·综　述·

鸢尾素调控葡萄糖稳态的研究进展

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[摘　要]　鸢尾素是一种肌细胞因子,具有诱导白色脂肪褐变、改善胰岛素抵抗等生物学作用。近年来,研究发现鸢尾素具有抑制胰岛β细胞凋亡、增加肌肉和脂肪组织葡萄糖摄取、促进肝糖原合成、抑制肝糖异生及脂肪堆积等作用。鸢尾素通过上述作用能有效维持机体葡萄糖平衡。基于以上理论研究,文章旨在阐述鸢尾素在调节葡萄糖稳态中的作用及其机制。

[关键词]　鸢尾素;糖尿病;葡萄糖稳态;肌细胞因子

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Research progress in regulation of glucose homeostasis by irisin

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[**Abstract**]　Irisin is a myokine with biological effects such as promoting white fat browning and improving insulin resistance. Recently, some studies have revealed that irisin has the functions of inhibiting pancreatic β-cell apoptosis, increasing glucose uptake in muscle and adipose tissue, promoting hepatic glycogen synthesis, and inhibiting gluconeogenesis and fat accumulation. Irisin can effectively maintain the glucose homeostasis in the body through the above effects. Based on the above theoretical studies, this paper aims to describe the role of irisin in regulating glucose homeostasis and its mechanism.

[**Key words**]　irisin; diabetes; glucose homeostasis; myokines

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研究表明,骨骼肌有内分泌功能,可分泌细胞因子和活性肽类物质,这类物质被称为"肌细胞因子"[1]。肌细胞因子是由肌纤维产生和释放,一方面以自分泌方式参与肌肉自身新陈代谢的调节,另一方面,也可通过旁分泌方式调节其他组织和器官(如肝脏、脂肪和大脑等),参与器官间通讯协调,进而调控相关系统功能和稳态[2]。在葡萄糖稳态调节中,骨骼肌细胞因子发挥重要作用。目前已知的肌细胞因子有数百种,如脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、白介素-6(interleukin-6, IL-6)、肌生成抑制素等[3]。其中,鸢尾素是一种重要的肌细胞因子,它通过刺激白色脂肪组织的"褐变",增加能量消耗,减少胰岛素抵抗,改善葡萄糖稳态[4],因此在肥胖和糖尿病等代谢性疾病的调节中起重要作用。进一步研究鸢尾素在葡萄糖代谢过程中扮演的角色及其机制,将有助于预防和治疗肥胖及2型糖尿病(type 2 diabetes mellitus, T2DM)。基于此,本文通过对相关文献总结,旨在阐明鸢尾素调节葡萄糖稳态的方式及其机制,以期为代谢性疾病的治疗提供新思路。

1　鸢尾素的概述

1.1　合成和表达

Boström等[5]在2012年发现一种由肌肉收缩分泌的蛋白分子,称之为鸢尾素。鸢尾素是一种112个

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氨基酸组成的分泌肽,由FNDC5(fibronectin type Ⅲ domain containing protein 5)经过蛋白水解、糖基化和二聚化后合成。FNDC5几乎分布于所有组织和器官中,包括骨骼肌、直肠、心包等组织,其中骨骼肌是表达FNDC5 mRNA最多的组织[6]。大鼠骨骼肌分泌的鸢尾素约72%,以上均提示肌肉组织是鸢尾素的主要来源[7]。骨骼肌收缩可促进过氧化物酶体增加,活化受体γ辅助激活因子-1α(peroxisome proliferators activated receptor gamma coactivator 1 alpha,PGC-1α),进一步使FNDC5高表达,促进鸢尾素分泌[8]。

