综　述

糖尿病知觉障碍性低血糖的研究进展

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[中图分类号]　R335+.6　　[文献标志码]　A　　[DOI]　10.11855/j.issn.0577-7402.1693.2025.0923
[声明]　本文所有作者声明无利益冲突
[引用本文]　李敏讷, 王岩, 靳方馨, 等. 糖尿病知觉障碍性低血糖的研究进展[J]. 解放军医学杂志, 2026, 51(2): 265-274.
[收稿日期]　2024-10-29　　[录用日期]　2025-08-06　　[上线日期]　2025-09-23

[摘要]　知觉障碍性低血糖(IAH)作为糖尿病患者血糖管控的核心障碍，可明显增加患者发生认知损伤、死亡等情况的风险，尤其在胰岛素治疗的1型糖尿病(T1DM)及晚期2型糖尿病(T2DM)患者中高发，已成为糖尿病管理的主要挑战。当前研究显示，IAH的病理机制并非单一因素所致，而是外周反调节失调(如胰岛α细胞功能障碍、交感神经-肾上腺轴抑制)与中枢神经代谢适应(如下丘脑葡萄糖敏感神经元功能异常、脑乳酸代谢异常)共同作用的结果，两种机制相互关联且放大损伤效应。现有的诊断问卷评估方法受持续血糖监测(CGM)普及的影响，准确性较低，血浆肾上腺素虽为反调节受损的金标准，但缺乏早期诊断价值。此外，当前用于治疗的人工胰腺、联合用药及结构化教育成效明显，然而多数药物干预仍停留在实验阶段。因此，本综述系统梳理IAH的临床特征、机制、诊断及防治研究现状，深入分析当前研究的局限，旨在为后续精准诊断的指标开发、靶向治疗突破及临床管理优化提供方向，并有助于解决糖尿病患者血糖安全管控中的难题。

[关键词]　糖尿病；知觉障碍性低血糖；低血糖反调节障碍

Progress on impaired awareness of hypoglycemia in diabetes mellitus

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This work was supported by the National Natural Science Foundation of China (81471048), the Natural Science Foundation of Shandong Province (ZR2020MH381), and the Weifang Science and Technology Development Plan (2021GX062)

[**Abstract**]　Impaired awareness of hypoglycemia (IAH), a core barrier to glycemic control in patients with diabetes, significantly increases the risks of cognitive impairment, mortality, and other adverse events. It has a particularly high prevalence among patients with insulin-treated type 1 diabetes mellitus (T1DM) and advanced type 2 diabetes mellitus (T2DM), thereby emerging as a critical challenge in diabetes management. Current research indicates that the pathogenesis of IAH is not attributed to a single factor. Instead, it results from the combined effects of peripheral counterregulatory dysfunction (e.g., pancreatic α-cell dysfunction, sympathetic-adrenal axis suppression) and central nervous system metabolic adaptation (e.g., abnormal function of glucose-sensitive neurons in the hypothalamus, abnormal cerebral lactate metabolism). These two mechanisms are interrelated and mutually reinforce the damaging effects. Regarding diagnosis, the accuracy of existing assessment questionnaires is relatively low due to the widespread adoption of continuous glucose monitoring (CGM). Although plasma epinephrine serves as the gold standard for detecting counterregulatory impairment, it lacks value for early diagnosis. In terms of treatment, approaches such as artificial pancreas systems, combination pharmacotherapy, and structured patient education have demonstrated clear efficacy. However, most pharmacotherapeutic interventions remain in the experimental stage. This review systematically summarizes the current research status of IAH, covering its clinical features, mechanisms, diagnosis, prevention, and treatment. It also conducts an in-depth analysis of

[基金项目]　国家自然科学基金(81471048)；山东省自然科学基金(ZR2020MH381)；潍坊市科学技术发展计划项目(2021GX062)
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the limitations in existing research. The review aims to provide directions for the subsequent development of precise diagnostic indicators, breakthroughs in targeted therapy, and optimization of clinical management, thereby helping to resolve the critical issue of safe glycemic control for patients with diabetes.

