Schaeffer L, Shragg P, et al. Role of hyperglucagonemia in maintenance of increased rates of hepatic glucose output in type Ⅱ diabetics[J]. Diabetes, 1987, 36(3): 274-283.

[58] Heimberg H, De Vos A, Pipeleers D, et al. Differences in glucose transporter gene expression between rat pancreatic alpha- and beta-cells are correlated to differences in glucose transport but not in glucose

utilization[J]. J Biol Chem, 1995, 270(15): 8971-8975.

[59] Suga T, Kikuchi O, Kobayashi M, et al. SGLT1 in pancreatic α cells regulates glucagon secretion in mice, possibly explaining the distinct effects of SGLT2 inhibitors on plasma glucagon levels[J]. Mol Metab, 2019, 19: 1-12.

[60] Zhang Q, Ramracheya R, Lahmann C, et al. Role of KATP channels in glucose-regulated glucagon secretion and impaired counterregulation in type 2 diabetes[J]. Cell Metab, 2013, 18(6): 871-882.

[61] Quesada I, Tudurí E, Ripoll C, et al. Physiology of the pancreatic alpha-cell and glucagon secretion: role in glucose homeostasis and diabetes[J]. J Endocrinol, 2008, 199(1): 5-19.

[62] Olsen HL, Theander S, Bokvist K, et al. Glucose stimulates glucagon release in single rat alpha-cells by mechanisms that mirror the stimulus-secretion coupling in beta-cells[J]. Endocrinology, 2005, 146(11): 4861-4870.

[63] Kawamori D, Kurpad AJ, Hu J, et al. Insulin signaling in alpha cells modulates glucagon secretion *in vivo*[J]. Cell Metab, 2009, 9(4): 350-361.

[64] Suppli MP, Lund A, Bagger JI, et al. Involvement of steatosis-induced glucagon resistance in hyperglucagonaemia[J]. Med Hypotheses, 2016, 86: 100-103.

[65] Richter MM, Galsgaard KD, Elmelund E, et al. The liver-α-cell axis in health and in disease[J]. Diabetes, 2022, 71(9): 1852-1861.

[66] Wewer Albrechtsen NJ, Pedersen J, Galsgaard KD, et al. The liver-α-cell axis and type 2 diabetes[J]. Endocr Rev, 2019, 40(5): 1353-1366.

[67] Habegger KM, Heppner KM, Geary N, et al. The metabolic actions of glucagon revisited[J]. Nat Rev Endocrinol, 2010, 6(12): 689-697.

[68] Nason SR, Kim T, Antipenko JP, et al. Glucagon-receptor signaling reverses hepatic steatosis independent of leptin receptor expression [J]. Endocrinology, 2020, 161(1): bqz013.

[69] Brown NF, Salter AM, Fears R, et al. Glucagon, cyclic AMP and adrenaline stimulate the degradation of low-density lipoprotein by cultured rat hepatocytes[J]. Biochem J, 1989, 262(2): 425-429.

[70] Guzman CB, Zhang XM, Liu R, et al. Treatment with LY2409021, a glucagon receptor antagonist, increases liver fat in patients with type 2 diabetes[J]. Diabetes Obes Metab, 2017, 19(11): 1521-1528.

[71] Longuet C, Sinclair EM, Maida A, et al. The glucagon receptor is required for the adaptive metabolic response to fasting[J]. Cell Metab, 2008, 8(5): 359-371.

[72] Yanai H, Hirowatari Y, Ito K, et al. Understanding of diabetic dyslipidemia by using the anion-exchange high performance liquid chromatography data[J]. J Clin Med Res, 2016, 8(5): 424-426.

[73] Yanai H, Adachi H, Hakoshima M, et al. Metabolic-dysfunction-associated steatotic liver disease-its pathophysiology, association with atherosclerosis and cardiovascular disease, and treatments[J]. Int J Mol Sci, 2023, 24(20): 15473.

[74] Wewer Albrechtsen NJ, Junker AE, Christensen M, et al. Hyperglucagonemia correlates with plasma levels of non-branched-chain amino acids in patients with liver disease independent of type 2 diabetes [J]. Am J Physiol Gastrointest Liver Physiol, 2018, 314(1): 91-96.

[75] Trefts E, Gannon M, Wasserman DH. The liver[J]. Curr Biol, 2017, 27(21): 1147-1151.

[76] Guzmán M, Castro J. Zonation of fatty acid metabolism in rat liver [J]. Biochem J, 1989, 264(1): 107-113.

[77] Jungermann K. Metabolic zonation of liver parenchyma[J]. Semin Liver Dis, 1988, 8(4): 329-341.

[78] Ikezawa Y, Yamatani K, Ogawa A, et al. Effects of glucagon on glycogenolysis and gluconeogenesis are region-specific in periportal and perivenous hepatocytes[J]. J Lab Clin Med, 1998, 132(6): 547-555.

