理论研究

糖脂代谢病的发病机制:多重打击学说

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摘要 血糖异常、血脂异常、非酒精性脂肪肝、超重、高血压、动脉粥样硬化性心脑血管病等代谢性疾病发病率居高不下,是世界性难题。临床流行病学研究目前已证实,2 型糖尿病、高脂血症等代谢性疾病常合并发生,但目前对导致上述代谢异常发生的分子机制尚未阐明,并制约了综合防控疗效优良的创新药物和诊疗手段的研发。郭姣教授率团队基于大样本临床流行病学、转化研究数据,提出"糖脂代谢病"创新理论,认为上述代谢异常以糖、脂代谢紊乱为特征,发病过程由遗传、环境、精神等多种因素参与,以神经-内分泌失调、胰岛素抵抗、氧化应激、炎性反应、肠道菌群失调为核心病理,以高血糖、血脂失调、非酒精性脂肪肝、超重、高血压及动脉粥样硬化等单一或合并出现为主要临床表现特点。本文综合神经-内分泌-免疫紊乱、胰岛素抵抗、氧化应激、炎性反应、肠道菌群失调等环节与糖脂代谢异常及其诱发多器官病变的病理机制的研究进展,提出糖脂代谢病发病机制的"多重打击学说"。该学说对于揭示多种代谢异常发生的核心、共性分子机制及从病证结合角度阐释中医证候的生物学本质具有重要意义。

关键词 糖脂代谢病;发病机制;神经-内分泌轴;胰岛素抵抗;氧化应激;代谢性炎性反应;肠道菌群失调

The Multiple-hit Pathogenesis of Glucolipid Metabolic Disorders

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Abstract The high prevalence and incidence of hyperglycemia, dyslipidemia, nonalcoholic fatty liver disease, obesity, hypertension, atherosclerosis and its related cardiovascular diseases has emerged as one of leading causes of morbidity and mortality worldwide. Epidemiological data well established that two or several above-mentioned metabolic disorders usually co-exist in obese subjects. However, the mechanisms underlying the co-existence of these metabolic disorders have not been well characterized currently, exerting negative effect on the development of new drugs and therapeutic approaches for these diseases. Based on the data from epidemiological and translational studies, Professor Jiao Guo and research team proposed a novel concept "Glucolipid Metabolic Disorders" (GLMD), which highlights the disorders in the metabolism of glucose and lipid as the key player in the pathogenesis of metabolic disorders. Genetic, environmental, and mental factors work together to contribute the development of GLMD. The dysfunction in neuroendocrine axis, insulin resistance, oxidative stress, metabolic inflammation, and alteration in gut microbiota represent the key mechanisms corresponding to the progression of these metabolic disorders. This article summarizes the recent findings in the relationship among these mechanisms and the development of GLDM and proposes the multiple-hit hypothesis for the pathogenesis of GLMD. This hypothesis is of significant importance for the clarification of the biological essence of Zheng in Traditional Chinese Medicine.

Key Words Pathogenesis; Dysfunction in neuroendocrine axis; Insulin resistance; Oxidative stress; Metabolic inflammation; Altered gut microbiota

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目前,多种糖脂代谢异常相关性疾病,包括 2 型糖尿病、血脂异常、高血压、非酒精性脂肪肝以及与其相关的多种心血管并发症已跻身于流行病行列,严重威胁人类健康。但目前对于糖脂代谢异常性疾病的临床诊疗面临以下难点问题:1)治疗策略仅关注单一发病环节、单一靶点;2)诊疗模式多采用分科诊治,导致多种代谢异常状态和药物疗效的随访信息难以完整采集,疾病预后难获全面评估;3)心血管事件等严重并发症的防控疗效欠佳。

疾病核心病理机制及关键介导分子的研究是新型诊疗策略及创新药物研发的重要基础。探索糖脂代谢相关疾病的核心发病机制,并制定有效防控策略成为当前医学研究的重大问题。郭姣教授率团队瞄准该病葡萄糖和脂类代谢异常的核心病理环节,对于该病的西医发病机制研究现状凝练出了 3 个关键与热点问题:1)多个代谢器官和组织(包括肝脏、胰腺和脂肪)的代谢功能作为整体进行认识和研究;2)应重视神经-内分泌轴对于糖脂代谢的系统性调控功能;3)介导糖脂代谢过程中器官串扰和组织对话的新型因子的功能和分子机制尚未完全阐明。针对以上关键问题,郭姣教授基于文献整理和前期临床研究,针对葡萄糖和脂类代谢异常这一核心病理机制,创新性提出“糖脂代谢病”创新理论,认为其是一种以糖、脂代谢紊乱为特征,由遗传、环境、精神等多种因素参与的疾病,其以神经内分泌失调、胰岛素抵抗、氧化应激、炎性反应、肠道菌群失调为核心病理,以高血糖、血脂失调、非酒精性脂肪肝、超重、高血压及动脉粥样硬化等单一或合并出现为主要临床表现特点,需要整体认识和一体化防控[1]。