[**Key words**] diabetes mellitus; impaired awareness of hypoglycemia; impaired hypoglycemic counterregulation

糖尿病是由多种因素引起的以慢性高血糖为特征的代谢性疾病，主要是胰岛素分泌和(或)利用缺陷所致[1-2]；外源性胰岛素降糖治疗可能增加低血糖的发生风险[3-4]。反复低血糖可引发低血糖反调节障碍，诱导低血糖知觉障碍的发生[5]。知觉障碍性低血糖(impaired awareness of hypoglycemia，IAH)是糖尿病患者常见的严重并发症[6-7]，即在低血糖发生时患者自主神经兴奋症状减弱甚至丧失，其感知低血糖、引发低血糖警告症状的能力下降，易引发严重低血糖，可增加患者发生认知障碍、头晕、意识模糊、抽搐、昏迷甚至死亡的风险[2,8-9]。因此，研究糖尿病IAH，对于血糖管控、减少糖尿病并发症，甚至低血糖诱发的死亡具有重要意义。本综述将围绕糖尿病IAH的临床认知、发病机制、诊断评估、预防治疗进行综述和讨论，以期为糖尿病IAH的研究和防治提供借鉴。

1 概　　述

研究表明，严格血糖控制特别是胰岛素的应用增加了发生低血糖的风险[10]。反复低血糖，即一天多次或多天一次的密集低血糖，往往导致血糖反调节反应(counterregulatory responses，CRRs)受损，进而形成IAH，引发“hypoglycemia begets hypoglycemia”即本次低血糖诱发下次低血糖的恶性循环[11]。由于1型糖尿病(type 1 diabetes mellitus，T1DM)和晚期2型糖尿病(type 2 diabetes mellitus，T2DM)主要依靠外源性胰岛素治疗[12]，所以低血糖为其常见的急性并发症。低血糖常于夜间发生，易诱发IAH，若未及时发现，往往危及生命[13]。T1DM患者的IAH发病率高达40%[9]，而T2DM患者约为10%[14]。据报道，T1DM患者IAH可使严重低血糖的风险增加6~10倍[15]。IAH的特点是感知低血糖发作的能力减弱或丧失，即IAH糖尿病患者自主神经低血糖症状减弱，或在自主神经低血糖症状(低血糖警告症状)出现之前，发生中枢神经元低血糖症状[16]。健康人对低血糖的反调节机制及临床表现具体见表1[12,17-18]。同时，常见的误解是IAH患者并不出现低血糖症状，实则其低血糖症状类型和血糖阈值发生了变化，例如，在血糖水平较低时也可能引发低血糖警告症状[19]。上述情形致使患者对降糖产生畏惧心理，拒绝接受相对严格的降糖治疗，进而对其血糖控制造成影响[12]。这一现象表明，对IAH的恐惧情绪，是当前糖尿病患者实现理想血糖控制及预防糖尿病并发症的主要阻碍。

表1 健康人对低血糖的反调节机制及临床表现

Tab.1 Mechanism of counterregulatory response to hypoglycemia and it's olinical manifestation in normal individuals

血糖(mmol/L)	激素变化及反调节机制[12]	临床表现
4.4~4.7	胰岛素↓：可抑制糖原、蛋白质、脂肪合成，限制葡萄糖的利用	
3.6~3.9	胰高血糖素↑：通过促进糖原分解、糖异生等途径升高血糖；肾上腺素↑，去甲肾上腺↑：通过促进肝糖原分解，增加肌肉糖酵解、减少胰岛素分泌等途径升高血糖	血糖在<3.3 mmol/L之前，很少发生低血糖症状[17]
3.7	生长激素↑：促进糖异生	
3.2	皮质醇↑：促进糖异生、肾上腺素分泌	自主神经低血糖症状：心悸、震颤、焦虑、出汗、饥饿感等
<2.8	健康人上述激素调节可保证大脑葡萄糖供应，基本不会出现大脑神经元低血糖症状	大脑神经元低血糖症状：认知障碍、头晕、意识模糊、抽搐、语言障碍、癫痫或昏迷等[18]

