DOI:10.12025/j.issn.1008-6358.2019.20181348

·综 述·

棕榈酸羟基硬脂酸抗代谢性炎症综合征作用机制的研究进展

于钟钰[1]，郭景春[2]，周厚广[1*]

1. 复旦大学附属华山医院老年病科，国家老年疾病临床医学研究中心，上海 200040

2. 复旦大学神经生物学国家重点实验室，上海 200032

[摘要] 老年代谢性炎症综合征(MIS)患病率高，患者体内普遍存在糖脂代谢紊乱和胰岛素抵抗，而新型化合物——羟基脂肪酸支链脂肪酸酯(FAHFAs)具有增强胰岛素敏感性和抗炎作用，其中棕榈酸羟基硬脂酸(PAHSA)是含量最高的一种同分异构体。体内 PAHSA 水平的改变主要受碳水化合物反应元件结合蛋白(CHREBP)的调节，并通过 G 蛋白偶联受体 120(GPR120)发挥生物学效应。本文主要就 PAHSA 抗 MIS 的作用机制研究进展作一综述。

[关键词] 棕榈酸羟基硬脂酸；代谢性炎症综合征；G 蛋白偶联受体 120；胰岛素抵抗；炎症反应

[中图分类号] R 587.1 [文献标志码] A

Research progress on mechanism of palmitic acid hydroxy stearic accid in anti-metabolic inflammatory syndrome

YU Zhong-yu[1], GUO Jing-chun[2], ZHOU Hou-guang[1*]

1. Department of Geriatrics, National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai 200040, China

2. State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China

[**Abstract**] The prevalence of metabolic inflammatory syndrome (MIS) in the elderly is high, and imbalance of glucose and lipid homeostasis and insulin resistance are common in these patients. The novel compound, branched fatty acid esters of hydroxy fatty acids (FAHFAs), has effects of enhancing insulin sensitivity and anti-inflammatory, among which the content of palmitic acid hydroxy stearic acid (PAHSA) is the highest. The level of PAHSA *in vivo* is primarily regulated by the carbohydrate response element binding protein (CHREBP), which exerts a biological effects *via* G protein coupled receptor 120 (GPR120). This review mainly describes the research progress on the mechanism of PAHSA in metabolic inflammatory syndrome.

[**Key Words**] palmitic acid hydroxy stearic acid; metabolic inflammatory syndrome; G protein coupled receptor 120; insulin resistance; inflammation

随着全球老龄化程度的不断加剧，2 型糖尿病(type 2 diabetes mellitus, T2DM)、动脉粥样硬化(atherosclerosis, AS)、非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)以及肥胖等常见老年代谢性炎症综合征(metabolic inflammatory syndrome, MIS)的发病率日益增长，严重威胁老年人身体健康和生活质量[1]。T2DM 患者高发 MIS，并普遍伴发糖脂稳态失衡和心脑血管疾病，已成为 T2DM 患者致死致残的主要原因[2-7]。胰岛素抵抗的患者体内，葡萄糖转运体 4(Glut4)的表达量下调；而上调 Glut4 可降低患者空腹血糖和提高胰岛素耐量[8-10]。多数脂肪酸被认为对人体健康有害无益，存在胰岛素抵抗和葡萄糖不耐受的个体，一般会伴有脂肪酸水平升高；然而体外补充 ω-3 脂肪酸则产生有益代谢的作用[11]。流行病学研究[12]揭示，血三酰甘油中的不饱和脂肪酸与饱和脂肪酸比例升高与 T2DM 患病风险降低相关，提示 Glut4 过表达虽然增加脂肪组织合成，但会产生一些有利于代谢效应的脂类分子。Yore 等[13]研究发现一种新型脂肪酸分子——棕榈酸羟基硬

[收稿日期] 2018-12-04 [接受日期] 2018-12-28

[基金项目] 国家自然科学基金(81871098,81571361). Supported by National Natural Science Foundation of China (81871098,81571361).