目前,借助宏基因组学、代谢组学等多组学技术、模式动物表型鉴定等生物医药领域前沿技术在糖脂代谢病基础、转化和临床研究中的广泛、深入应用,逐步揭示出糖脂代谢病是由于神经-内分泌对于糖脂代谢的调控功能异常诱发的、由多个代谢器官功能异常参与的复杂性、系统性疾病。郭姣教授提出,在糖脂代谢病发生过程中,神经-内分泌紊乱、胰岛素抵抗、氧化应激、慢性炎性反应和肠道菌群失调等核心病理环节网络交织,形成多重打击(Multiple Hits),共同参与糖脂代谢病的发生和进展。

1　神经-内分泌轴功能紊乱

机体通过神经、内分泌两大系统调节神经递质、激素和细胞因子释放,大脑中的特定神经元可感知代谢底物的变化,并通过与进入脑内的瘦素、胰岛素及其他细胞因子交互作用,构成精密的调节网络,维持机体糖类和脂类代谢稳态。

临床研究和模式动物的研究结果均证实,中枢神经系统在调控能量和葡萄糖代谢稳态中发挥关键作用[2]。大脑中的多个功能区域,特别是下丘脑,通过感知和整合来自外周组织的信号和代谢的生理变化而对机体的能量代谢发挥系统性调控作用。伸长细胞、瘦素和 5-羟色胺是参与神经内-分泌轴调控糖脂代谢的关键细胞和信号传递分子。

1.1　伸长细胞　伸长细胞(Tanycytes,TAs)是一种特殊的室管膜胶质细胞,主要位于下丘脑正中隆起(ME)、第三脑室腹侧和弓状核附近的室周器[3-4]。内酰胺酶是一种在胶质细胞中特异产生的多肽家族,可与苯二氮䓬受体结合[5]。伸长细胞通过分泌内酰胺酶介导中枢系统对葡萄糖摄取的感应[6]。在辐照诱发的伸长细胞损伤的小鼠模型中,体重、能量消耗和机体活动等系统性能量代谢指标发生显著改变[7]。

1.2　瘦素　瘦素的典型反应神经元包括下丘脑弓状核的 AgRP/NPY 和 POMC。瘦素抑制促食型 AgRP/NPY 神经元,激活厌食性 POMC 神经元,从而诱发摄食调节信号传递到二级神经元;当阻断 AgRP/NPY 神经元后,小鼠体质量显著增加[8]。选择性阻断脑腹内侧核(VMH)上 SF1 神经元的瘦素受体导致肥胖易感性显著升高[9]。下丘脑瘦素受体缺失的基因修饰动物出现高血糖、高胰岛素血症、易饥和肥胖等多种代谢异常表型,也说明下丘脑瘦素受体在维持葡萄糖代谢稳态中发挥重要作用[10-11]。

1.3　5-羟色胺　5-羟色胺通过多种 5-羟色胺受体(5-HTRs)调控葡萄糖和脂类代谢,例如激活 5-HT2CR,上调 POMC 神经元的表达,在调剂胰岛素敏感性和肝内葡萄糖代谢稳态中发挥关键作用[12]。5-羟色胺受体 5-HT2CR 和 5-HT1BR 在调节机体系统性代谢状态中发挥重要作用。5-HT2CR 激活 POMC 神经细胞亚群时会受到局部抑制,而 5-HT1BR 可以解除该种抑制,提示 5-HT2CR 激动剂与 5-HT1BR 激动剂可作为治疗肥胖症的潜在药物[13]。动物研究结果显示,5-羟色胺的神经元激活能够完全恢复瘦素受体失活转基因老鼠的代谢表型,说明 5-羟色胺在介导瘦素调节食欲和能量代谢的功能中发挥重要作用[14-15]。