2 发病机制

IAH的发生是外周激素反调节障碍与中枢神经代谢适应共同作用的结果，其核心诱因是“反复低血糖暴露”。

2.1 外周反调节失调　正常低血糖时，机体通过“胰岛α细胞-交感神经-肾上腺”轴启动外周反调节：胰高血糖素分泌增加(促进肝糖原分解)，交感神经兴奋引发肾上腺素释放(抑制胰岛素分泌、促进糖异生)[20]。而IAH患者的这一轴系存在多层损伤：

2.1.1 胰岛α细胞功能障碍　糖尿病患者胰岛α细胞功能障碍，可影响正常的胰高血糖素释放。有研究发现，T1DM患者胰岛α细胞中晚期糖基化终末产物受体(receptor for advanced glycation end products，RAGE)高表达；RAGE与胰岛α细胞胰高血糖素的分泌呈负相关[21]，提示或许高表达的RAGE影响了低

血糖时胰岛α细胞分泌胰高血糖素。也有研究发现，在T1DM动物模型中存在胰岛α细胞转化为胰岛β细胞的现象；细胞类型的转换可能对胰岛α细胞表达胰高血糖素存在影响[22]。

2.1.2 交感神经-肾上腺功能减退 胰高血糖素释放障碍可使低血糖诱导的反调节更加依赖自主神经系统[23]，而机体低血糖的临床表征主要源于交感神经兴奋引起的自主神经症状[24]。然而，IAH患者交感神经反应弱于血糖知觉正常的T1DM患者，存在交感抑制[25]。1994年，有研究提出“低血糖自主神经衰竭(hypoglycemia associated autonomic failure，HAAF)”，认为低血糖警告症状由交感反应受抑制及反调节障碍引发，可诱导IAH并促进低血糖反复发作[26]。胰岛素治疗的晚期T2DM患者因内源性胰岛素绝对缺乏，常发生HAAF而形成IAH[27]。

肾上腺髓质嗜铬细胞分泌的神经肽Y(neuropeptide Y，NPY)可通过Y1受体抑制肾上腺素释放[28]。研究表明，小鼠低血糖反复发作后NPY分泌增加；大量的NPY可降低肾上腺素的分泌能力，加剧反调节障碍并诱发IAH[29]。低血糖时，人体血浆中的β-内啡肽等内源性阿片类物质水平升高[30]，进而激活阿片受体，抑制肾上腺素等升糖激素的反应[31]。反复低血糖可能使这种抑制作用持续存在，并削弱机体对低血糖的反调节能力，进而促进IAH的形成。

2.2 中枢神经系统的代谢适应与感知重塑 大脑作为葡萄糖依赖的器官，在低血糖反复发作时可启动“适应性代谢重塑”，导致低血糖感知障碍。

2.2.1 下丘脑葡萄糖敏感神经元功能异常 下丘脑腹内侧核(ventromedial hypothalamus，VMH)的葡萄糖兴奋性(glucose-excited，GE)和抑制性(glucose-inhibited，GI)神经元是血糖感知的核心[32]。当葡萄糖浓度升高时，葡萄糖通过葡萄糖转运蛋白(GLUT-2)进入GE神经元，邻近线粒体同葡萄糖激酶(glucokinase，GK)聚集于GE神经元胞膜ATP敏感钾通道下方；代谢产生的ATP与ATP敏感钾通道结合，使此通道失活关闭，胞膜去极化；Ca^{2+}通过电压依赖性钙通道(voltage dependent calcium channels，VDCC)进入神经元，从而使GE神经元的代谢活动增强。当葡萄糖浓度降低时，星形胶质细胞糖原代谢产生的乳酸可通过单羧酸转运体(monocarboxylate，MCT)进入GE神经元；进入神经元后乳酸代谢产生的ATP水平足以关闭胞膜表面的ATP敏感钾通道，从而导致GE神经元激活。GK是许多GE和GI神经元中葡萄糖感知的主要调节剂。葡萄糖敏感神经元可通过与内脏交感神经建立多突触连接，从而控制胰腺分泌胰岛素、胰高血糖素，控制肾上腺髓质分泌肾上腺素，以调控血糖水平[33](图1)。反复低血糖发作时，GE神经元通过上调GK维持低葡萄糖环境下的ATP生成，导致反调节启动阈值降低(即需更低血糖才触发反应)[32]；同时，GI神经元因氧化应激受损[34]，而无法有效传递“低血糖信号”[35]。