[作者简介] 于钟钰，硕士生. E-mail: yuzhongyu2018@163.com

*通信作者(Corresponding author). Tel: 021-52887192; E-mail: zhg7376@163.com

脂酸(PAHSA)具有改善胰岛素敏感性及抗炎症作用,而9-PAHSA是其含量最高的一类同分异构体,通过手性拆分可得到左旋体S-9-PAHSA和右旋体R-9-PAHSA[14]。但是,PAHSA对糖尿病等老年代谢综合征的保护性机制至今尚不清楚。因此,本文主要就PAHSA发挥生物学作用的可能途径进行综述,为今后开展抗MIS的临床前药效学研究奠定理论基础。

1 PAHSA的生物学效应

2014年,Yore等[13]首次发现和鉴定了羟基脂肪酸支链脂肪酸酯(branched fatty acid esters of hydroxy fatty acids, FAHFAs,简称支链脂肪酸酯)。这类分子具有增强胰岛素敏感性和抗炎作用,同时在小鼠血清中共发现有16种同分异构体。通过质谱分析,FAHFAs由2个脂肪酸分子构成,分别具有1个羟基和1个羧基,两者脱水形成支链脂肪酸酯。不同的脂肪酸分子结合形成不同的FAHFAs,其中发挥主要生物学效应的PAHSA是由1分子16碳的棕榈酸(palmitic acid, PA)与羟硬脂酸(hydroxy stearic acid, HAS)结合形成。PAHSA的生物学作用类似于ω-3脂肪酸,但与ω-3脂肪酸不同的是,PAHSA在人类和其他哺乳动物中是内源性合成的[13]。PAHSA在体内的水平随人体的生理状态变化而变化,如禁食、肥胖、胰岛素抵抗等;同时,体内PAHSA水平存在组织特异性和同分异构体特异性[13]。人体内PAHSA水平的改变被证实是受碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, CHREBP)的调节,而CHREBP是一种调节糖酵解和脂肪生成的转录因子[15-16],提示PAHSA与糖脂代谢密不可分。研究[17]表明FAHFAs可通过G蛋白偶联受体120(G-protein coupled receptor 120, GPR120)发挥增强胰岛素敏感性和抗炎症的作用,从而起到调节糖脂稳态的生物学效应。

2 PAHSA调控糖脂代谢的作用机制

2.1 *改善胰岛素敏感性* 众所周知,T2DM的发病机制是外周胰岛素抵抗和胰岛素分泌异常[18]。通过给高脂饮食的小鼠模型单独口服PAHSA,可增强葡萄糖耐量和改善胰岛素敏感性[12]。研究表明,PAHSA可直接刺激胰岛细胞增加胰岛素的分泌,也可通过刺激胃肠道细胞系STC-1分泌胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)来间接刺激胰岛素分泌。研究证实PAHSA可通过GPR120和GPR40发挥维持糖稳态的作用[12,19];而且脂类分子可通过细胞膜G蛋白偶联受体(G-protein-coupled receptor, GPCRs)促进GLP-1的分泌和Glut4的表达[20-22]。近年来研究[23-25]证实,细胞膜上存在游离脂肪酸的特异性受体——GPCRs,后者与脂肪酸结合参与众多生理过程。GPR120是GPCRs中比较特殊的一类,多不饱和脂肪酸可通过与GPR120受体结合增加HEK293细胞胞质中游离Ca^{2+}的浓度,但是却不能促进cAMP的产生,这一现象说明与GPR120偶联的G蛋白受体是Gq蛋白家族,而非Gs或者Gi/o蛋白家族[20]。通过ω-3脂肪酸刺激,可以使GPR120和GPR40受体与其下游蛋白β-arrestin-2发生级联反应,从而起到抗炎症的生物学效应[12],而通过Ca^{2+}信号通路可以对代谢性疾病产生预防作用[26]。GPR120的激动剂可以抑制PKC的活性[27],并且,激活GPR120受体后,可通过PI3K/Akt、JNK、p38和ERK1/2信号通路[22,24],改善胰岛素敏感性,维持糖脂代谢稳态,从而对MIS发挥预防作用。

同时,脂肪组织的从头合成对胰岛素的敏感性有积极影响,并可减少肥胖和胰岛素抵抗的发生。CHREBP作为一种脂肪生成的转录因子[28],可以促进白色脂肪组织的从头合成,从而调节脂质代谢、改善胰岛素敏感性[29-31]。从而推测,人体内可能存在CHREBP对PAHSA的水平变化的调节机制,进而对代谢综合征患者的糖脂代谢紊乱发挥至关重要的作用。

2.2 *抗炎症效应* PAHSA作为一种活性脂肪酸不仅可通过GPCRs调节胰岛素敏感性,改善胰岛素抵抗,而且还可以发挥抗炎作用[32-34]。T2DM等代谢综合征本身是一种慢性低度炎症反应,伴随着脂肪细胞和巨噬细胞内炎症信号通路的激活、炎症因子的释放和免疫细胞的浸润等病理改变。脂肪组织不仅是能量储存器官,而且是重要的内分泌组织,在肥胖和T2DM等代谢性疾病情况下,脂联素的释放下降,而一系列的促炎性脂肪因子(瘦素、TNF-α、IL-1β、IL-6等)分泌增加,促进巨噬细胞的浸润[35-37]。且体内实验表明:高脂饮食喂养的小鼠脂肪组织巨噬细胞是激活的,主要表现为$Cd11c^{+}$、促炎性的巨噬细胞M1亚群增多,而通过GPR120受体激活剂干预后,可减弱炎症反应[22]。通过给高