2　胰岛素抵抗

胰岛素抵抗(Insulin Resistance,IR)是指外周组织(主要为骨骼肌、肝脏和脂肪组织)对内源性或外源性胰岛素的敏感性和反应性降低,导致生理剂量

的胰岛素调控葡萄糖代谢等多种生理效应减弱或发生障碍[16]。IR 主要发生在骨骼肌细胞、脂肪细胞和肝细胞，其在血管内皮和胰岛 β 细胞也可发生[17]，IR 涉及多个分子和信号传递机制，包括胰岛素及其拮抗物、胰岛素受体底物、磷脂酰肌醇-3 激酶（PI-3K）途径、葡萄糖转运子基因及蛋白质、促分裂原活化蛋白激酶（MAPK）等[18]。目前已证实，IR 与原发性高血压、冠心病、高脂血症等多种糖脂代谢异常密切关联，是导致上述疾病的共同病理基础[19-21]。

2.1 高血糖 在轻度 IR 中，由胰腺 β 细胞增加胰岛素分泌及随后导致的代偿性高胰岛素血症可维持正常血糖。然而在 2 型糖尿病早期发病阶段即出现轻度 IR 状态。胰腺 β 细胞通过增加胰岛素分泌维持血糖的正常水平，产生代偿性高胰岛素血症。随着 IR 状态的持续，超过胰腺 β 细胞通过代偿性增加分泌调控血糖稳态的阈值时，出现葡萄糖不耐受（Glucose Intolerance）和高血糖[22]。此外，持续的高血糖进一步降低机体胰岛素敏感性（葡萄糖毒性），从而引发恶性循环[23]。高胰岛素血症会通过干扰多个代谢器官（包括脂肪组织、肝脏和骨骼肌）的胰岛素信号通路，加重 IR[24]。因此，在糖脂代谢病中，由于 IR 而导致的高胰岛素血症和高血糖，会负反馈使 IR 加剧，形成恶性循环。

2.2 高脂血症 正常情况下，胰岛素通过抑制脂蛋白脂肪酶阻止脂肪组织脂解（Lypolysis）在调控机体脂代谢中发挥重要作用。在 IR 状态下，胰岛素抑制脂肪分解的作用显著减弱，导致大量游离脂肪酸（Free Fatty Acids）释放到体循环中[25]。游离脂肪酸的增加导致肝细胞内甘油三酯的合成和释放增多，引起低密度脂蛋白增多，高密度脂蛋白减低，形成高甘油三酯血症[26]。同时，游离脂肪酸的增加通过脂质毒性（Lipotaxicity）抑制外周组织对葡萄糖的摄取，产生 IR。上述环节形成正反馈环路，加速糖脂代谢病的发生和进展[27]。

2.3 高血压 IR 和高胰岛素血症通过诱发机体钠盐代谢障碍间接调控高血压的发生。生理状态下，胰岛素可增强钠盐的重吸收，该作用在 IR 条件下显著增强。临床研究发现，IR 患者肾脏近端肾小管的钠重吸收率较正常组显著升高[28]。此外，胰岛素可促进血管平滑肌细胞增殖和血管紧张素Ⅱ产生，而血管紧张素Ⅱ是醛固酮合成的主要刺激因子[29]。另一方面，胰岛素可能通过刺激一氧化氮释放而起到血管扩张作用在 IR 状态下减弱[30-31]。因此，IR 在调控血管功能稳态和高血压的发生中发挥重要作用。

3 氧化应激

氧化应激（Oxidative stress）也称为活性氧-抗氧化失衡，由机体产生的自由活性氧簇（Reactive Oxygen Species，ROS）超过自身的抗氧化能力而导致，自由活性氧簇生成过多或抗氧化系统功能障碍是氧化应激发生的主要原因[27]。ROS 包括超氧阴离子（O^{2-}）、羟自由基（OH^{-}）和过氧化氢（H_2O_2）等，其中 O^{2-} 具有较高活性和细胞毒性，主要由好氧型微生物产生[32]。如果细胞抗氧化系统不能够抑制 ROS，好氧型微生物与细胞大分子发生反应，导致脂质过氧化，引起细胞 DNA 损伤、影响核酸修饰及蛋白质的产生[33]。同时 ROS 在损伤细胞时产生的氧化或硝化物会降低体内各种因子的生物活性，影响细胞信号传递及其他细胞功能，引发多种炎性反应，导致 IR、血管内皮细胞损伤，进而引起心脑及外周血管疾病和糖脂代谢疾病等[34-36]。

3.1 氧化应激与肥胖状态下脂肪组织功能失常 肥胖状态下脂肪组织过度增生促进氧化应激，进而导致 IR 等多种代谢紊乱。动物实验和临床研究结果均表明，脂肪和碳水化合物摄入过多后，线粒体中电子传递链的饱和，导致 FFA 产生增加，诱发 ROS 产生[37]。反过来，氧化应激可刺激脂肪细胞的增殖、分化和成熟，及脂肪细胞的大小增加脂肪的积累[38-39]。在肥胖状态下，脂肪组织是机体产生 ROS 的主要来源。脂肪蓄积诱导的氧化应激可导致抵抗素、内脂素、脂联素、瘦素、PAI-1、肿瘤坏死因子-α 和白细胞介素-6 等多种脂肪细胞因子的合成失调，引发糖脂代谢病发生[27]。