2.2.2 脑乳酸代谢与糖原储备异常 低血糖时，星形胶质细胞的糖原分解为乳酸[36]，通过单羧酸转运体(monocarboxylate，MCT)供能给神经元[37](图1)。IAH患者的脑乳酸氧化速率明显增高[38]，使神经元在低血糖时仍能维持功能[39]，从而掩盖预警信号[40]。此外，啮齿类动物相关的研究表明，低血糖后的“糖原超代偿”(脑糖原含量较基线增加数倍)[41]可在随后反复发生的低血糖过程中提供额外的能量，从而形成低血糖反调节障碍，诱导IAH的发生。

2.2.3 神经递质与氧化应激的协同作用 (1)下丘脑神经信号转导的改变：γ-氨基丁酸(γ-aminobutyric acid，GABA)是一种主要的抑制性神经递质，可通过离子型受体$GABA_A$、$GABA_C$及代谢型受体$GABA_B$发挥作用。有研究表明，哺乳类动物下丘脑GABA信号在调节CRRs中发挥重要作用[42]。VMH葡萄糖供应量不足可减少其GABA的释放，进而激活低血糖诱发的激素分泌[43]。研究发现，VMH内GABA的活性增加与IAH密切相关[14]；暴露于反复低血糖的啮齿类动物，其下丘脑GABA基线水平升高，且难以通过降低GABA水平以应对低血糖[44]；啮齿类动物对低血糖CRRs减弱时，局部阻断$GABA_A$受体可恢复低血糖CRRs[45]。此外，在T1DM患者中也发现激活$GABA_A$受体可减弱低血糖的交感神经反应[46]。(2)脑氧化应激的增加：急性低血糖可增加下丘脑活性氧(reactive oxygen species，ROS)水平[47]。一氧化氮(nitric oxide，NO)和NO受体可溶性鸟苷酸环化酶(soluble guanylyl cyclase，sGC)的激活是低血糖时激活VMH GI神经元和启动反调节反应的关键[48]。ROS水平升高可导致sGC发生亚硝基化，从而使sGC对NO不敏感[49]，即低血糖诱导下丘脑ROS增加，使NO对其受体sGC的作用受损[50]，从而导致低血糖反调节障碍。

在非糖尿病大鼠中，通过N-乙酰-半胱氨酸(N-acetyl-cysteine，NAC)预处理后可增强谷胱甘肽抗氧化防御，并预防低血糖诱导的VMH ROS的生成，进而可预防IAH发生[50]。因此，使用NAC增加谷胱甘肽的作用可能是治疗IAH的有效方法。然而，暴露于反复性低血糖的糖尿病大鼠，用NAC进行预处理并不能保持VMH内GI神经元的激活[51]。此外，与糖尿病相关的高血糖也可增高大脑的ROS水平[52]。有研究发现，使用与NAC相关的谷胱甘肽可能不足以补偿糖尿病大鼠反复低血糖和高血糖所导致的氧

