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综 述

花生四烯酸代谢与肝脏糖脂代谢稳态调控

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摘 要：花生四烯酸(arachidonic acid, AA)是一种ω-6多不饱和脂肪酸，在生物体内主要是以磷脂的形式存在于细胞膜上。AA在细胞内主要通过环氧合酶(cyclooxygenase, COX)途径、脂氧合酶(lipoxygenases, LOX)途径、细胞色素P450单氧化酶(cytochrome P450 monooxygenase, CYP450)途径等进行代谢。糖脂代谢的稳态调控是维持机体基本生命活动的基础，肝脏是糖脂代谢调控的中枢器官。肝脏糖脂代谢紊乱与2型糖尿病、非酒精性脂肪性肝病等代谢性疾病的发生和发展密切相关。已有研究表明AA代谢与肝脏糖脂代谢紊乱有密切的关系。本文就AA代谢在肝脏糖脂代谢稳态调控中的作用及其作为脂肪肝和胰岛素抵抗等代谢性疾病治疗靶点的价值作一综述。

关键词：花生四烯酸；肝脏；代谢；脂质介质；代谢性疾病
中图分类号：Q493.4；Q493.5；Q493.9

Arachidonic acid metabolism in liver glucose and lipid homeostasis

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Abstract: Arachidonic acid (AA) is an ω-6 polyunsaturated fatty acid, which mainly exists in the cell membrane in the form of phospholipid. Three major enzymatic pathways including the cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 monooxygenase (CYP450) pathways are involved in AA metabolism leading to the generation of a variety of lipid mediators such as prostaglandins, leukotrienes, hydroxyeicosatetraenoic acids (HETEs) and epoxyeicoastrienoic acids (EETs). These bioactive AA metabolites play an important role in the regulation of many physiological processes including the maintenance of liver glucose and lipid homeostasis. As the central metabolic organ, the liver is essential in metabolism of carbohydrates, lipids and proteins, and its dysfunction is associated with the pathogenesis of many metabolic diseases such as type 2 diabetes mellitus, dyslipidemia and non-alcoholic fatty liver disease (NAFLD). This article aims to provide an overview of the enzymatic pathways of AA and discuss the role of AA-derived lipid mediators in the regulation of hepatic glucose and lipid metabolism and their associations with the pathogenesis of major metabolic disorders.

Key words: arachidonic acid; liver; metabolism; lipid mediator; metabolic diseases

花生四烯酸 (arachidonic acid, AA)，也称为全顺式 -5,8,11,14- 二十碳四烯酸，是一种 ω-6 多不饱和脂肪酸，主要以磷脂形式存在于细胞膜中 [1]。当细胞受到刺激时，膜磷脂在磷脂酶 A2 和磷脂酶 C 作

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用下向胞浆释放出游离的 AA。

游离的 AA 通过以下四大酶促反应途径进行代谢，并生成大量具有广泛生物活性和功能的 AA 代谢产物。(1) AA 可在环氧合酶 -1 (cyclooxygenase-1, COX-1) 和 -2 (COX-2) 的作用下生成前列腺素 (prostanoids, PGs)，包括前列腺素 E2 (prostaglandin E2, PGE2)、PGD2、PGF2α、前列环素 (prostacyclin, PGI2) 和血栓烷 A2 (thromboxane A2, TXA2)；(2) AA 在六种脂氧合酶 (lipoxygenases, LOX)，即 15-LOX、15-LOX-2、12-LOX、12R-LOX、Elox-3 和 5-LOX 的作用下生成白三烯 (leukotrienes, LTs) 和脂氧素 (lipoxins, LXs) 等多种生物活性产物；(3) AA 在细胞色素 P450 单氧化酶 (cytochrome P450 monooxygenase, CYP450) 的作用下生成环氧二十碳三烯酸 (epoxyeicoastrienoic acids, EETs) 或羟基二十碳四烯酸 (hydroxyeicosatetraenoic acid, HETE)；(4) 当组织细胞损伤时，AA 还可在脂肪酸酰胺水解酶 (fatty acid amide hydrolase, FAAH) 的作用下产生大麻素 (anandamides)，通过与大麻素 1 型受体 (cannabinoid receptor 1, CB1) 相互作用，促进组织再生和细胞增殖 [2, 3]。此外，在氧化应激时，组织细胞内大量的活性氧和活性氮可通过非酶促反应途径将 AA 代谢生成异前列腺素 (isoprostanes) 和亚硝基二十碳四烯酸，促进血管收缩，平滑肌细胞增殖 [4, 5]。上述 AA 代谢产物统一被称为类花生酸 (eicosanoids)，是有效的自分泌和旁分泌生物活性介质，广泛参与机体的各种生理和病理生理过程 (图 1)。