3.2 氧化应激与葡萄糖代谢异常、IR 氧化应激通过氧化生物分子和刺激各种应激敏感细胞内通路如 c-Jun、N-末端激酶、ERK1/2 和 NF-κB 等多种转录因子与应激激酶，产生慢性低度炎性反应，进而导致 IR[40-41]。Song D 等证实人体抗氧化机制可阻断氧化应激，并抑制 IR 及其不良代谢后果，同样，果糖喂养的大鼠在服用抗氧化剂后会减少氧化应激的产生并抑制 IR[42]。值得注意的是，IR 又通过质子电化学梯度产生过量的自由基和超氧化物，进而摧毁多种组织的抗氧化防御能力[43-44]，同时也会影响具有抗氧化防御功能的葡萄糖转运体-GLUT1 和去氢抗坏血酸的表达，加重氧化应激[45]。

4 代谢性炎性反应

由于机体是一个免疫和代谢系统高度整合的复杂系统，免疫功能和糖脂代谢过程在多个层面相互

影响[46]。目前已证实,慢性、低度和系统性炎性反应是糖脂代谢病的重要特征,也是影响糖脂代谢病发生和进展的核心机制之一[47]。炎性反应因子及细胞通过广泛交织的免疫网络,参与调节肝、脂肪、肌肉、胰腺等组织器官的糖、脂代谢功能。脂肪细胞增生、肥大,导致脂肪组织的内分泌功能异常,促使其表达的诸多脂肪因子谱发生改变,引起众多免疫细胞和促炎因子增加,进而激活炎性反应信号通路,诱导大量炎性反应递质的产生,使机体长期处于慢性炎性反应状态,从而导致 IR、多种代谢异常及糖脂代谢病的发生[46-48]。

4.1　天然免疫与代谢性炎性反应

机体天然免疫反应(Innate Immunity)由多种免疫细胞所介导,包括巨噬细胞、中性粒细胞、NK 细胞和树突状细胞[49]。大量临床及动物研究证据提示,天然免疫反应应答诱发的代谢性炎性反应与糖脂代谢病的发生关系非常密切[47-50]。

4.1.1　巨噬细胞　巨噬细胞(Macrophages)又被称为 $F4/80^+CD11b^+$ 细胞,是一种重要的天然免疫细胞,它不仅吞噬非自身抗原和细胞碎片,而且作为专业抗原提呈细胞,与树突状细胞一起,激活适应性免疫系统的 T 淋巴细胞。在肥胖状态,巨噬细胞在脂肪组织中浸润或膨胀[51],这些细胞数量和功能的改变会影响脂肪组织炎性反应和全身胰岛素敏感性[52-53]。

4.1.2　嗜酸性粒细胞　嗜酸性细胞(Eosinophils)仅占循环白细胞的 1% ~3%,主要参与吞噬并杀死细菌和其他病原体如寄生虫[54]。WuD 等,发现小鼠嗜酸性粒细胞水平和肥胖呈负相关,嗜酸性粒细胞可分泌 IL-4 和 IL-13 促进 M2 型巨噬细胞在脂肪组织中极化,极化后的 M2 型巨噬细胞可诱导炎性反应抑制因子的表达,从而减轻 IR[55]。

4.1.3　肥大细胞　肥大细胞(Mast cells)可分泌大量的促炎性反应因子和免疫调节因子(如组胺)、细胞因子和趋化因子,在过敏反应和组织稳态、重塑中起重要作用[56]。Liu J 等研究表明,肥大细胞在肥胖小鼠的脂肪组织中增加,同时在高脂饮食十二周后,肥大细胞基因敲除的 $Kit^{W-sh/W-sh}$ 小鼠体重增加减缓,葡萄糖稳态提高,能量消耗增多[57-58]。并且,肥大细胞与组织蛋白酶、细胞外基质蛋白水解酶、微血管生长等有关,参与动脉粥样硬化发病[59-60]。

