

鞘脂类对胰岛素信号的调控*

——Ⅱ型糖尿病研究的新兴领域

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摘要 胰岛素抵抗是Ⅱ型糖尿病的病理基础之一, 近年来已成为Ⅱ型糖尿病研究的关键和热点. 众多研究发现, 机体内鞘脂类物质水平的改变直接影响胰岛素信号的强弱. 神经酰胺和神经节苷脂 GM3 对胰岛素信号具有负向调控作用, 介导胰岛素抵抗的形成, 该调节效应依赖于细胞膜上微囊蛋白. 1-磷酸鞘氨醇则通过氧化还原途径增强胰岛素信号. 微囊蛋白功能性活动和 1-磷酸鞘氨醇的介导作用均与钙信号相关, 因此, 可通过实时检测细胞外钙内流和细胞内钙瞬间变化, 从离子通道水平进一步探索鞘脂类调节胰岛素信号的相关机制. 本文综述了鞘脂类物质调控胰岛素信号的机制, 干预鞘脂类水平和改善胰岛素抵抗的策略, 将为鞘脂类物质在Ⅱ型糖尿病预防和治疗的研究及应用提供有力的帮助.

关键词 鞘脂类, 神经酰胺, 神经节苷脂 GM3, 1-磷酸鞘氨醇, 胰岛素抵抗, 钙信号

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随着人们生活水平的提高, 高糖高脂食物摄入过多, 肥胖和Ⅱ型糖尿病的发病率越来越高. 尽管并非肥胖病者都有Ⅱ型糖尿病, 然而迄今发现的肥胖病患者都存在胰岛素敏感性降低现象, 即胰岛素抵抗(insulin resistance). 胰岛素抵抗是Ⅱ型糖尿病研究的关键和热点^[1], 也是肥胖病和糖尿病的共同病理基础^[2]. 近年来研究发现, 体内鞘脂类物质水平的改变, 直接影响胰岛素信号的强弱^[3]. 脂质代谢异常与胰岛素抵抗的形成密切相关, 一方面, 脂质过度积累引起的氧化损伤, 可诱发胰岛素抵抗^[4], 另一方面, 脂质代谢中的鞘脂类物质, 通过调节胰岛素信号分子, 介导胰岛素抵抗的形成^[5].

鞘脂类(sphingolipids)主要包括神经酰胺(ceramide)、葡糖神经酰胺(glucosylceramide)及其衍生物^[6], 虽然在组织中含量不高, 却对细胞信号转导, 尤其是胰岛素信号起重要的调节作用^[7]. 胰岛素信号下游分为代谢效应和增殖效应. 代谢效应表现为细胞膜上胰岛素受体激活受体底物, 受体底物活化磷酸肌醇-3-激酶(phosphoinositide-3-kinase, PI3K), 最终使葡萄糖转运体 4(glucose transporter 4, GLUT4) 扦插到质膜上, 促进葡萄糖摄取. 同时,

PI3K 能激活丝氨酸/苏氨酸蛋白激酶 Akt, 而活化的 Akt 可抑制糖原合酶 3 β (glycogen synthase kinase-3 β , GSK3 β), 解除 GSK3 β 对糖原合成的抑制作用^[8]. 增殖效应表现为启动 Ras-MAPK-ERK 信号通路, 介导细胞有丝分裂过程, 调节细胞增殖、分化、凋亡和炎症反应^[9]. 在骨骼肌、肝脏和心脏等组织细胞中, 胰岛素信号主要表现为代谢效应的调控^[10]. 鞘脂类调节胰岛素抵抗的研究已成为当前研究的热点, 形成Ⅱ型糖尿病研究的新兴领域^[1].

1 鞘脂类物质合成与代谢

神经酰胺和葡糖神经酰胺在鞘脂类代谢中处于关键位置^[11]. 神经酰胺的合成途径包括从头合成

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(de novo) 和鞘糖脂 (glycosphingolipid) 及鞘磷脂 (sphingomyelin) 分解两种方式^[12]。简言之, 神经酰胺由丝氨酸和十六酰辅酶 A 在一系列酶的作用下形成。同时, 神经酰胺能够转化为多种鞘脂类物质, 如鞘磷脂、鞘氨醇 (sphingosine) 和葡糖神经酰胺等。其中, 鞘氨醇可转化成 1- 磷酸鞘氨醇 (sphingosine-1-phosphate, S1P)^[13], 葡糖神经酰胺可转化成单唾液酸神经节苷脂 (ganglioside monosialo 3, GM3)^[14]。该过程中, 对胰岛素信号具有显著调控效应的产物包括神经酰胺、神经节苷脂 GM3 和 1- 磷酸鞘氨醇。神经酰胺和神经节苷脂 GM3 对胰岛素信号起负向调控作用, 促进胰岛素抵抗的形成^[10, 12]。相反地, 1- 磷酸鞘氨醇可增强胰岛素信号, 遏制胰岛素抵抗的产生^[15] (图 1)。