糖脂代谢稳态对维持机体内环境平衡发挥着至关重要的作用。糖脂代谢紊乱是导致 2 型糖尿病、非酒精性脂肪性肝病 (nonalcoholic fatty liver disease, NAFLD)、肥胖、高血压、高血脂和动脉粥样硬化等重大慢性代谢疾病的重要原因。肝脏作为调控糖脂代谢过程的中枢器官，在多种能量代谢紊乱性疾病的发生和发展中发挥重要作用；然而，迄今为止肝脏糖脂代谢稳态调控的机制尚未完全阐明。越来越多的研究表明，AA 代谢的 COX 途径、LOX 途径和 CYP450 途径与肝脏糖脂代谢稳态的调控有着密切的联系，其代谢障碍广泛参与了重大代谢性疾

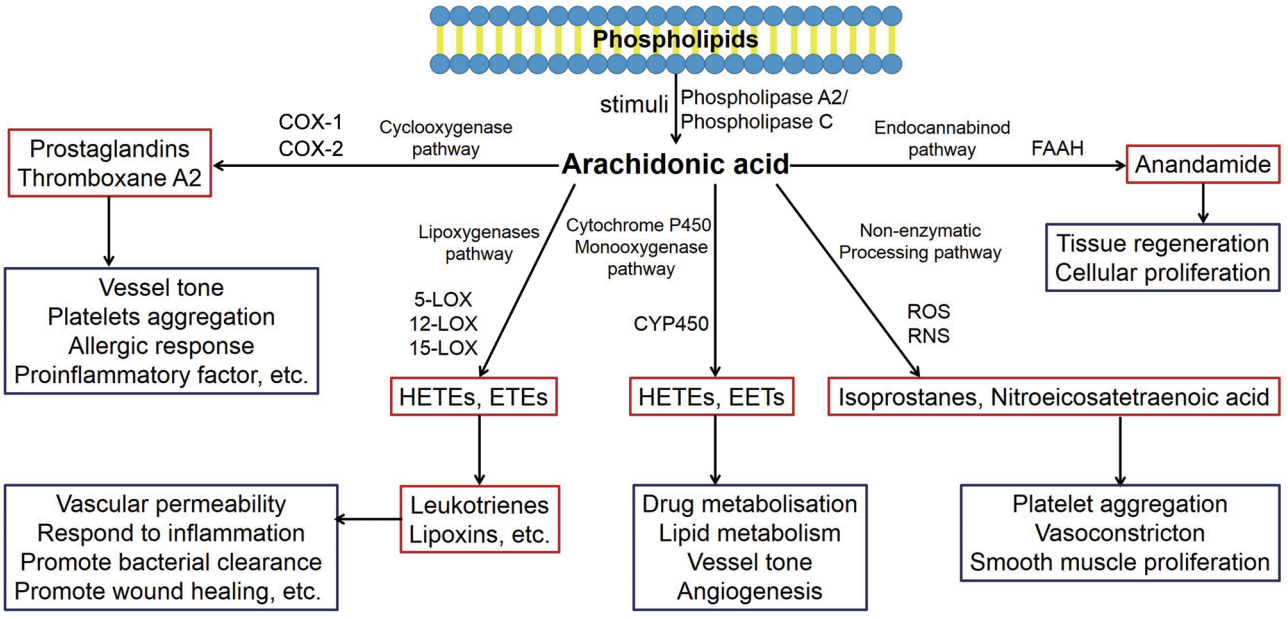

图 1. 花生四烯酸的代谢及其代谢产物的生物学功能

Fig 1. Metabolism of arachidonic acid (AA) and biological functions of its metabolites. When needed, AA is mainly released from cell membrane phospholipids processed by phospholipase A2 (PLA2) and phospholipase C (PLC). AA is mainly metabolized by four kinds of enzymatic pathways involving cyclooxygenase (COX), lipoxygenase (LOX), cytochrome P450 monooxygenase (CYP450) and fatty acid amide hydrolase (FAAH). AA can be converted into a set of bioactive metabolites including prostaglandins (PGs), leukotrienes (LTs), lipoxins (LXs), and hydroxyeicosatetraenoic acids (HETEs). In addition to these enzymatic pathways, AA is also processed by non-enzymatic reactions to form isoprostanes and nitroeicosatetraenoic acid by reactive oxygen species (ROS) and reactive nitrogen species (RNS). AA-derived metabolites are highly bioactive and play diverse functions in the body.