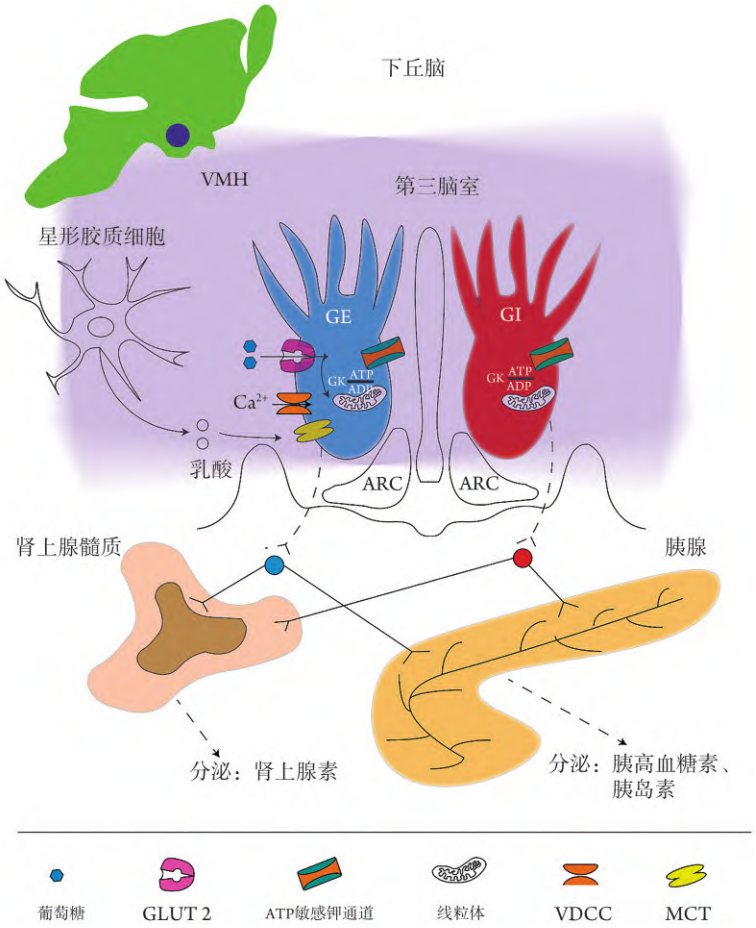

图1 GE与GI神经元的血糖调节模式

Fig.1 Schematic diagram of blood glucose regulation patterns of GE and GI neurons

VMH. 下丘脑腹内侧核；GE. 葡萄糖兴奋性神经元；GI. 葡萄糖抑制性神经元；ARC. 弓状核；GLUT 2. 葡萄糖转运蛋白2；VDCC. 电压依赖性钙通道；MCT. 单羧酸转运体

化应激[51]。而在链脲佐菌素(STZ)诱导的糖尿病大鼠暴露于反复低血糖之前，VMH内硫氧还蛋白-1(thioredoxin-1，Trx-1)的过表达可保留VMH GI神经元的反调节反应[51]。硫氧还蛋白(thioredoxin，Trx)系统由还原型烟酰胺腺嘌呤二核苷酸磷酸、硫氧还蛋白还原酶(thioredoxin reductase，TrxR)和Trx组成，此为抵御氧化应激的关键抗氧化系统[53]。因此，上述研究提示，在VMH中谷胱甘肽和Trx抗氧化系统的联合应用可减弱甚至防止糖尿病患者IAH的发生。

3 诊断及评估

鉴于IAH是当前糖尿病最佳血糖控制的主要障碍，因此其诊断与评估显得尤为重要。由于IAH的诱发主要源于胰岛素的降糖治疗，因此IAH的诊断与评估仅局限于接受胰岛素治疗的糖尿病患者，主要依赖问卷调查，涉及的核心内容包括低血糖病史及对低血糖的认识水平。目前，已开发了多种IAH诊断问卷，其中3种已经过临床验证[54-55]，可满足大样本的需要[11,55]，但同样也存在如下不足。(1)Gold Score问卷：评估低血糖时，受试者只需回答一个问题：您知道您的低血糖发作是何时开始的吗？患者使用特制的量表进行回答[56]。但由于持续血糖监测设备的普及，问卷仅通过单一问题判断，无法区分“自身症状识别”还是“血糖检测器提示”[57]。(2)Clark Score问卷：调查涉及多个维度，由8个问题组成，用于客观回答对低血糖的认识[58]，分值为0~7分，总分≥4分即表示发生IAH[58-59]。然而，该问卷主要依据严重低血糖症状进行评分，持续血糖监测设备的普及导致部分患者严重低血糖的发生减少，同样存在“自身症状识别”还是“血糖检测器提示”这个难以分辨的问题[60]。(3)Pedersen-Bjergaard Score问卷：要求患者回顾以往的低血糖经历，并评估他们识别低血糖症状的能力，该问卷已提供知觉正常、知觉障碍及无知觉等多个水平的独特理解[61]。但该问卷评分特异性不足，存在IAH诊断过度的情况[11]。此外，HypoA-Q问卷为近年来新开发的低血糖评估工具，用于描述IAH的特征。研究表明，与其他问卷相比，此问卷为更加可靠的IAH评估工具[62-63]。

