·文献综述·

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内脂素与糖尿病大血管并发症的关系

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[关键词] 内脂素; 炎症因子; 糖尿病; 血管并发症

[摘 要] 内脂素是一种主要由内脏脂肪细胞分泌的蛋白质细胞因子,具有调节糖脂代谢、炎症等多种生物学活性。临床研究发现肥胖、2型糖尿病和代谢综合征患者血清中内脂素显著增高,其中伴动脉粥样硬化患者更为显著,从而推测血清中内脂素可能与糖尿病大血管并发症的发生密切相关。文章拟对内脂素的生物学效应及在糖尿病大血管并发症发生发展中的作用进行综述。

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The Relationship of Visfatin and Macrovascular Complications in Diabetes Mellitus

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[KEY WORDS] Visfatin; Inflammatory Cytokines; Diabetes Mellitus; Vascular Complications

[ABSTRACT] Visfatin is a novel pro-inflammatory adipokine which was predominantly produced and secreted in visceral fat, involved in regulating glucose and lipid metabolism, inflammation, and so on. In clinical study, serum visfatin was obviously elevated in patients with obesity, type 2 diabetes and metabolic syndrome, especially higher among patients with atherosclerosis. The results suggest that visfatin is closely correlated to macrovascular complications in diabetes mellitus. This paper will review the biological effects of visfatin and its influence on macrovascular complications in diabetes mellitus.

内脂素(visfatin)最早是在研究人前 B淋巴细胞成熟、活化过程中发现、分离出来的一种称为前 B细胞克隆增强因子(pre-B cell colony-enhancing factor, PBEF)的免疫多肽,属于一种生长因子。后来日本科学家 FuKuhara等[1]在研究一种内脏脂肪组织特异性高表达的分泌性蛋白时发现其 cDNA片段与 PBEF基因 5'端非翻译区的基因序列一致,故又命名为内脂素。近年来,越来越多的研究表明,内脂素不仅能跟胰岛素受体结合发挥类胰岛素作用;还具有尼克酰胺磷酸核糖转移酶(nicotinamide phosphoribosyl transferase, NAmPRTase)活性,促进尼克酰胺腺嘌呤二核苷酸(NAD)合成;促进内皮细胞、单核巨噬细胞等表达白细胞介素 1(interleukin-1, IL-1)、肿瘤坏死因子 α(tumor necrosis factor alpha, TNF-α)和 IL-6等炎性介质,在肥胖、糖尿病及心血管疾病的发病机制中可能起重要作用。本文拟对内脂素的生物学功能及其对糖尿病大血管并发症的作用及机制做一综述。

1 内脂素的结构、基因表达及调控

内脂素是由 473个高度保守的氨基酸序列组成,相对分子质量为 52 kDa。其基因位于 7号染色体长臂 7q22.1~7q31.33区域,包括 11个外显子和 10个内含子,全长约 34.7 kb[2,3]。5'端上游 3.2 kb包括富含 GC的长约 1.4 kb近端启动子片段和富含 AT的长约 1.6 kb远端启动子片段。近端启动子片段含有 12个 SP1和多个 AP-2、LF1结合位点,远端启动子片段含有多个 TATA盒及 CAAT盒,同时还含有与 CCAAT/NF1、核因子 κB、GR、AP-1结合的转录调节元件。两个启动子片段都含有多种激素和化学应答调节元件,如糖皮质激素受体、促肾上腺皮质激素释放激素、cAMP反应元件结合蛋白的结合位点,对其转录激活起重要作用,这在一定程度上也提示内脂素在不同组织中的表达可能不同[3]。

内脂素除在内脏脂肪组织中高度表达外,淋巴细胞、单核巨噬细胞、肝脏、肌肉、肾脏和心脏等组织细胞中也有表达[4,5]。体外研究发现,生长激素、异丙肾上腺素、TNF-α和 IL-6显著抑制 3T3-L1细胞表达内脂素,而地塞米松则刺激其表达内脂素[6]。Haider等[7]对健康人随机双盲对照试验发现,高浓度葡萄糖能显著升高循环中内脂素水平,同时外源性胰岛素和生长抑素可降低高糖对内脂素的刺激作用。这些研究说明,内脂素与肥胖、糖尿病的发生高度相关。