病的发生和发展。本文将围绕上述三个代谢途径，综述 AA 代谢在肝脏糖脂代谢调控过程中的作用以及其与重大代谢疾病发生的关系。

1 COX途径

COX 又称为前列腺素 G/H 合酶，包括 COX-1 和 COX-2 两种，是催化 AA 转化为多种 PGs 的关键酶 [6, 7]。总体而言，COX-1 为组成型 COX，其稳定表达并广泛存在于全身各个组织，特别是胃肠道上皮组织、血小板和肾脏，参与维持胃肠黏膜的完整性，调节血管舒缩、血小板聚集及肾功能等 [8–10]；COX-2 为可诱导型 COX，其表达在正常情况下几乎检测不到，只有在组织细胞受到各种损伤性应激原刺激后才会被诱导表达，COX-2 作用于 AA 而生成的 PGs，主要促发炎症反应和组织损伤 [11]。

胰岛素功能正常是肝脏糖脂代谢稳态调控的关键因素之一，胰岛素抵抗 (insulin resistance, IR) 在 2 型糖尿病和 NAFLD 等代谢性疾病的发病过程中发挥重要作用。已有研究表明，IR 与组织细胞的慢性轻度炎症状态有关，提示炎症是 IR 发生和发展的重要原因 [12]。迄今为止，众多的体内外实验研究表明 COX 非选择性抑制剂阿司匹林具有降低糖尿病患者血糖的作用 [13]。核因子 κB (nuclear factor-kappaB, NF-κB) 正常情况下与核因子 κB 抑制蛋白 (inhibitor of NF-κB, IκB) 结合处于失活状态，机体在受到外界应激原 (如炎症等) 刺激时 ，经过一系列的信号传递使细胞内的磷酸化激酶 IκB 激酶 (IκB kinase, IKKs) (包括 IKKα、IKKβ 和 IKKγ 三个亚基) 激活，磷酸化 IκB，因此 NF-κB 发生核转位，进而促进一系列靶基因 (如炎症反应等) 的表达增加；已有研究表明高剂量的阿司匹林及水杨酸钠可以通过抑制 IKKβ 的活性，从而抑制 NF-κB 通路下游的炎症反应途径，发挥其改善 IR 的作用 [14–16]。

尽管已明确炎症导致的促炎细胞因子的积聚可以刺激 COX-2 的表达，但在成年肝实质细胞中促炎物质刺激却无法诱导 COX-2 的表达。Francés 等人认为，肝实质细胞中 COX-2 无法被炎症诱导表达可能是 IR 发生和发展的先决条件；在小鼠肝细胞中特异性过表达 COX-2 基因后，其代谢 AA 产生的 PGs 可能通过增加肝细胞脂质氧化对高脂饮食喂养 (high fat diet, HFD) 引起的肥胖、炎症和全身性 IR 发挥保护作用 [17]。甲硫氨酸 - 胆碱缺乏饮食 (methionine- and choline-deficient diet, MCD) 喂养可以在短时间内使动物模型的肝细胞出现脂肪变和炎症反应。Motino 等研究表明，肝脏特异性过表达 COX-2 的小鼠能显著抵抗 MCD 饮食诱导的 NAFLD 发病；其机制可能与 PGs 产生增加促进组织再生和抑制炎症因子释放有关 [18]。微小 RNA (microRNA, miRNA) 是非编码 RNA，可作为基因表达的转录后关键调控因子。有研究表明 COX-2 可通过 PI3K/p300 信号通路增加 DEAD-box 解旋酶 p68 (DDX5) 的水平，抑制肝细胞中 miR-183 的表达，继而发挥改善 IR 的作用 [19, 20]。