4.2　脂肪组织代谢性炎性反应　脂肪堆积导致炎性反应可能机制包括以下几个方面:1)肠道:肥胖会增加肠道通透性,导致肠道革兰氏阳性细菌的细胞壁外膜脂多糖(Lipopolysaccharides,LPS)循环水平升高,肠源性脂多糖(LPS)通过激活模式识别受体(Pattern Recognition Receptors,PRR)如脂肪细胞中的 TLR 4 受体,引发炎性反应级联反应[61]。2)脂肪酸:饮食或肥胖导致游离脂肪酸水平升高,后者通过适配蛋白 Fetuin A 与 TLR 4 和 TLR 2 间接结合,从而激活 NF-κB 和 JNK 1 促进炎性反应[62-63]。3)组织缺氧:随着脂肪组织的不断扩张和发展,脂肪组织的相对低灌注或耗氧量的增加,导致脂肪细胞缺氧,并通过诱导 HIF1 基因而引发炎性反应[64]。4)机械压力:脂肪细胞通过多种途径与其细胞外基质(Extracellular Matrix,ECM)相互作用,调控肥胖发展[65]。在 ECM 固定的环境中,脂肪细胞扩张可以增加机械压力。MMP14、MMP12 等胶原酶以及胶原基因缺失,对脂类合成、能量代谢有重要影响,参与肥胖诱发的脂肪组织的持续、低水平炎性反应[66-68]。

4.3　肝脏代谢性炎性反应与非酒精性脂肪肝　动物实验和临床研究均证实,非酒精性脂肪肝的肝组织中促炎基因表达增加。库普弗细胞(Kupffer Cell)作为肝脏驻留的巨噬细胞,参与了肥胖激活的肝脏促炎性反应通路[69-70]。肥胖状态下,肿瘤坏死因子 TNF-α 和白细胞介素诱导 Kupffer 细胞激活和募集的肝巨噬细胞浸润,产生多种局部性的炎性趋化因子和细胞因子,抑制糖原合成,引起肝细胞 IR[71]。非酒精性脂肪肝会因为一系列炎性反应通路激活和纤维化,进展成非酒精性脂肪性肝炎(Nonalcoholic Steatohepatitis,NASH)甚至肝硬化[72]。

5　肠道菌群失调

肠道菌群对于机体的糖脂代谢具有重要影响,可通过调节炎性反应、免疫系统等影响糖脂代谢。在健康状态下,肠道菌群通过发酵肠中不可消化的膳食成分为宿主提供营养和能量,并与宿主的新陈代谢和免疫系统保持平衡[73-74]。

饮食是肠道菌群组成的重要因素,人体难以消化的碳水化合物经细菌代谢分解成单糖、多糖和其他碳氢化合物,包括支链脂肪酸、氨、胆碱、硫化氢、胺、酚类、吲哚和巯基[75],其中胆碱、短链脂肪酸(SCFAs)和丁酸盐尤为重要。胆碱水平的改变通过毒性甲胺的作用促进非酒精性脂肪肝的发生,同时胆碱水平也与心血管疾病相关化合物如致动脉粥样硬化的三甲胺-N-氧化物(Trimethylamine-N-oxide,TMAO)的合成密切相关[76]。丁酸盐能刺激脂肪细胞产生瘦素及肠黏膜 L 细胞分泌 GLP 1[77]。短链脂肪酸(SCFAs)由细菌双糖化酶发酵纤维时产生,SC-

FAs 可以激活位于肠内分泌细胞的 G 蛋白偶联受体 GPR41 和 GPR43 传导信号[78]。GPR41 基因敲除小鼠与野生型普通微生物组小鼠相比较脂肪会减少，而无菌野生型小鼠和 GPR41 基因敲除小鼠脂肪水平相当，这些研究表明，SCFAs 受体在脂肪沉积中具有重要作用[79]。

6 讨论

目前对于血糖异常、血脂异常、非酒精性脂肪肝、超重、高血压、动脉粥样硬化性心脑血管病等代谢性疾病的发病机制研究取得了显著进展，但上述疾病发病率仍居高不下，综合防控率不佳仍是世界性难题。

郭姣教授综合文献研究和团队前期临床、基础和转化研究结果，提出糖脂代谢病发生机制的“多重打击”学说（Multiple-hit Hypothesis）。认为神经-内分泌-紊乱、IR、氧化应激、炎性反应、肠道菌群失调是糖脂代谢病发生的主要病理机制。上述关键机制和环节相互影响，呈网络交织，共同作用导致糖脂代谢性疾病的发生和进展。该学说从病理生理学角度解释糖脂代谢病是由于神经-内分泌对于糖脂代谢的调控功能异常诱发的、由多个代谢器官功能异常参与的复杂性、系统性疾病，对于揭示多种代谢异常发生的核心、共性分子机制及从病证结合角度阐释中医证候的生物学本质具有重要意义。同时，“多重打击”学说为糖脂代谢病的整体认识和一体化防控策略奠定了基础。

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