1.2 生物学效应

鸢尾素通过调控多种细胞内信号,如丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)、腺苷酸激活蛋白激酶[adenosine 5'-monophosphate(AMP)-activated protein kinase,AMPK]、Wnt信号通路(wingless/integrated,Wnt)、信号转导与转录激活因子(signal transducer and activator of transcription3,STAT3)、磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase,PI3K)/蛋白激酶B(protein kinase B,AKT)等途径发挥生物学作用。MAPK作为细胞信号重要的传递者,鸢尾素通过活化MAPK参与成骨细胞的增殖和分化、神经细胞分化、胰岛细胞增殖以及白色脂肪褐变[9-12]。此外,鸢尾素也激活AMPK通路刺激骨骼肌葡萄糖摄取,改善骨骼肌胰岛素抵抗[13]。在脂代谢方面,鸢尾素可作为Wnt信号通路的激活剂,抑制脂肪细胞分化[14]。鸢尾素也在脑部器质性病变,如"阿尔兹海默症"中发挥作用,其可通过血脑屏障进入中枢系统激活STAT3信号通路,促进海马增生,降低阿尔兹海默症的患病风险[15]。重要的是,PI3K/AKT通路是癌细胞生长、增殖和存活的关键通路之一[16],鸢尾素通过抑制PI3K/AKT途径阻滞肺癌的迁移、增殖和侵袭[17]。综上所述,鸢尾素可作为预防/治疗包括癌症在内的多种疾病,因此进一步深入了解鸢尾素的作用机制对于鸢尾素的临床应用至关重要。

2 鸢尾素参与葡萄糖稳态调节

2.1 葡萄糖稳态

在正常情况下,血液中葡萄糖水平在3.89~6.11 mmol/L范围内波动,这种状态称之为葡萄糖稳态。当机体摄入葡萄糖时,可激活下丘脑葡萄糖抑制神经元,引起迷走神经兴奋,刺激胰岛β细胞释放胰岛素,同时迷走神经通过刺激胃肠道激素释放间接促进胰岛素分泌。胰岛素作为机体内唯一降糖激素,其降低血糖的主要机制包括:①促进肌、脂肪细胞摄取葡萄糖;②加速肝、肌糖原的合成及抑制糖原分解;③增加葡萄糖有氧氧化;④抑制肝内糖异生;⑤抑制脂肪组织内的激素敏感性脂肪酶,减少脂肪动员进而以葡萄糖分解获能。当血糖浓度降低,刺激下丘脑内侧核,引起交感神经兴奋,抑制胰岛素分泌,促进胰高血糖素分泌,其主要机制为:①增加肝糖原分解;②促进糖异生;③增加脂肪分解;此外肾上腺素、糖皮质激素等也参与血糖升高的调节[18-21]。综上所述,机体葡萄糖稳态平衡是在神经系统和体液共同调控下,使得胰腺、肝、肌、脂肪组织等各器官协调作用,以维持体内葡萄糖含量的相对稳定(图1)。

2.2 鸢尾素调节葡萄糖稳态平衡的机制

鸢尾素可以降低胰岛素抵抗,有效改善血糖和减轻体重。Pang等[22]研究发现,经过腹腔注射鸢尾素10 d的T2DM大鼠,其空腹血清胰岛素和空腹血糖水平均明显下降。Liu等[9]研究显示,鸢尾素治疗T2DM大鼠8周可降低大鼠体重和空腹血糖,改善葡萄糖耐量。基于此,鸢尾素在改善葡萄糖稳态失调方面具有重要作用,并且鸢尾素调节葡萄糖稳态的机制主要以降糖为主,目前认为主要有以下几点(图1)。

2.2.1 鸢尾素促进胰岛β细胞增殖、抑制胰岛β细胞凋亡

鸢尾素可以影响参与凋亡通路的蛋白,如半胱氨酸天冬氨酸蛋白酶-3(cysteinyl aspartate specific proteinase,caspase-3)、caspase-9、B细胞淋巴瘤-2(B-cell lymphoma,Bcl-2)、Bcl-x等的活性,逆转高糖诱导的胰岛β细胞凋亡。在体外实验,鸢尾素处理高糖诱导的胰岛细胞可使caspase-3、caspase-9、Bad、Bax等促凋亡蛋白水平下调,Bcl-2和Bcl-xl等抗凋亡蛋白上调,同时,鸢尾素也可通过激活细胞外信号调节激酶(extracellular signal-regulated kinase,ERK)/p38MAPK通路促进胰岛β细胞增殖,使得胰岛素分泌增多,改善胰岛β细胞的功能[9]。在动物试验中,鸢尾素治疗肥胖小鼠2周可促进胰岛β细胞增殖,并且增加胰岛β细胞/胰岛α细胞比值[23]。