多种 PGs 参与了肝脏糖脂代谢的调控过程。有研究表明 COX-2 选择性抑制剂塞来昔布可以改善 HFD 诱导的大鼠的肝脏脂质沉积和 IR [21–23]。Hsieh 等发现其机制可能是通过抑制 HFD 诱导的大鼠脂肪组织中 COX-2 的表达和 PGE2 合成，进而对抗 HFD 诱导的高瘦素血症而改善 IR [22, 24]。同样，COX-2 另外一种特异性抑制剂尼美舒利也被发现能对抗 HFD 诱导的小鼠 NAFLD 和 IR 的发病，其机制可能是通过降低 COX-2 代谢 AA 产生的 15d-PGJ2 的水平，从而降低 PPARγ 活性来发挥其改善作用 [25]。Chan 等人研究发现，给予 *db*/*db* 小鼠服用塞来昔布或 EP3 抑制剂处理可以显著性改善 *db*/*db* 小鼠的 IR，表明 COX-2-PGE2-EP3 通路在 IR 的发病过程中发挥着重要的作用 [26]；此外，*EP3*$^{-/-}$ 小鼠 HFD 诱导的肝脏脂质沉积和 IR 加重，也表明 COX-PGE2-EP3 参与了 NAFLD 的发病过程 [27]。多不饱和脂肪酸大麻子油可以通过抑制 COX-2 的表达水平发挥其抵抗 HFD 诱导的肝脏脂质沉积的作用 [28]。除此之外，绿茶也可以通过抑制 COX-2-PGE2 通路改善 HFD 诱导的肝脏脂质沉积 [29]。内皮细胞特异性过表达 AMPKα1 的小鼠通过诱导 COX-2 的表达水平加重 HFD 诱导的肝脏脂质沉积 [30]。Yan 等人的研究发现，COX-2-PGI2-IP 通路在饥饿小鼠、HFD 喂养小鼠和 *ob*/*ob* 小鼠肝脏中的活性增加，*IP*$^{-/-}$ 小鼠 HFD 诱导的 NAFLD 和 IR 发生显著性改善，PGI2-IP 通过激活 PKA 信号通路和抑制 AKT 信号通路调控肝脏糖异生过程 [31]。同样，Wang 等人发现，COX-$PGF_{2\alpha}$-FP 通路在饥饿小鼠、HFD 喂养小鼠和 *ob*/*ob* 小鼠肝脏中的活性增加，特异性敲减 *ob*/*ob* 小鼠肝脏 FP，可以显著性改善 *ob*/*ob* 小鼠的 IR，$PGF_{2\alpha}$-FP 通过激活 FOXO1 信号通路调控肝脏糖异生过程 [32]。

以上研究结果表明，COX 通路与肝脏糖脂肪代谢稳态调节的关系及其在 IR 和 NAFLD 发生中的

作用还存在争议，需要进一步的研究。有趣的是，最近 Yu 课题组的研究显示，致炎介质 PGE2 受体 EP3 在调节肝脏胆固醇代谢中发挥重要作用，肝脏 EP3 缺陷可以导致高胆固醇血症并加重动脉粥样硬化的发生，提示激活肝脏 EP3 可能在治疗高脂血症和动脉粥样硬化中有重要价值 [33]。

2 LOX途径

LOX 是不含有血红素的双加氧酶。在人类和小鼠体内，已知有六种 LOX 亚型，即 15-LOX、15-LOX-2、12-LOX、12R-LOX、Elox-3 和 5-LOX。LOX 可催化多不饱和脂肪酸 (如亚油酸和 AA) 形成相应的氢过氧化物 (15-HETE、12-HETE 和 5-HETE)，然后将其进一步转化为生物活性脂质介质 (如 LTs 和 LXs 等)。另一方面，LOX 是调节细胞氧化还原稳态的关键因素，而氧化还原稳态是基因表达调控的重要组成部分。LOX 主要表达在免疫细胞、上皮细胞和肿瘤细胞，具有多种生理和病理生理功能，在炎症、皮肤病和肿瘤发生中发挥重要作用 [34, 35]。近年来，越来越多的研究发现 LOX 与肝脏糖脂代谢的调控有重要关联。