上述评分量表虽可在一定程度上量化低血糖知觉，但受个人感知、文化差异影响较大[57,61,64]。所以，寻找IAH更客观、使用范围更广的生化指标已成为必然。交感-肾上腺髓质系统由交感神经、肾上腺髓质组成，其受损可部分解释IAH的机制[65]。交感神经系统肾上腺素能作用主要通过儿茶酚胺去甲肾上腺素调节，测量突触释放至循环中的去甲肾上腺素可量化交感神经反应，但此策略忽略了去甲肾上腺素的再摄取及其局部代谢，致使低血糖时交感神经的激活状态被严重低估[66-67]。去甲肾上腺素可通过苯乙醇胺N-甲基转移酶转化为肾上腺素，血浆肾上腺素的测量相对容易、准确，虽然不能直接反映交感神经的活动状态[68-69]，但由于交感神经可通过促进肾上腺髓质释放肾上腺素，起到低血糖反调节的作用，因此血浆肾上腺素已作为交感神经活化的指标。当前诸多研究提示，血浆肾上腺素是低血糖反调节受损的金标准[10,12,70]。

4 预防与治疗

糖尿病IAH主要受糖尿病病程、低血糖发生频率、血糖管控的程度及年龄的影响[71]。有研究发现，T1DM IAH患者进行2周的低血糖预防，其低血糖警告症状可恢复正常；3个月的低血糖预防，其低血糖分泌性反调节如胰高血糖素反应等可恢复正常[12]。因此，避免低血糖的发生是糖尿病IAH防治的关键[72]。当前，血糖监测及管控、降糖药物的选择及低血糖教育等是防治糖尿病IAH的重要手段。

4.1 血糖监测与管控 人工胰腺(闭环式胰岛素治疗系统)、实时动态血糖监测(real-time continuous glucose monitoring，rt-CGM)和间歇性扫描式持续血糖监测(intermittently scanned continuous glucose monitoring，isCGM)的问世，使血糖动态监测成为可能[73]。区别于传统的针刺指尖血糖检测，新兴的血糖监测技术减轻了患者的痛苦，增加了依从性。不仅如此，通过计算机算法，人工胰腺可通过改变给药剂量调整胰岛素的基础速率，进而有效地规避低血糖的发生[74]。

此外，良好的生活习惯、适量运动对于血糖的控制至关重要。有研究表明，乙醇为低血糖的重要影响因素，乙醇与血糖降低、反调节障碍、IAH风险增加相关[75]。美国糖尿病学会建议T1DM成年患者适度饮酒，女性每天少于1杯、男性每天少于2杯(1杯约350 ml啤酒或150 ml葡萄酒)，并强调饮酒后血糖监测的必要性[76]。此外，有研究表明，T1DM的IAH患者进行单次高强度间歇运动(high intensity interval training，HIIT)后，再次经历低血糖时，去甲肾上腺素、胰高血糖素及自主神经症状便有所恢复；HIIT可在T1DM患者，即使是极易发生低血糖的患者中安全地实施[77]。

4.2 药物治疗

4.2.1 降糖药物选择 由于糖尿病为慢性代谢性疾病，药物联合使用可明显减少并发症的发生[78]。整合药物的有效性而不增加低血糖的风险是临床医师和患者需要共同面对的问题[79]。有研究发现，T1DM患者使用胰岛素与钠-葡萄糖协同转运蛋白抑制剂可延长餐后葡萄糖的吸收，在不增加低血糖风险的情况下改善患者的血糖和体重[80]。于T2DM患者而言，二甲双胍、胰高血糖素样肽1受体激动剂(glucagon-like peptide-1 receptor agonist，GLP-1RA)或二肽基肽酶4(dipeptidyl peptidase-4，DDP-4)抑制剂的联合应用表现出较低的低血糖风险和更佳的血糖控制[81]。同样，在单独使用胰岛素血糖控制不佳的T2DM患者中，与单独增加胰岛素剂量相比，胰岛素与GLP-1RA或DDP-4抑制剂联用的患者糖化血红蛋白(glycated hemoglobin A_{1c}，HbA_{1c})水平明显降低，且低血糖等不良事件减少[82]。