2.2.2 鸢尾素增加骨骼肌葡萄糖摄取

葡萄糖吸收入血需依赖葡萄糖转运蛋白(glucose transporter,GLUT)转运至细胞膜表面。以GLUT4最为重要,其主要存在于肌肉和脂肪组织中,以胰岛素依赖的方式摄取葡萄糖[24]。研究发

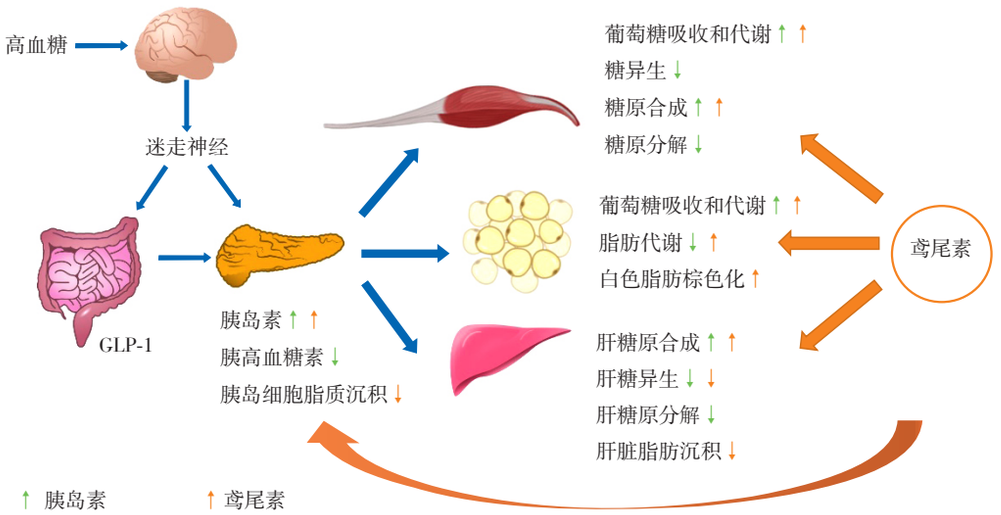

图1　鸢尾素调节葡萄糖稳态的途径

Figure 1　The pathways of irisin regulating glucose homeostasis

现，鸢尾素可以促使细胞内GLUT4易位，促进骨骼肌葡萄糖摄取。一方面，经鸢尾素处理的胰岛素抵抗小鼠C2C12肌细胞以浓度梯度依赖的方式促进AMPK的磷酸化，进而加强GLUT4易位[13,25]。另一方面，Ye等[26]研究也显示，予胰岛素抵抗小鼠C2C12肌细胞鸢尾素处理后，鸢尾素可依赖于p38MAPK/PGC-1α通路促进骨骼肌内GLUT4易位增加，逆转高糖诱导的胰岛素抵抗。同时，AMPK和p38MAPK信号并不是彼此孤立，而是存在复杂的交互作用[27]，鸢尾素可通过钙/活性氧（reactive oxygen species，ROS）介导AMPK途径进一步激活p38MAPK磷酸化，促进骨骼肌葡萄糖摄取及GLUT4易位[28]。

2.2.3　*鸢尾素增加脂肪组织葡萄糖摄取*

白色脂肪“褐变”在葡萄糖稳态中发挥重要作用[29]，鸢尾素可诱导白色脂肪向棕色脂肪转化，增加机体胰岛素敏感性和促进脂肪葡萄糖摄取，在维持机体葡萄糖稳态平衡中具有重要作用[30]。在体外试验中，鸢尾素处理人皮下成熟脂肪细胞发现，鸢尾素可通过p38MAPK和ERK途径迅速上调棕色脂肪标志物，如解偶联蛋白1（uncoupling protein 1，UCP-1）、PGC-1a等表达，促进白色脂肪“褐变”，提高新陈代谢，增加外周组织对胰岛素的敏感性[31]。随后，此团队进一步探讨鸢尾素在内脏脂肪中的效应，发现鸢尾素可以促进内脏脂肪细胞产热但并不能显著增加棕色脂肪基因，如UP1、CD137等表达，且p38MAPK和ERK通路并未被激活[32]，这提示鸢尾素未能激活内脏脂肪组织“褐变”。而近年研究表明，鸢尾素可通过激活p62/核因子E2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）/血红素氧合酶-1（hemeoxygenase-1，HO-1）通路，上调棕色脂肪特异性标记蛋白PGC1-α、PRDM16和UCP-1的表达，诱导小鼠前脂肪细胞白色褐变[33]。综上所述，鸢尾素可诱导白色脂肪“褐变”，促进葡萄糖摄取，但其机制尚未完全阐明，仍需进一步研究。