无论是 NAFLD 患者还是 NAFLD 小鼠模型体内都存在 5-LOX 和 15-LOX 的激活；其中，5-LOX 代谢产物水平与 NAFLD 严重程度具有相关性，5-LOX 代谢 AA 的产物 LTs 参与了 NAFLD 的发病过程 [36–39]。NAFLD 患者经过饮食干预治疗后，肝脏脂质沉积明显减少的同时伴随 5-LOX 代谢产物 5-HETE 等的水平降低 [40, 41]。通过抑制 5-LOX 代谢途径，如敲除 *ApoE*$^{-/-}$ 小鼠的 5-LOX 可显著改善 HFD 诱导的肝损伤和 IR；同野生型小鼠相比，5-LOX 代谢产物 LB_4 受体 LB1 缺陷小鼠可以抵抗 HFD 诱导的肝脏脂质沉积和 IR [42, 43]。此外，与野生型小鼠相比，*ob*/*ob* 小鼠肝脏 5-LOX 活性及其代谢产物 LTB4、LTC4、LTD4 和 LTE4 明显增高；给予 *ob*/*ob* 小鼠 5-LOX 特异性抑制剂处理后，可通过增加肝脏脂肪酸分泌蛋白 MTTP 和 apoB 以及降低肝脏脂肪酸转运相关基因 LFABP 和 FAT/CD36 的表达水平降低肝脏脂质沉积 [44]。

MCD 诱导的 NAFLD 小鼠模型体内 12-LOX 的活性及其代谢产物 12-HETE 的水平均明显上调 [45]，己酮可可碱 (pentoxifylline, PTX) 改善 NAFLD 患者的肝脏病理学改变的同时伴随体内的 12-HETE 水平的下调 [46]。同野生型小鼠相比，ApoE 缺陷小鼠肝脏中 12/15-LOX 的活性及其产物 12-HETE 显著性增加，并且发生明显的肝细胞脂质蓄积，而 ApoE 和 12/15-COX 同时缺陷小鼠的肝脏脂质含量显著降低；同样，给予 HFD 喂养后，与单纯 ApoE 缺陷小鼠相比，双重缺陷小鼠 HFD 诱导的 NAFLD 和 IR 显著改善 [47]。

综上所述，AA 的 LOX 代谢途径激活导致肝脏糖脂代谢失调，出现 IR 和 NAFLD 表型，除促炎细胞因子的作用外，其确切机制还未阐明。现有的证据提示 LOX 有望成为 IR 和 NAFLD 的潜在治疗靶点。

3 CYP450途径

CYP450 是一类以还原态与 CO 结合后在 450 nm 处具有最高吸收峰的含血红素的单链蛋白质超家族。CYP450 是一组重要的末端加氧酶系，主要表达于肾脏、肝脏、大脑和血管等组织，在生物体内具有氧化内源性脂质的功能，某些疏水的外源性物质经 CYP450 蛋白催化后可形成极性更高的物质或通过与水溶性物质结合而被生物体排泄。AA 通过 CYP450 途径产生的代谢产物主要是 19-HETE、20-HETE 和 EETs[48]。在人体内，约 50%~75% 的 20-HETE 和 13%~28% 的 EETs 产生有赖于肝脏 AA-CYP450 的代谢途径 [49]，然而其在肝脏的功能，特别是与糖脂代谢调控的关系至今仍不十分清楚。

我们课题组利用蛋白质组学的方法发现，与健康对照组相比，NAFLD 患者肝脏 CYP2E1、CYP2C19、CYP1A2、CYP4A11、CYP2C18、CYP4A22 以及 CYP2C9 的表达水平不同程度的上调 [50]。Park 等 [51] 在 2 型糖尿病小鼠模型 *db*/*db* 小鼠的研究中也证实了产生 19- 和 20-HETE 的 CYP4A10、CYP4A12 和 CYP4A14 在肝脏组织中表达显著上调。给予 *db*/*db* 小鼠或高脂喂养小鼠 HET0016 (20-HETE 特异性抑制剂 [52, 53]) 处理后，其血糖和血清胰岛素水平明显降低、IR 明显减轻；特异性敲低 *db*/*db* 小鼠肝脏 CYP4A 表达水平后，血糖水平明显降低，胰岛素利用率增加，IR 明显改善 [51]；20-HETE 可以促进 IR 的发生和发展 [54–56]。我们前期研究成果也发现，同野生型小鼠相比，CYP4A14 基因缺陷小鼠能通过抑制 FAT/CD36 的表达显著减轻 HFD 或 MCD 诱导的肝脏脂质沉积及 MCD 诱导的非酒精性脂肪性肝炎 (nonalcoholic steatohepatitis, NASH) [57]。以上研究成果提示 AA-CYP4A-20-HETE 代谢途径可

