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影响胰岛素抵抗的多种因素

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摘　要

在现代社会中，肥胖率和2型糖尿病的患病率都飞速增长，因此这两种病症的发病原因得到了广泛的关注。经过许多实验研究发现，胰岛素抵抗是引发这类疾病的一个重要原因，同时也是加重病症的因素之一。为从源头上减少肥胖、2型糖尿病等疾病的发病率，引起胰岛素抵抗的各种影响因素就成为了研究热点。本文综述了多种与胰岛素抵抗相关的因素，包括运动、维生素D、昼夜节律等，能够为开发治疗胰岛素抵抗的药物起到参考作用，也可为在日常生活中如何预防胰岛素抵抗指明方向。

关键词

胰岛素抵抗，运动，维生素D，昼夜节律

Multiple Factors Affecting Insulin Resistance

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Abstract

In modern society, the prevalence of obesity and type 2 diabetes is increasing rapidly, so the causes of these two diseases have received extensive attention. After many experimental studies, it has been found that insulin resistance is an important cause of these diseases, and it is also one of the factors that aggravate the disease. In order to reduce the incidence of obesity, type 2 diabetes and other diseases from the source, various factors that cause insulin resistance have become the focus of research. This article reviews a variety of factors related to insulin resistance, including exercise, vitamin D, circadian rhythm, etc., which can serve as a reference for the development of drugs for the treatment of insulin resistance, and can also point out how to prevent insulin resistance in daily life.

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Keywords

Insulin Resistance, Exercise, Vitamin D, Circadian Rhythm

1. 引言

胰岛素抵抗的概念可以追溯到 Himsworth [1]的观察，他注意到糖尿病患者同时注射葡萄糖和胰岛素，会产生两种不同的结果。部分糖尿病患者在同时注射两者后，血糖显著升高。在正常的血浆胰岛素水平下，靶组织无法形成正常的协同降糖作用，降糖作用包括抑制内源性葡萄糖生成、抑制脂肪分解、促进细胞摄取葡萄糖等[2] [3] [4] [5] [6]。这种现象被定义为胰岛素抵抗，这种胰岛素抵抗可以通过增加人体自身增加胰岛素分泌量来进行补偿，因此会导致空腹血浆胰岛素水平增加，随着这一现象不断恶化，最终会恶化为高胰岛素血症[3] [7]。与此同时，在胰岛素抵抗的情况下，持续的营养过剩会产生高胰岛素血症和胰岛素抵抗的恶性循环，最终导致 β 细胞衰竭，发展成 2 型糖尿病[3] [8]。

因此，了解胰岛素抵抗的影响因素和机制对于持续开发有效的治疗策略来治疗这些流行疾病至关重要。高胰岛素血症与胰岛素抵抗的关系是复杂的，较为普遍的一种观点是，胰腺产生更多的胰岛素来补偿胰岛素信号缺陷引起的血糖水平升高[3]。另一种观点是高胰岛素血症可能引发并扩大胰岛素抵抗[9]。然而，这两种观点在真实的人体中很有可能并不是单独出现，而是同时存在的。

2. 运动与胰岛素抵抗

运动是生活方式干预、预防糖尿病的基石[10]，也是增强胰岛素敏感性的有力工具。通过评估急性和慢性有氧或无氧运动如何影响与胰岛素抵抗相关的肌肉脂质含量、组成和定位，可能有助于揭示运动胰岛素增敏效应的机制。并且，通过了解运动如何改变肌肉脂质从而影响胰岛素敏感性，也可以揭示肥胖、缺乏运动和久坐行为如何导致了肌肉胰岛素抵抗、2 型糖尿病。

在急性有氧运动之后，胰岛素敏感性会增加 18%~30%，并持续 48 小时[11]。对这一时段的反应过程进行研究发现，在此期间，糖原会一直持续降解，并且运动后增强的胰岛素敏感性在第六小时达到峰值，说明糖原降解并不是胰岛素敏感性增强的唯一影响因素[12]。此外，已经有研究小组指出，体外刺激其收缩的肌肉只有在血清中时才会出现胰岛素敏感性的增加，这表明除了糖原消耗外，体液在胰岛素敏感性中也起着重要作用[13]。这些具体的体液影响因素目前尚不清楚。与有氧运动类似，无氧运动在一个运动阶段后也会增加胰岛素敏感性[14] [15]，但缺乏机制研究来解释这些影响。无氧运动的代谢和生理应激均不同于有氧运动，因此，这两种运动方式的分子机制可能有很大的不同。