总之，无论是胰岛素还是口服药物的使用，联合用药对于并发症的控制更加有效，但联合用药的选择要极为慎重，个体化的用药方能在控制血糖的同时减少低血糖的发生，进而避免糖尿病IAH的发生。

4.2.2 药物干预 除在IAH发病机制中提及的GABA拮抗剂、NAC-谷胱甘肽抗氧化系统对IAH药物干预有效外，尚有如下研究：

4.2.2.1 阿片受体拮抗剂 研究发现，低血糖时静脉注射纳洛酮(阿片受体拮抗剂)可增强机体血浆肾上腺素对低血糖的反应[83]。在健康人群[84]和T1DM患者[85]中，低血糖时输注纳洛酮可预防随后反复低血糖IAH的发生。阿片受体拮抗剂作为预防和治疗IAH的药物已进入临床研究阶段[86]。

4.2.2.2 腺苷酸活化蛋白激酶(AMPK) AMPK为一种丝氨酸-苏氨酸激酶，可使多种参与细胞新陈代谢的蛋白质磷酸化，且AMPK可作为葡萄糖的传感器[87-88]。McCrimmon等[89]在反复性低血糖大鼠VMH中注射5-氨基咪唑-4-甲酰胺核糖核苷酸(5-aminoimidazole-4-carboxamide ribonucleotide，AICAR)以刺激AMPK的表达，结果显示，除肝糖生成大量增加外，CRRs也有明显改善。Alquier等[90]在大鼠脑血管内注射AICAR以刺激AMPK的表达，结果发现CRRs可部分恢复。Fan等[91]在T1DM大鼠模型中研究AMPK的激活作用，结果显示，与生理盐水对照组相比，AICAR治疗的糖尿病大鼠的低血糖CRRs有明显改善，提示激活AMPK对IAH治疗有效。鉴于AICAR需要脑内注射，因此，尚需开发一种具有中

枢神经系统渗透性的AMPK外周给药激活剂。最近的研究发现，二甲双胍可激活AMPK，且通过血脑屏障发挥神经保护作用[92-93]，但仍需大规模的临床验证。Cruz等[94]利用健康大鼠研究了一种新型脑渗透性化合物R481，结果发现其药效高于二甲双胍，可提高健康大鼠低血糖时的血浆胰高血糖素峰值。目前，R481制剂对糖尿病啮齿类动物及人类IAH防治的有效性和安全性仍需进一步探讨。

4.2.2.3 ATP敏感性钾通道(K_{ATP})激动剂 K_{ATP}作为葡萄糖的传感器参与胰岛内分泌激素的分泌及其介导的血糖调控，可表达于VMH[95]。McCrimmon等[96]将二氮嗪和替芬那嗪(K_{ATP}激动剂)注入健康大鼠VMH中，发现肾上腺素和胰高血糖素的分泌明显增加；且二氮嗪作用于反复性低血糖大鼠时其作用依然有效，提示K_{ATP}激动剂对IAH有治疗作用。同时，一项针对T1DM患者的人体试验中，7 mg/kg剂量的二氮嗪可明显增加儿茶酚胺的分泌[97]。然而，长时间暴露于ATP敏感钾通道激动剂(如替芬那嗪)可使K_{ATP}构象发生变化，导致对葡萄糖的感知减弱[98]。

4.2.2.4 甲氧氯普胺 甲氧氯普胺常用于治疗糖尿病胃痉挛和胃食管反流病，可拮抗外周和中枢神经系统多巴胺D_2受体。在IAH的啮齿类动物模型中，甲氧氯普胺在恢复低血糖的CRRs中显示出良好的效果[16,99]。目前，一项最新的随机临床试验正在研究甲氧氯普胺对低血糖状态的T1DM患者恢复低血糖意识的作用[16]。