脂饮食的小鼠急性喂养 3 d PAHSA 后发现：TNF-α 阳性的脂肪组织巨噬细胞比例恢复正常，IL-1β 阳性或 TNF-α 和 IL-1β 双阳性脂肪组织巨噬细胞比例显著下降[12]。由此可见，PAHSA 具有明显的体内抗炎症效应。

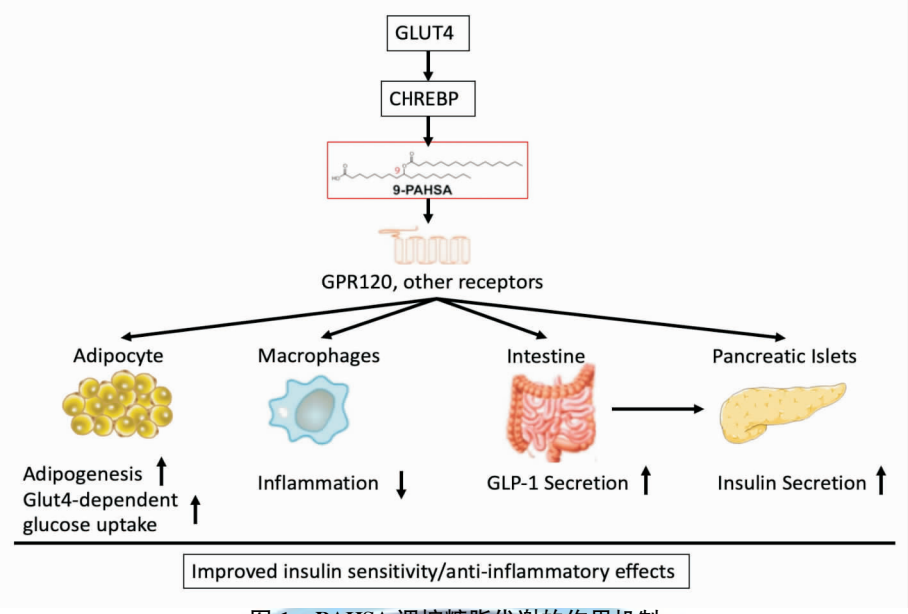

图 1 PAHSA 调控糖脂代谢的作用机制

2.3 PAHSA 的其他可能机制 糖脂代谢紊乱和胰岛素抵抗的患者体内普遍存在细胞凋亡增加、自噬活性减弱及氧化应激系统的激活，从而对人体的重要脏器（心脏、脑、肝脏等）产生不良后果。自噬、凋亡和氧化应激是老年 MIS 发生发展的主要机制之一，Beclin1 是联系自噬、凋亡与氧化应激的核心枢纽信号蛋白。本课题组实验结果发现体内 PAHSA 水平高低与 Beclin1 的表达水平密切相关。PAHSA 可能通过调控 Beclin1 的活性，对糖脂代谢紊乱发挥正向调控作用。同时，在本研究中，利用高糖高脂培养基模拟体外糖尿病环境干预小鼠脑血管内皮细胞（bEnd. 3），Western 印迹结果显示激活型 Caspase-3 表达量增加以及 ROS 释放增加，而 PAHSA 干预后可逆转这种趋势。此外，有报道[39]认为 PAHSA 在体内的生物合成过程与 Nrf2 介导的抗氧化反应密切相关，且 PAHSA 增强外周组织胰岛素敏感性的作用与抗氧化应激的活性密切相关。但关于 PAHSA 是否具有降糖效应近期也有不同观点，有研究[39]认为，无论短期或者长期口服 PAHSA 均无明显降血糖的效应。总之，有关 PAHSA 抗 MIS 的生物学效应及其内在机制仍需进一步的研究证实。