2 内脂素的生物学功能

2.1 胰岛素样功能

内脂素可显著降低糖尿病小鼠的血糖,其效果与注射剂量呈正相关。敲除小鼠的内脂素基因,其血浆内脂素浓度下

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降同时血糖浓度升高,转染含有内脂素编码基因质粒,血糖和胰岛素水平明显下降[2]。通过非竞争性结合并启动胰岛素受体,启动下游的磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)-蛋白激酶 B(proteinkinaseB, PKB)/AKt信号转导分子,可促进葡萄糖载体(GLUT4)活化,模拟胰岛素作用,诱导肌肉细胞(L6)和脂肪细胞(3T3-L1)摄取葡萄糖,抑制肝细胞(H4ⅡEC3)糖原分解。在对成骨细胞钙化的研究中也发现内脂素类似胰岛素样效应[8]。这些都提示内脂素应该具有类似于胰岛素的作用。

2.2 尼克酰胺磷酸核糖转移酶活性

烟酰胺(nicotinamide adenine dinucleotide, NAD)是Ⅲ型组蛋白去乙酰化酶(histone deacetylase, HDAC)又称沉默信息调节因子(silence information regulators, SIRT)的必需辅助因子,高度保守的 SIRT1/Sir2α蛋白调节一系列细胞生物过程,如应激、分化、新陈代谢和细胞成熟[9]。内脂素具有NAmPRTase活性,能促进血管平滑肌细胞中 NAD^+ 表达量,增加 NAD^+ 依赖的去乙酰化酶活性,激活 SIRT1介导的去乙酰化和加速 p53的降解,诱导血管平滑肌细胞的成熟和抑制其凋亡[10]。敲除内脂素基因可抑制血管平滑肌的分化成熟并促进其凋亡,转染内脂素编码基因的载体可得到逆转[11]。

2.3 促炎性细胞因子功能

运用荧光激活细胞分类法,Curat等[12]发现内脂素在人内脏脂肪组织的巨噬细胞高水平表达,证明肥胖人群内脏脂肪中内脂素水平的增高可能与脂肪组织中巨噬细胞的浸润、活化有关。内脂素与 IL-7、SCF协同,共同促进前 B淋巴细胞集落形成和细胞的成熟、活化[13]。通过抑制半胱氨酸蛋白酶(caspase-8和 caspase-3)的活性延缓脓毒症危重病人中粒细胞凋亡[14];诱导 $CD14^+$ 单核细胞表达 IL-1β、TNF-α和 IL-6,刺激 BALB/c小鼠体内血浆 IL-6浓度的增高[15]。临床观察发现血清内脂素水平与 IL-6及 C反应蛋白(CRP)呈显著正相关,在排除年龄、性别、体质指数、体脂百分比和腰围等多因素影响后,血清内脂素与 IL-6或 CRP仍然有显著相关性[16]。

3 内脂素与糖尿病大血管并发症

3.1 内脂素与糖尿病

内脂素诱导小鼠胰岛 β细胞中几个关键的糖尿病相关的基因(如肝细胞核因子 HNF-1β)表达,能够促进胰岛素的分泌,而这种作用可被内脂素特异性抑制剂 FK866抑制[17]。流行病学调查发现,糖尿病患者血浆内脂素随胰岛 β细胞功能减退而升高[18],2型糖尿病一级亲属中肥胖者和单纯肥胖者内脂素水平高于 2型糖尿病一级亲属非肥胖者和健康对照组,并且内脂素与空腹血糖呈独立负相关[19]。而初诊 2型糖尿病患者血浆内脂素水平也与糖代谢和肥胖类型(中心型肥胖)有关[20]。减肥后,肥胖患者体内升高的内脂素可降低,胰岛 β细胞功能可以得到改善[21]。但是目前这个结果仍然存在争议[22,23],并且肥胖及糖代谢异常者血浆内脂素水平的增高是由于对胰岛素作用的代偿还是炎症细胞因子作用所致也不清楚。