[79] Braeuning A, Ittrich C, Köhle C, et al. Differential gene expression in periportal and perivenous mouse hepatocytes[J]. FEBS J, 2006, 273(22): 5051-5061.

[80] Bass NM. Fatty acid-binding protein expression in the liver: its regulation and relationship to the zonation of fatty acid metabolism[J]. Mol Cell Biochem, 1990, 98(1/2): 167-176.

[81] Hijmans BS, Grefhorst A, Oosterveer MH, et al. Zonation of glucose and fatty acid metabolism in the liver: mechanism and metabolic consequences[J]. Biochimie, 2014, 96: 121-129.

[82] Cheng XP, Kim SY, Okamoto H, et al. Glucagon contributes to liver zonation[J]. Proc Natl Acad Sci USA, 2018, 115(17): E4111-E4119.

[83] Heebøll S, Risikesan J, Ringgaard S, et al. Impaired glucagon-mediated suppression of VLDL-triglyceride secretion in individuals with metabolic dysfunction-associated fatty liver disease (MAFLD)[J]. Diabetes, 2022, 71(11): 2402-2411.

[84] Hædersdal S, Andersen A, Knop FK, et al. Revisiting the role of glucagon in health, diabetes mellitus and other metabolic diseases[J]. Nat Rev Endocrinol, 2023, 19(6): 321-335.

[85] Yang JX, MacDougall ML, McDowell MT, et al. Polyomic profiling reveals significant hepatic metabolic alterations in glucagon-receptor (GCGR) knockout mice: implications on anti-glucagon therapies for diabetes[J]. BMC Genomics, 2011, 12: 281.

[86] Petersen KF, Hansen BA, Vilstrup H. Time dependent stimulating effect of glucagon on the capacity of urea-N synthesis in rats[J]. Horm Metab Res, 1987, 19(2): 53-56.

[87] Hamberg O, Vilstrup H. Regulation of urea synthesis by glucose and glucagon in normal man[J]. Clin Nutr, 1994, 13(3): 183-191.

[88] Hamberg O, Vilstrup H. Effects of insulin and glucose on urea synthesis in normal man, independent of pancreatic hormone secretion [J]. J Hepatol, 1994, 21(3): 381-387.

[89] Vilstrup H, Hansen BA, Almdal TP. Glucagon increases hepatic efficacy for urea synthesis[J]. J Hepatol, 1990, 10(1): 46-50.

[90] Almdal TP, Holst JJ, Heindorff H, et al. Glucagon immunoneutralization in diabetic rats normalizes urea synthesis and decreases nitrogen wasting[J]. Diabetes, 1992, 41(1): 12-16.

[91] Takiguchi M, Mori M. Transcriptional regulation of genes for ornithine cycle enzymes[J]. Biochem J, 1995, 312(Pt 3): 649-659.

[92] Elmelund E, Galsgaard KD, Johansen CD, et al. Opposing effects of chronic glucagon receptor agonism and antagonism on amino acids, hepatic gene expression, and alpha cells[J]. iScience, 2022, 25(11): 105296.

[93] Suppli MP, Bagger JI, Lund A, et al. Glucagon resistance at the level of amino acid turnover in obese subjects with hepatic steatosis[J]. Diabetes, 2020, 69(6): 1090-1099.

[94] Jarak I, Pereira SS, Carvalho RA, et al. Gastric bypass with different biliopancreatic limb lengths results in similar post-absorptive metabolomics profiles[J]. Obes Surg, 2020, 30(3): 1068-1078.

[95] Chastain MA. The glucagonoma syndrome: a review of its features and discussion of new perspectives[J]. Am J Med Sci, 2001, 321(5): 306-320.

[96] Challis BG, Albrechtsen NJ, Bansiya V, et al. Heterogeneity of glucagonomas due to differential processing of proglucagon-derived peptides[J]. Endocrinol Diabetes Metab Case Rep, 2015, 2015: 150105.

[97] Galsgaard KD, Winther-Sørensen M, Ørskov C, et al. Disruption of glucagon receptor signaling causes hyperaminoacidemia exposing a possible liver-alpha-cell axis[J]. Am J Physiol Endocrinol Metab, 2018, 314(1): E93-E103.

[98] Eriksen PL, Vilstrup H, Rigbolt K, et al. Non-alcoholic fatty liver disease alters expression of genes governing hepatic nitrogen conversion [J]. Liver Int, 2019, 39(11): 2094-2101.

[99] De Chiara F, Heebøll S, Marrone G, et al. Urea cycle dysregulation in non-alcoholic fatty liver disease[J]. J Hepatol, 2018, 69(4): 905-915.

[100] Kim J, Okamoto H, Huang ZJ, et al. Amino acid transporter Slc38a5 controls glucagon receptor inhibition-induced pancreatic α cell hyperplasia in mice[J]. Cell Metab, 2017, 25(6): 1348-1361.