肌肉中的脂质积累，特别是 DAG 和鞘脂这两种脂质，与人类胰岛素敏感性降低有关。特定种类的脂类似乎发挥着不同的作用，有数据表明，这些脂类的定位能够诱导胰岛素抵抗的发生或者进一步恶化胰岛素抵抗。而有氧运动和无氧运动都能提高胰岛素敏感性，每一种运动方式也都能影响肌肉中脂质的积累。然而，关于急性和慢性运动训练如何影响与胰岛素抵抗相关的特定脂质种类的含量和定位，还有很多需要我们去研究了解。通过了解运动如何改变生物活性脂类的特定种类和异构体，以及如何改变这些脂类的定位，有可能发现最能影响胰岛素敏感性的特定脂类。

有氧运动持续增加胰岛素敏感性[16]。这种训练效果并不仅仅是由于糖原消耗，还有其他机制可以导致胰岛素敏感性的增加，包括 GLUT4 含量、毛细血管密度和线粒体含量的增加[17] [18] [19]。许多研究[12] [20] [21] [22] [23]表明，运动诱导的胰岛素敏感性增强可能与肌细胞内脂质的改变有关。关于有氧运动是否比其他运动更能够有效提高胰岛素敏感性的研究非常的复杂，同时也缺乏详细的机制研究[24]。

3. 维生素 D 缺乏引起胰岛素抵抗

研究发现，维生素 D 的分子作用不仅在胰腺 β 细胞中，也在胰岛素作用的靶器官中，参与维持正常的 ROS 和 Ca^{2+}的静息水平。维生素 D 能够降低与胰岛素抵抗相关的病理程度，如氧化应激和炎症[25]。最近，研究还表明，维生素 D 可以预防与胰岛素抵抗和糖尿病相关的表观遗传改变[26]。

目前，维生素 D 缺乏较为常见，且同时与多种疾病的发病机制有关，比如代谢异常等[27]。也有研究指出维生素 D 缺乏对胰岛素抵抗也有影响[28]。大量临床研究表明，补充维生素 D 可降低 T2DM 患者的总胆固醇(TC)、低密度脂蛋白(LDL)、甘油三酯(TG)、糖化血红蛋白(HbAlc)等代谢参数水平，降低胰岛素抵抗指标[29] [30]。

多项研究表明，维生素 D 可能是胰岛素分泌、Ca^{2+}水平和胰腺 β-细胞存活的潜在影响因素，维生素 D 缺乏可导致大鼠胰腺 β-细胞中葡萄糖介导的胰岛素分泌量降低[31] [32] [33] [34]。也有研究人员称，葡萄糖介导的胰岛素分泌可以通过补充维生素 D 恢复[31] [32]。但目前关于这一现象没有统一的说法，有的研究认为补充维生素 D 与改善胰岛素分泌有关[35]，有的[36] [37]则表示反对。

维生素 D 在胰腺 β-细胞中似乎是通过维生素 D 与维生素 D 受体(VDR)结合直接发挥作用的[35] [38]。功能性 VDR 缺失的小鼠在葡萄糖过多后会出现胰岛素分泌降低。它还与胰腺 β-细胞合成胰岛素减少有关[39]。也有研究发现，维生素 D 缺乏会增加 Ca^{2+}浓度，从而降低 GLUT-4 的活性，导致胰岛素抵抗[40]。

4. 昼夜节律与胰岛素抵抗

胰岛素抵抗是 2 型糖尿病发病和死亡的主要影响因素。昼夜节律系统由下丘脑视交叉上核的中央大脑时钟和各种外周组织时钟组成。昼夜节律计时系统负责许多日常生理过程的协调，包括人体葡萄糖代谢的节律，中央时钟调节食物摄入、能量消耗和全身胰岛素敏感性，而这些行为又由局部外围时钟进一步微调。例如，肠道内的外周时钟调节葡萄糖吸收，肌肉、脂肪组织和肝脏内的外周时钟调节局部胰岛素敏感性，胰腺内的外周时钟调节胰岛素分泌。由于基因、环境或行为因素导致的昼夜节律系统与睡眠－觉醒行为或食物摄入的日常节律之间的不一致可能是出现胰岛素抵抗的重要因素[41]。具体来说，生物钟基因突变、暴露在人工光暗循环下、睡眠紊乱、轮班工作和社交时差都可能导致昼夜节律紊乱。

昼夜节律系统可能参与胰岛素抵抗的病理生理学的第一个线索是，20 世纪 60 年代观察到 T2DM 患者糖耐量的日节律改变[42]。后来，一些研究人员对 Clock 突变小鼠 10 的代谢综合征发展进行了研究，发现在错误的昼夜节律阶段(习惯性睡眠阶段)摄入食物会引起肥胖，同时发现昼夜节律失调会引起人类葡萄糖耐量的下降，并最终提出了昼夜节律紊乱假说[43]。后期复杂的组织特异性胰[44] [45]、肝[46]、肌肉[47]和脂肪[48]转基因和敲除模型等实验也进一步支持了这一假设。另一方面，目前昼夜节律紊乱假说目前还不能被证实，存在一些转基因小鼠模型[49] [50]和非同步食物摄入[51]的研究表明昼夜节律紊乱没有负面代谢影响。