3.2 内脂素与血管内皮细胞

血管内皮功能障碍是动脉粥样硬化发生的起始阶段,也是其中心环节。内皮细胞是众多动脉粥样硬化危险因子作用的重要靶点,并合成和释放多种活性因子,在血管自稳态调节中起重要作用。Takebayashi等[24]研究发现 2型糖尿病患者血浆内脂素水平与 FMD和内生肌酐清除率呈负相关;慢性肾脏疾病患者血浆中升高的内脂素明显与 CD40L、细胞间黏附分子(intercellular adhesion molecule, ICAM)、血管细胞黏附分子(vascular cell adhesion molecule, VCAM)和 CD146相关联[25];这些均提示内脂素与损伤的内皮功能有关。但是内脂素对血管内皮细胞功能的影响及机制目前尚不明了。有研究发现,内脂素通过激活细胞信号调节激酶 ERK1/2,使血管内皮细胞成纤维生长因子 2(fibroblast growth factor-2, FGF-2)表达上调,内皮细胞迁移、浸润及形成新生血管芽,抑制 ERK的活性,FGF-2表达下调,并且能明显降低内脂素诱导新生血管和小鼠主动脉环的内皮细胞芽的形成[26,27]。内脂素还可通过激活 p38丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)、核因子 κB和 PI3K途径,促进血管内皮细胞表达 IL-6、血管内皮生长因子(vascular endothelial growth factor, VEGF)、基质金属蛋白酶 2(matrix metalloprotease-2, MMP-2)/9和细胞黏附分子 ICAM-1、VCAM-1,诱导内皮细胞炎性损伤、单核细胞的黏附以及单核细胞向内皮下迁移,其作用成时间和剂量依赖性[28-30]。关于内脂素对血管内皮细胞功能的影响目前研究结果并不一致,也有学者认为血管内皮细胞中内脂素/Nampt活性的增强,可能有利于在高糖环境中损伤的血管内皮细胞修复和再生,延缓动脉粥样硬化及糖尿病其他相关血管并发症的发生[31]。这些不同的研究结果可能与相关的研究较少、研究的对象及细胞内外环境不同有关。

3.3 内脂素与糖尿病大血管病变

血管壁慢性的低度炎症反应是糖尿病大血管并发症的病理生理基础。代谢性疾病患者体内升高的内脂素可能通过激活 ERK1/2和核因子 κB,促进血管平滑肌细胞炎症反应,加速血管功能紊乱和功能异常[32]。临床研究发现,代谢综合征伴动脉粥样硬化斑块者、冠状动脉疾病或急性冠状动脉综合征患者以及急性缺血性脑卒中患者血浆内脂素明显增高,通过多元回归分析发现内脂素是动脉粥样硬化的独立相关影响因子,其动脉内膜中膜厚度与血清内脂素浓度相关[33-35]。在有症状的颈动脉狭窄患者的颈动脉斑块中发现内脂素表达明显高于无症状患者,急性心肌梗死患者斑块破裂区内脂素免疫组织化学染色强阳性并且聚集于富含脂质的巨噬细胞中;氧化型低密度脂蛋白和 TNF-α促进单核细胞株 THP-1表达内脂素,同时内脂素增强单核细胞 THP-1的 MMP-9活性,并增加外周单核细胞 IL-8和 TNF-α表达,并有很强的基质降解和炎症作用[36]。但也有研究发现血清内脂素水平与 2型糖尿病有关,与有无血管并发症无关[37]。

4 结束语

内脂素是一种主要由脂肪组织分泌的具有结合并激活

胰岛素受体、模拟胰岛素作用的促炎症因子,与肥胖、胰岛素抵抗、糖尿病和动脉粥样硬化等多种病理生理状态相关,目前已引起人们越来越多的关注。到目前为止,其作用机制及调节等方面已经取得了一些成果,但很多研究结果并不完全一致,其确切生理作用也并不十分清楚,尚存在争议。总之,对内脂素的深入研究可能进一步揭示肥胖、胰岛素抵抗、糖尿病等代谢性疾病及其大血管并发症的发生机制,并将为糖尿病及代谢综合征提供新的治疗方法和思路。

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