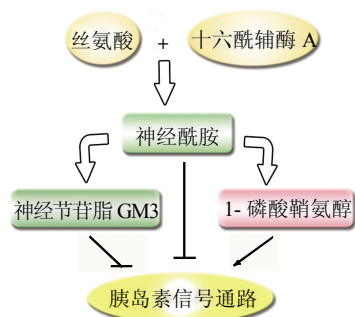


Fig. 1 Sphingolipids synthesis and the regulation of insulin signaling

图 1 鞘脂类物质合成及对胰岛素信号的调控

⇨: 转化反应; →: 增强效应; ┐: 抑制效应。

2 鞘脂类对胰岛素信号的调控

鞘脂类与细胞多种生理功能密切相关, 参与有丝分裂、细胞凋亡、炎症反应等过程的调控^[16-17]。研究表明, 鞘脂类物质, 尤其是神经酰胺、神经节苷脂 GM3 和 1- 磷酸鞘氨醇, 可调控胰岛素信号通路, 介导胰岛素抵抗的形成^[11, 15]。

2.1 神经酰胺对胰岛素信号的作用

实验证明, 神经酰胺可抑制胰岛素信号。其中, 胰岛素受体及其底物未受影响, 但丝氨酸 / 苏氨酸激酶 Akt 的活化水平产生变化^[18]。Akt 是胰岛素信号通路的关键分子, 其活化水平的降低将直接导致胰岛素抵抗的形成^[19]。目前认为神经酰胺对 Akt 的抑制存在两种机制, 一是阻断 Akt 向质膜转运, 二是先激活蛋白磷酸酶 PP2A (protein phosphatase 2A), PP2A 再使 Akt 去磷酸化, 导致 Akt 失活^[18]。

神经酰胺可通过非典型蛋白激酶 C (protein kinase C, PKC) λ/ζ 亚型干扰细胞内 Akt 的转运。PKC λ/ζ 半胱氨酸富集结构域与神经酰胺结合, 从而激活 PKC λ/ζ , 活化的 PKC λ/ζ 磷酸化位于 Akt 内第 34 位丝氨酸或苏氨酸残基 (pleckstrin 同源结构域 (PH domain) 所在片段), 降低 PH 与 PIP3 的亲合力, 导致 Akt 无法正常富集到质膜, 影响其后续活化^[12]。

此外, 神经酰胺对 Akt 信号通路的负向调节机制可以相互转换。这取决于质膜的结构组成。在微囊蛋白富集区域 (caveolin-enrich microdomain, CEM), 神经酰胺通过 PKC ζ 途径发挥效应。在缺乏 CEM 的区域, 神经酰胺通过 PP2A 途径抑制 Akt 活性。运用腺病毒转染, 使微囊蛋白超量表达, 可使 PP2A 途径为 PKC ζ 途径所取代^[20]。实验证明, 往糖尿病模型肥胖小鼠肝脏转染微囊蛋白基因, 使微囊蛋白超表达, 表现出胰岛素信号增强^[21]。由此可见, 微囊蛋白在神经酰胺调控胰岛素信号中起关键作用, 提示微囊蛋白可以作为防治肥胖和 II 型糖尿病的潜在靶点。

2.2 神经节苷脂 GM3 对胰岛素信号的影响

神经节苷脂通过非共价键与细胞膜上的分子相连, 其表达水平为胞外信号所诱导, 细胞因子 TNF α 可提高神经节苷脂 GM3 的水平^[19]。各种神经节苷脂物质中, GM3 是膜上主要成分之一, 参与胰岛素信号的调控。细胞膜上存在质膜微囊 (caveolae) 结构, 该区域富含鞘脂类和微囊蛋白 -1 (caveolin-1, Cav1), 同时, 胰岛素受体位于该区域并与 Cav1 相互作用。当质膜上 GM3 表达量过高时, GM3 通过与胰岛素受体 β 亚型跨膜片段上第 944 位赖氨酸结合, 与 Cav1 争夺胰岛素受体, 使胰岛素受体移至微囊外而丧失功能, 导致胰岛素抵抗形成^[19]。与此相反, 提高微囊蛋白 -1 或微囊蛋白 -3 表达水平, 则促进微囊结构的形成, 进而增强胰岛素信号, 提高胰岛素受体磷酸化水平, 促使糖原合成^[21]。