[101] Winther-Sørensen M, Galsgaard KD, Santos A, et al. Glucagon acutely regulates hepatic amino acid catabolism and the effect may be disturbed by steatosis[J]. Mol Metab, 2020, 42: 101080.

[102] Kazda CM, Ding Y, Kelly RP, et al. Evaluation of efficacy and safety of the glucagon receptor antagonist LY2409021 in patients with type 2 diabetes: 12- and 24-week phase 2 studies[J]. Diabetes Care, 2016, 39(7): 1241-1249.

[103] Vajda EG, Logan D, Lasseter K, et al. Pharmacokinetics and pharmacodynamics of single and multiple doses of the glucagon receptor antagonist LGD-6972 in healthy subjects and subjects with type 2 diabetes mellitus[J]. Diabetes Obes Metab, 2017, 19(1): 24-32.

[104] Vons C, Pegorier JP, Girard J, et al. Regulation of fatty-acid metabolism by pancreatic hormones in cultured human hepatocytes[J]. Hepatology, 1991, 13(6): 1126-1130.

[105] Nair KS. Hyperglucagonemia increases resting metabolic rate in man during insulin deficiency[J]. J Clin Endocrinol Metab, 1987, 64(5): 896-901.

[106] Kleinert M, Sachs S, Habegger KM, et al. Glucagon regulation of energy expenditure[J]. Int J Mol Sci, 2019, 20(21): 5407.

[107] Stunkard AJ, VAN ITALLIE TB, Reis BB. The mechanism of satiety: effect of glucagon on gastric hunger contractions in man[J]. Proc Soc Exp Biol Med, 1955, 89(2): 258-261.

[108] Penick SB, Hinkle LE Jr. Depression of food intake induced in healthy subjects by glucagon[J]. N Engl J Med, 1961, 264: 893-897.

[109] Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients[J]. J Clin Endocrinol Metab, 2001, 86(8): 3717-3723.

[110] Willms B, Werner J, Holst JJ, et al. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1) - (7-36) amide in type 2 (noninsulin-dependent) diabetic patients[J]. J Clin Endocrinol Metab, 1996, 81(1): 327-332.

[111] Sisley S, Gutierrez-Aguilar R, Scott M, et al. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect[J]. J Clin Invest, 2014, 124(6): 2456-2463.

[112] Sadry SA, Drucker DJ. Emerging combinatorial hormone therapies for the treatment of obesity and T2DM[J]. Nat Rev Endocrinol, 2013, 9(7): 425-433.

[113] Tillner J, Posch MG, Wagner F, et al. A novel dual glucagon-like peptide and glucagon receptor agonist SAR425899: Results of randomized, placebo-controlled first-in-human and first-in-patient trials [J]. Diabetes Obes Metab, 2019, 21(1): 120-128.

[114] Ambery P, Parker VE, Stumvoll M, et al. MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study[J]. Lancet, 2018, 391(10140): 2607-2618.

[115] Seghieri M, Christensen AS, Andersen A, et al. Future perspectives on GLP-1 receptor agonists and GLP-1/glucagon receptor co-agonists in the treatment of NAFLD[J]. Front Endocrinol, 2018, 9: 649.

[116] Sánchez-Garrido MA, Brandt SJ, Clemmensen C, et al. GLP-1/glucagon receptor co-agonism for treatment of obesity[J]. Diabetologia, 2017, 60(10): 1851-1861.

[117] Müller TD, Blüher M, Tschöp MH, et al. Anti-obesity drug discovery: advances and challenges[J]. Nat Rev Drug Discov, 2022, 21(3): 201-223.

[118] Dupre J, Ross SA, Watson D, et al. Stimulation of insulin secretion by gastric inhibitory polypeptide in man[J]. J Clin Endocrinol Metab, 1973, 37(5): 826-828.

[119] Adrian TE, Bloom SR, Hermansen K, et al. Pancreatic polypeptide, glucagon and insulin secretion from the isolated perfused canine pancreas[J]. Diabetologia, 1978, 14(6): 413-417.

[120] Christensen M, Vedtofte L, Holst JJ, et al. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans[J]. Diabetes, 2011, 60(12): 3103-3109.

[121] Meier JJ, Gallwitz B, Siepmann N, et al. Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia[J]. Diabetologia, 2003, 46(6): 798-801.

[122] Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease[J]. Diabetes Obes Metab, 2018, 20(Suppl 1): S5-S21.

[123] Coskun T, Urva S, Roell WC, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept[J]. Cell Metab, 2022, 34(9): 1234-1247.

[124] Urva S, Coskun T, Loh MT, et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial[J]. Lancet, 2022, 400(10366): 1869-1881.

（收稿：2024-11-12；修回：2025-01-25；录用：2025-02-13）

（责任编辑：李青颖）

本文引用格式：

于静静，姚振宇，周象宁，等. 胰岛素抵抗状态下胰高糖素对肝脏代谢的调节机制[J]. 重庆医科大学学报，2025，50(9)：1178-1186.