能在肝脏糖脂代谢调控中发挥着重要的作用，阻断该通路有望成为脂肪肝和 IR 治疗的新策略。

除 CYP4A 亚家族外，CYP 其他亚家族也在肝脏糖脂代谢调控过程中发挥重要作用。CYP3A4 不仅在 NAFLD 和糖尿病患者肝脏中的表达水平显著下降，在 HFD 诱导的 NAFLD 小鼠肝脏中的表达也明显下降，提示 CYP3A4 可能参与了肝脏糖脂代谢的调控过程 [58, 59]。CYP2B1 在 MCD 诱导的 NAFLD 小鼠肝脏中表达明显降低，但是在 HFD 诱导的 NAFLD 小鼠肝脏中的表达水平无明显改变，该研究结果有助于更好地探究 CYP2B1 介导的代谢过程对 NAFLD 的影响，从而对靶向开发 NAFLD 患者 CYP2B 亚家族药物底物的安全性和药代动力学研究具有重要意义 [60]。CYP2C 和 2J 亚家族主要将 AA 催化为具有抗炎作用的 EETs。多项研究表明，通过敲除 EETs 降解酶水溶性环氧化合物水解酶 2 (soluble epoxide hydrolase 2, sEH2) 或使用 TPPU 抑制其活性提高小鼠肝脏 EETs 水平可显著改善 MCD 诱导的脂质蓄积和纤维化 [61–63]。同样，内皮细胞过表达 CYP2J 的转基因小鼠可能通过 14,15-EET 的抗炎作用显著减轻 HFD 诱导的 NAFLD 发生 [64]。最近，一项在 NAFLD 患者的研究发现循环 EETs、DHET 和 CYP 表氧酶活性的下降与脂肪肝的严重程度显著相关，进一步提示 CYP2C 和 CYP2J 产生的 EETs 对脂肪肝具有重要的保护作用及预后价值 [65]。

越来越多的研究证实 CYP2E1 参与了 NAFLD 和 IR 的发生和发展，CYP2E1 升高是肝脏产生活性氧和脂质过氧化的主要因素 [66]。Isabelle 等研究发现，在给予 MCD 喂养后，同野生型小鼠相比，CYP2E1 缺陷小鼠肝脏脂质蓄积的程度明显加重，可能与体内同时存在的 CYP4A 加重 MCD 诱导 CYP2E1 缺陷小鼠肝脏脂质过氧化水平有关 [67]。然而，令人不解的是，给予 HFD 处理显著改善 CYP2E1 缺陷小鼠 NAFLD 和 IR 的发生和发展 [68, 69]，而且肝脏特异性过表达 CYP2E1 可以加重小鼠肝脏的脂质沉积和 IR [70–72]。目前，还不清楚是什么原因导致了不同脂肪肝模型之间 CYP2E1 作用的差异。

迄今为止，AA-CYP450 代谢通路在肝脏脂质代谢中的作用仍知之甚少，但已有的证据显示 CYP450 系统在肝脏 AA 代谢调节中作用复杂。总体而言，抑制 CYP4A-HETEs 通路和增强 CYP2C/J-EETs 通路可能在肝脏糖脂代谢紊乱疾病 (如 IR 和 NAFLD) 治疗中有积极的意义。

4 总结和展望

AA 代谢作为人体内最复杂的调节系统之一，其不同代谢酶及产物不仅在各种细胞和组织中表达水平不一，而且生物学作用复杂多样，广泛参与机体众多生理过程调节和重大疾病发生。大量证据显示，AA 在肝脏糖脂代谢稳态调节中发挥重要作用，其代谢异常可能与包括脂肪肝、IR 和高脂血症在内的很多代谢性疾病的发生和发展有关。但是由于 AA 代谢产物和功能的复杂性，对其确切作用机制的探讨仍然具有一定的困难。根据已有的研究成果，阻断肝脏 COX-2 活性、抑制肝脏 LOX 和 CYP4A 通路、增强 CYP2C/2J 功能有望成为脂肪肝和 IR 的治疗策略。相信随着医学科研新方法的建立，包括实时和细胞特异性基因、蛋白和脂质组分析手段，人们将能够更好地阐明 AA 的代谢调节通路及其产物的生物学功能，从而为肝脏糖脂代谢紊乱相关代谢性疾病的治疗提供新的思路。

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