3 展 望

老年人群 MIS 患病率高，并发症多，危害严重。MIS 患者体内普遍存在胰岛素抵抗、慢性低度炎症及糖脂代谢紊乱。PAHSA 作为一种新发现的羟基脂肪酸，可通过受体 GPR120 改善胰岛素抵抗和炎症反应，进而调控糖脂代谢紊乱，有望开发成为一种新型的胰岛素增敏剂，对 MIS 具有一定潜在的干预价值。此外，血清 PAHSA 水平也可能成为 MIS 或 T2DM 的潜在生物学标志物。但目前有关 PAHSA 在人体内的合成代谢途径、组织器官分布、生物学效应及其分子作用机制等尚缺乏全面认识。这无疑成为深入开展 PAHSA 功能和机制研究的主要科学瓶颈之一。因此，深入探讨 PAHSA 的生物学效应和分子作用图谱对阐明 MIS 的发病机制和干预途径具有重要的科学意义和临床价值。

参考文献

[1] 胡仁明，谢 颖，鹿 斌，等. 2 型糖尿病患者高发“代谢性炎症综合征”[J]. 中华内分泌代谢杂志，2016，32(1)：27-32.

[2] ZHOU H, ZHANG X, LU J. Progress on diabetic cerebrovascular diseases[J]. Bosn J Basic Med Sci, 2014, 14(4): 185-190.

[3] SHORE A C, COLHOUN H M, NATALI A, et al. Use of vascular assessments and novel biomarkers to predict cardiovascular events in type 2 diabetes: the summit VIP study[J]. Diabetes Care, 2018, 41(10): 2212-2219.

[4] Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to

occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies[J]. Lancet Diabetes Endocrinol, 2018, 6(7):538-546.

[5] STRIEPE K, JUMAR A, OTT C, et al. Effects of the selective sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function and central hemodynamics in patients with type 2 diabetes mellitus[J]. Circulation, 2017,136(12): 1167-1169.

[6] 马俊花,陆建灿,王 星,等.2型糖尿病合并代谢综合征患者血清趋化素水平变化及其与白细胞介素6的相关性[J]. 中国临床医学,2018,25(5):748-752.

[7] 张晓明,郭景春,周厚广.糖脂稳态失衡性动脉粥样硬化与血管衰老[J].中国临床医学,2017,24(2):296-300.

[8] ABEL E D, PERONI O, KIM J K, et al. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver[J]. Nature, 2001,409(6821):729-733.

[9] CARVALHO E, KOTANI K, PERONI O D, et al. Adipose-specific overexpression of GLUT4 reverses insulin resistance and diabetes in mice lacking GLUT4 selectively in muscle[J]. Am J Physiol Endocrinol Metab, 2005,289(4): E551-E561.

[10] SHEPHERD P R, GNUDI L, TOZZO E, et al. Adipose cell hyperplasia and enhanced glucose disposal in transgenic mice overexpressing GLUT4 selectively in adipose tissue[J]. J Biol Chem, 1993,268(30):22243-22246.

[11] VIRTANEN J K, MURSU J, VOUTILAINEN S, et al. Serum omega-3 polyunsaturated fatty acids and risk of incident type 2 diabetes in men: the Kuopio ischemic heart disease risk factor study[J]. Diabetes Care, 2014,37(1): 189-196.

[12] RHEE E P, CHENG S, LARSON M G, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans[J]. J Clin Invest, 2011,121(4):1402-1411.

[13] YORE M M, SYED I, MORAES-VIEIRA P M, et al. Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects[J]. Cell, 2014, 159(2):318-332.

[14] NELSON A T, KOLAR M J, CHU Q, et al. Stereochemistry of endogenous palmitic acid ester of 9-hydroxystearic acid and relevance of absolute configuration to regulation[J]. J Am Chem Soc, 2017,139(13):4943-4947.

[15] IIZUKA K, BRUICK R K, LIANG G, et al. Deficiency of carbohydrate response element-binding protein (ChREBP) reduces lipogenesis as well as glycolysis[J]. Proc Natl Acad Sci USA, 2004,101(19):7281-7286.

[16] KIM M S, KRAWCZYK S A, DORIDOT L, et al. ChREBP regulates fructose-induced glucose production independently of insulin signaling[J]. J Clin Invest, 2016, 126(11): 4372-4386.

[17] MORAES-VIEIRA P M, SAGHATELIAN A, KAHN B B. GLUT4 expression in adipocytes regulates *de novo* lipogenesis and levels of a novel class of lipids with antidiabetic and anti-inflammatory effects[J]. Diabetes, 2016,65(7):1808-1815.

[18] SAMUEL V T, SHULMAN G I. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux[J]. J Clin Invest, 2016,126(1):12-22.

[19] SYED I, LEE J, MORAES-VIEIRA P M, et al. Palmitic acid hydroxystearic acids activate GPR40, which is involved in their beneficial effects on glucose homeostasis[J]. Cell Metab, 2018,27(2):419-427.