2.2.4　*鸢尾素促进肝糖原合成、抑制糖异生*

肝脏是糖原合成和糖异生的主要器官，主要受糖原合成酶激酶3（glycogen synthase kinase-3，GSK3）、糖原合成酶、磷酸烯醇式丙酮酸羧激酶（phosphoenolpyruvate carboxykinase，Pepck）和葡萄糖-6-磷酸酶（glucose-6-phosphatase，G6pase）调控，其在糖尿病中异常激活。Liu等[34]研究发现，鸢尾素通过PI3K/Akt/叉头转录因子O1（forkhead box transcription factor O1，FOXO1）途径，下调糖异生关键酶Pepck和G6pase表达，减少肝脏糖异生，同时鸢尾素激活PI3K/Akt/GSK3通路上调糖原合成酶表达，促进肝糖原合成。进一步在体实验证实，鸢尾素也可通过激活AMPK通路降低Pepck和G6pase在肝脏中的表达，抑制糖异生，增加糖尿病小鼠的肝脏组织葡萄糖利用率[13,35]。

2.2.5　*鸢尾素抑制脂肪堆积*

当葡萄糖摄入量超过机体储存和氧化能力时，过量的葡萄糖和血脂协同促脂质沉积于肝细胞、β细胞等组织中，这是发生肝脏胰岛素抵抗和β细胞功能衰竭的主要发病机制[36-37]。鸢尾素可调节脂肪合成因子，如肝X受体α（liver X receptor α，LXRα）、胆固醇调节元件结合因子（sterol regulatory element binding transcription factor，SREBP）1c的活性，阻止棕榈酸诱导肝细胞脂质积累，降低甘油三酯含量，

改善肝脏胰岛素抵抗[35,38-39]。鸢尾素也可抑制脂肪合成关键酶,如乙酰辅酶A羧化酶(acetyl-CoA carboxylase,ACC)和脂肪酸合成酶(fatty acid synthase,FAS)的表达,阻止脂质沉积。Tang等[40]研究发现,鸢尾素通过激活AMPK抑制SREBP2、FAS的表达,降低小鼠原代肝细胞和肥胖小鼠的胆固醇含量。同样的,这一作用在胰岛β细胞中也有类似发现,鸢尾素处理饱和脂肪酸-高葡萄糖培养基培养的胰岛细胞,可激活AMPK通路抑制ACC和FAS的表达,减缓胰岛细胞内脂质的过度积聚,从而降低高糖、高脂对胰岛β细胞的不利影响,提高胰岛细胞的生存率[41]。

3 展 望

鸢尾素作为一种多效性蛋白已受到广泛关注,将成为治疗肥胖、骨质疏松、肿瘤、心脑血管疾病和代谢性疾病的潜在靶点,在临床应用中具有一定前景。大量研究表明,鸢尾素在降糖途径中发挥了重要作用,这揭示了调控鸢尾素具有诊治以高血糖为特征的葡萄糖稳态失调性疾病,如T2DM。

与传统胰岛素注射剂相比,鸢尾素在降低血糖的同时可以减少脂肪堆积,更好地控制患者体重,但是鸢尾素的体内半衰期只有0.5~1 h,这为鸢尾素制剂的开发应用带来挑战。随着鸢尾素受体的不断涌现,如整合素αV/β5,可以进一步研发鸢尾素类似物来取代鸢尾素在体内发挥的作用,以此规避鸢尾素半衰期短的弊端。同时,进一步阐明鸢尾素在葡萄糖稳态失调所致疾病不同阶段的表达差异,可为该类疾病诊断及预防带来新的可能。近年来它与临床药物相关的研究不断深入,已有文章报道,部分降糖药物,如二甲双胍,通过激活鸢尾素发挥药物疗效[42],但目前尚无鸢尾素特异性调节剂,进一步深入研究鸢尾素的激活或抑制剂,可加速鸢尾素在基础-临床转化医学应用中的研究进程,为葡萄糖稳态失调所致疾病的治疗开辟新路径。

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