神经节苷脂是神经酰胺的下游产物, 在 I 型高雪氏症 (Gaucher disease)——一种遗传性溶酶体贮积症 (lysosomal storage disorder) 中, 葡糖神经酰胺不能被正常降解而积累, 导致 GM3 水平过高, 影响胰岛素信号通路并诱导了胰岛素抵抗, 最终导致葡萄糖摄取能力降低^[22]。在 II 型糖尿病、高血糖和高血脂患者中观察到 GM3 水平高于正常水平^[23]。运用药理学方法抑制葡糖神经酰胺合酶, 限制细胞

糖神经酰胺合酶的 AMP-DNM 和 Genz-123346 等^[12].

此外, 饱和脂肪酸作为神经酰胺合成的来源, 加速胰岛素抵抗的形成^[40]. 超量表达十八酰辅酶 A 的去饱和酶, 使饱和脂肪酸转化为单不饱和脂肪酸, 能够提高胰岛素信号的敏感性^[41]. 另有报道, 单不饱和脂肪酸可通过 PI3K 途径维持胰岛素敏感性^[42]. 十二碳五烯酸(eicosapentaenoic acid, EPA) 通过降低 PPAR α/δ 和增加 GLUT4, 强化胰岛素信号通路^[43]. ω -3 多不饱和脂肪酸亦能防止饱和脂肪酸诱导的脂联素(adiponectin)失调与胰岛素抵抗, 其中, 脂联素具有促进脂肪酸氧化和提高胰岛素敏感性的功效^[44]. 然而, ω -6 多不饱和脂肪酸却使肌细胞神经酰胺水平升高, 并诱发葡萄糖耐受不良(glucose intolerance)^[45]. 这说明, 协调体内饱和脂肪酸与不饱和脂肪酸, 有助于胰岛素信号的维持, 可作为预防胰岛素抵抗的优化策略.

5 小结与展望

鞘脂类是细胞结构的物质基础, 也是细胞信号转导的调节因子. 大量报道证明, 神经酰胺和神经节苷脂 GM3 对胰岛素信号具有负向调控作用, 并且两者均与微囊蛋白有关^[20-21]. 1-磷酸鞘氨醇则通过氧化还原途径增强胰岛素信号^[15]. 无论微囊蛋白的活动, 还是氧化还原途径, 都提示钙信号的参与^[15, 32]. 因此, 建立实时检测细胞外钙内流和细胞内钙瞬时变化的体系, 可探索防控胰岛素抵抗的新策略.

干预神经酰胺从头合成与抑制葡萄糖神经酰胺合酶, 可分别降低神经酰胺和神经节苷脂 GM3 的水平, 以防治胰岛素抵抗^[12]. 另外, 协调饱和脂肪酸与不饱和脂肪酸, 亦有助于维持胰岛素信号^[41]. 机体代谢和细胞代谢极其复杂, 调控鞘脂类水平对于改善胰岛素抵抗、预防肥胖和 II 型糖尿病等代谢型疾病具有重要意义.

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Modulation of Sphingolipids on Insulin Signal*

—an Emerging Research Field of Type 2 Diabetes Mellitus

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Abstract Insulin resistance is a pathological basis for the development of type 2 diabetes mellitus (T2DM), and has been a key and hot topic for T2DM research recently. Furthermore, an increasing number of reports demonstrate that some sphingolipids play a critical role in regulating insulin signal. For instance, both ceramide and ganglioside monosialo 3 (GM3) can reduce insulin signal sensitivity and lead to insulin resistance. Their mechanisms may be associated with caveolin localization and formation of caveolae on membrane. On the contrary, another remarkable sphingolipid, sphingosine-1-phosphate (S1P), dramatically enhances insulin signal by redox signaling pathway. Both negative and positive effects of sphingolipids on insulin signal imply the involvement of calcium signal. Thus it can be seen that detecting both extracellular calcium influx and intracellular calcium transient in real time may satisfy the speculation of insulin signal regulation with sphingolipids at the ion channel level. Therefore, we will review the mechanisms of modulation of some sphingolipids, including ceramide, GM3 and S1P, on insulin signal. The potential strategies of sphingolipids activity alteration and insulin resistance improvement will be involved in this review as well, which will make great strides in T2DM research.

Key words sphingolipids, ceramide, ganglioside monosialo 3, sphingosine-1-phosphate, insulin resistance, calcium signal

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