4.2.2.5 肾上腺素能阻断剂 在健康人体内，通过反复输注肾上腺素激活肾上腺素受体，可使CRRs受损导致低血糖[100]。暴露于反复低血糖的糖尿病大鼠模型服用非特异性β肾上腺素能受体阻断剂卡维地洛可防止低血糖CRRs受损[101]。然而，肾上腺素能阻断剂对预防或治疗人类IAH的作用效果仍需进一步的研究证实。

4.2.2.6 生长抑素受体2拮抗剂 有研究表明，在T1DM大鼠模型中，新型生长抑素受体2拮抗剂ZT-01可有效延迟低血糖发作和增加胰高血糖素分泌[102]。在T2DM大鼠模型中，ZT-01治疗可提高胰高血糖素对低血糖的反应，缩短低血糖暴露的时间[103]，甚至在患病前期的大鼠模型中，ZT-01治疗亦可增加胰高血糖素反应性，并延迟胰岛素诱导的低血糖发作[104]。总之，糖尿病IAH的药物干预已受到重点关注并进行了初步研究，目前仍需进一步的动物实验及大量的临床试验来确定糖尿病IAH药物的有效性和安全性。

4.3 结构化教育 《美国内分泌临床实践指南》提倡对糖尿病患者进行结构化教育，即由内分泌专科医师、护士、营养师、心理医师等相关专业人员组成的专业患教团队对各年龄段患者及家属进行个体化、系统化的健康教育[105]。借助动态血糖监测在及时掌握血糖变化的同时，对患者进行治疗和生活的指导可更好地控制血糖，在避免远期并发症的同时可积极预防低血糖的发生[106]。研究表明，接受结构化教育的干预组糖尿病患者的死亡发生率(5.52%)明显低于对照组(9.03%)，提示结构化教育明显降低了糖尿病的死亡风险[107]。T1DM青少年接受结构化教育干预的研究表明，干预3个月时干预组的HbA_{1c}较对照组降低(P=0.019)[108]，提示结构化教育也可明显改善T1DM的疾病控制。

IAH不仅涉及生理改变，还与心理状态密切相关[109]。研究表明，T1DM的IAH人群接受结构化心理教育干预，发生严重低血糖的风险降低[110]，因恐惧低血糖而回避控制高血糖的行为减少[111]。因此，建立和完善社会支持体系对帮助IAH患者具有重要意义，如提供心理咨询、教育培训、社区支持等服务，以帮助IAH患者更好地管理疾病，从而提高其生活质量。随着对IAH研究的不断深入，跨学科合作正成为一个重要的趋势。内分泌学、神经科学、心理学等领域的专家共同合作，通过整合各自领域的专业知识和技术，可为IAH的预防和治疗提供最佳思路和最优策略。

5 总结与展望

IAH是糖尿病患者血糖管控的核心障碍，可由反复低血糖诱发“外周反调节失调-中枢神经代谢适应”双重病理改变；其核心特征为自主神经预警症状减弱、反调节激素分泌缺陷；机制包括外周胰岛α细胞功能障碍、交感神经-肾上腺轴抑制，与中枢下丘脑葡萄糖感知重塑。IAH的治疗中，人工胰腺、联合用药、结构化教育等干预措施疗效显著，但其他的药物治疗多处于动物实验或早期临床阶段，缺乏大规模循证依据的支持。此外，当前关于IAH的研究存在明显的局限：外周反调节失调-中枢神经代谢适应机制未完全阐明；问卷在CGM普及后准确性下降，诊断缺乏客观、早期的特异性指标；药物治疗转化瓶颈突出，靶向药物开发滞后；疾病管理研究未覆盖全年龄人群及特殊人群(如妊娠期糖尿病患者)。因此，未来的研究应聚焦于使用先进技术进一步分析其发病机制，明确关键的靶点；开发CGM的风险预测模型与特异性检测指标，优化诊断；构建多学科团队，将IAH的筛查纳入常规评估，制定个体化目标，完善社会支持，实现从“被动预防”到“主动调控”的转变，为血糖的安全管控提供新支撑。

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