[20] HIRASAWA A, TSUMAYA K, AWAJI T, et al. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120[J]. Nat Med, 2005, 11(1): 90-94.

[21] TALUKDAR S, OLEFSKY J M, OSBORN O. Targeting GPR120 and other fatty acid-sensing GPCRs ameliorates insulin resistance and inflammatory diseases[J]. Trends Pharmacol Sci, 2011,32(9):543-550.

[22] OH D Y, WALENTA E, AKIYAMA T E, et al. A Gpr120-selective agonist improves insulin resistance and chronic inflammation in obese mice[J]. Nat Med, 2014, 20(8): 942-947.

[23] HARA T, KIMURA I, INOUE D, et al. Free fatty acid receptors and their role in regulation of energy metabolism[J]. Rev Physiol Biochem Pharmacol, 2013,164:77-116.

[24] YONEZAWA T, KURATA R, YOSHIDA K, et al. Free fatty acids-sensing G protein-coupled receptors in drug targeting and therapeutics[J]. Curr Med Chem, 2013, 20(31):3855-3871.

[25] LI Z, QIU Q, GENG X, et al. Free fatty acid receptor agonists for the treatment of type 2 diabetes: drugs in preclinical to phase Ⅱ clinical development[J]. Expert Opin Investig Drugs, 2016,25(8):871-890.

[26] OZDENER M H, SUBRAMANIAM S, SUNDARESAN S, et al. CD36- and GPR120-mediated Ca^{2+} signaling in human taste bud cells mediates differential responses to fatty acids and is altered in obese mice[J]. Gastroenterology, 2014,146(4):995-1005.

[27] SÁNCHEZ-REYES O B, ROMERO-ÁVILA M T, CASTILLO-BADILLO J A, et al. Free fatty acids and protein kinase C activation induce GPR120 (free fatty acid receptor 4) phosphorylation[J]. Eur J Pharmacol, 2014, 723:368-374.

[28] ZHANG D, TONG X, VANDOMMELEN K, et al. Lipogenic transcription factor ChREBP mediates fructose-induced metabolic adaptations to prevent hepatotoxicity[J]. J Clin Invest, 2017,127(7):2855-2867.

[29] TANG Y, WALLACE M, SANCHEZ-GURMACHES J, et al. Adipose tissue mTORC2 regulates ChREBP-driven de novo lipogenesis and hepatic glucose metabolism[J]. Nat

Commun, 2016,7:11365.

[30] SANCHEZ-GURMACHES J, TANG Y, JESPERSEN N Z, et al. Brown fat AKT2 is a cold-induced kinase that stimulates ChREBP-mediated de novo lipogenesis to optimize fuel storage and thermogenesis[J]. Cell Metab, 2018,27(1):195-209.

[31] EISSING L, SCHERER T, TÖDTER K, et al. *De novo* lipogenesis in human fat and liver is linked to ChREBP-β and metabolic health[J]. Nat Commun, 2013,4:1528.

[32] OH D Y, TALUKDAR S, BAE E J, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects[J]. Cell, 2010, 142(5):687-698.

[33] ZHANG D, LEUNG P S. Potential roles of GPR120 and its agonists in the management of diabetes[J]. Drug Des Devel Ther, 2014,8:1013-1027.

[34] ULVEN T, CHRISTIANSEN E. Dietary fatty acids and their potential for controlling metabolic diseases through activation of FFA4/GPR120[J]. Annu Rev Nutr, 2015,35:239-263.

[35] PACKER M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium[J]. J Am Coll Cardiol, 2018, 71(20): 2360-2372.

[36] ZHAO P, WONG K I, SUN X, et al. TBK1 at the crossroads of inflammation and energy homeostasis in adipose tissue[J]. Cell, 2018,172(4):731-743.

[37] AGUDELO L Z, FERREIRA D M S, CERVENKA I, et al. Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation[J]. Cell Metab, 2018,27(2): 378-392.

[38] KUDA O, BREZINOVA M, SILHAVY J, et al. Nrf2-mediated antioxidant defense and peroxiredoxin 6 are linked to biosynthesis of palmitic acid ester of 9-hydroxystearic acid [J]. Diabetes, 2018,67(6):1190-1199.

[39] PFLIMLIN E, BIELOHUBY M, KORN M, et al. Acute and repeated treatment with 5-PAHSA or 9-PAHSA isomers does not improve glucose control in mice[J]. Cell Metab, 2018,28 (2):217-227.

[本文编辑] 廖晓瑜，贾泽军