5. 重度抑郁与胰岛素抵抗

由于对环境和心理压力的敏感性增加，重度抑郁症通常与高皮质醇血症有关。压力诱导的下丘脑－垂体－肾上腺轴(HPA)活性增加与促炎细胞因子的作用相互促进[52] [53]。

在正常的生理条件下，血液和组织中葡萄糖的升高会刺激胰腺分泌胰岛素，增加葡萄糖运输到组织的效率，包括最重要的大脑。葡萄糖是大脑的主要能量来源，据估计，尽管大脑约占成年人体重的 2%，但它至少消耗 20%的可用葡萄糖[54]。因此，可以预期，如果进入大脑的胰岛素依赖型葡萄糖运输量减少，这可能会对大脑能量代谢产生不利影响。胰岛素抵抗导致脑葡萄糖代谢受损，与重度抑郁症相关[55]。

虽然由糖皮质激素和促炎细胞因子引起的胰岛素抵抗的机制仍有待充分阐明，但很明显，功能失调的胰岛素受体和受体途径会影响葡萄糖通过血脑屏障的转运过程以及随后被吸收到神经元和神经胶质细胞中的生理过程[55]。在大脑中，胰岛素能够刺激葡萄糖摄取并增加神经元和神经胶质细胞中葡萄糖转运蛋白 mRNA 的合成[56]。因此，胰岛素抵抗引起脑葡萄糖功能缺陷后，对血糖的控制发生变化容易引起情感心理状态的改变[57]。

与此同时，神经元的凋亡和部分神经原纤维缠结的增加可能导致大脑的结构变化。由于杏仁核和海马是含有高密度胰岛素受体的区域，因此发现胰岛素抵抗与认知和学习缺陷有关也就不足为奇了[58]。众所周知，患有慢性抑郁症的患者，尤其是老年人，一般同时患有记忆障碍和认知缺陷[57] [59]。因此，长期葡萄糖缺乏后的神经退行性变化可能为痴呆症提供结构基础[27]。

6. 硫化氢与胰岛素抵抗

糖尿病的患病率越来越高，并已成为全球性的健康挑战。胰岛素抵抗是一种异常状态，即骨骼肌、脂肪、肝脏等组织对胰岛素作用的敏感性受损。这种情况通常由胰腺 β 细胞功能障碍引起的高胰岛素血症来补偿，最终促进了糖尿病的发展[7] [60]。因此，胰岛素抵抗的发病机制和 β-细胞功能障碍仍是重要的科学问题。研究表明，合成胰岛素的胰腺 β 细胞和胰岛素的靶器官如肝脏、脂肪、肌肉等可产生新型的气体信号分子硫化氢(H_2S) [61] [62]。与对照组相比，糖尿病患者血浆 H_2S 浓度降低[63]。此外，H_2S 还可调节胰岛素敏感性和胰岛素分泌[62]。10~100 mol/L H_2S 供体 NaHS 可以产生约 3~35 mol/L H_2S，对胰岛素代谢具有重要的生理作用，而 200~1000 M NaHS 可以释放约 70~350 mol/L H_2S，导致毒性作用[64]。因此，调节 H_2S 水平已成为治疗糖尿病的一种有前景的策略。

7. 总结

胰岛素抵抗的综合生理机制是由于胰岛素在靶细胞中的作用缺陷，胰岛素控制我们体内的糖和脂代谢，促进葡萄糖的摄取，并将其转化为糖原和脂质，在代谢组织中储存能量，从而维持适当的血糖水平。对于人体维持葡萄糖稳态来说，正常的胰岛素水平是非常重要的。当血液中存在高于正常水平的胰岛素，可能引发持续的高胰岛素血症或最终发展为糖尿病，这些均与胰岛素抵抗有关。胰岛素抵抗也被作为代谢性疾病的标志之一，包括 2 型糖尿病和动脉粥样硬化[65]。

因此，针对目前代谢性疾病发病率增多、治疗疗程长等特点，我们需要从源头考虑预防此类疾病的方法。胰岛素抵抗作为这类代谢性疾病的主要促进原因之一，如何对抗胰岛素抵抗，增强胰岛素受体敏感性就成为了一个重要的研究课题。而再好的治疗也比不上日常生活中的预防，因此，本文列出了多种较为日常的胰岛素抵抗影响因素，在日常生活中坚持运动健身，拥有规律的生活节奏，远离熬夜，保持乐观向上的心情，就能增强胰岛素受体敏感性，从而避免肥胖、2 型糖尿病等疾病的发生。

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