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治疗非酒精性脂肪性肝病的相关药物及机制

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摘　要

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)发病率逐渐升高，该病不断进展为肝纤维化和肝癌，已成为全球亟待解决的问题，目前还没有治疗NALFD的特效药。该综述总结了与NAFLD相关药物及其作用机制，为开展新的研究、寻求NALFD治疗方案提供新的思路及依据。

关键词

非酒精性肝病，发生机制，治疗

Drugs and Mechanisms Related to the Treatment of Nonalcoholic Fatty Liver Disease

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Abstract

The incidence of nonalcoholic fatty liver disease (NAFLD) is gradually increasing, and the disease continues to progress to liver fibrosis and liver cancer, which has become an urgent problem worldwide, and there is no specific drug for the treatment of NALFD. This review summarizes the drugs related to NAFLD and their mechanisms of action, providing new ideas and basis for carrying out new studies and seeking NALFD treatment options.

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Keywords

Nonalcoholic Fatty Liver Disease, Mechanism, Treatment

1. 前言

由于肥胖患病率的不断增加，非酒精性脂肪性肝病(NAFLD)逐渐成为备受关注的对象。NAFLD 的经典定义为无其他肝病情况下的肝脂肪变性[1]。NAFLD 包括单纯性脂肪肝(Nonalcoholic fatty liver, NAFL)、非酒精性脂肪性肝炎(Nonalcoholic steatohepatitis, NASH)、肝硬化等广泛疾病[2]。随着病情的进展，非酒精性脂肪性肝炎患者的肝脏疾病和心血管疾病的发病率和死亡率逐渐增加[3]。以下为治疗 NAFLD 相关药物及具体机制。

2. 相关药物

2.1. 二甲双胍

二甲双胍被广泛用于非胰岛素依赖型糖尿病的药物，具有调节葡萄糖和脂质代谢紊乱的作用[4]。有研究表明[5]，二甲双胍可通过阻断线粒体呼吸链复合物 I 来抑制肝糖异生并改善外周葡萄糖利用。另有研究发现[6]，二甲双胍可以激活腺苷酸活化蛋白激酶，具有减少肝脏脂肪生成，影响肝脏对胰岛素的敏感性，控制肝糖输出的作用。转录因子 EB (TFEB)属于 bHLH-亮氨酸拉链转录因子家族，作为溶酶体和自噬相关基因的主要转录因子，TFEB 在脂质代谢中起关键作用，TFEB 可促进过氧化物酶体增殖物激活受体 γ 共激活因子 1α (PGC1α)的表达，进而加快脂质降解、促进脂肪酸氧化和减少脂肪生成[7]。最新研究表明二甲双胍依赖 TFEB 具有减轻肝脏脂肪变性、抑制过度肝脏脂质蓄积和减少胰岛素抵抗的作用[8]。二甲双胍可通过阻断线粒体呼吸链、TFEB 通路、调控脂肪和细胞因子、调节肠道菌群、减少胰岛素抵抗等途径改善肝脏脂肪变性，延缓 NAFLD 进展[9]。因此，二甲双胍用于治疗 NAFLD 逐渐被人们所接受。

2.2. 吡格列酮

噻唑烷二酮类药物是核转录因子过氧化物酶体增殖物激活受体 γ (PPAR)-c 的配体，对糖脂代谢以及血管生物学和炎症具有广泛作用[10]。在一项早期研究中发现，Belfort 等[11]对 55 例 NASH 和糖尿病前期或 T2DM 患者进行了吡格列酮(45 mg/天)的随机对照试验，结果发现吡格列酮提高了胰岛素敏感性，使转氨酶、脂肪变性、炎症和气球样变得到改善。Aithal [12]等在 74 例 NASH 患者中进行了吡格列酮 30 mg/日或安慰剂治疗 12 个月的随机对照试验中发现，吡格列酮显著改善了 NASH 患者肝细胞损伤和纤维化。但是，体重增加是吡格列酮最常见的副作用，同时也可能导致膀胱癌、骨质疏松等情况发生[13] [14]。因此，在开始治疗前，应与每例患者讨论风险和获益，若无确切的药物安全性和有效性证据，吡格列酮不推荐用于治疗 NAFLD。

2.3. 利拉鲁肽

胰高血糖素受体激动剂可能是一个新的 NAFLD 治疗靶点，GLP-1 可通过下丘脑和脑干的中枢机制对饱腹感产生剂量依赖性效应[15]。GLP-1 能有效降低肝脏和脂肪组织的胰岛素抵抗，降低了脂解诱导的

FFA 和甘油三酯衍生的毒性代谢物水平[16] [17]。另有研究表明[18]，GLP-1RA 可通过多种途径改善进餐试验期间的餐后血脂，包括减少肠道运动和直接抑制乳糜微粒合成和分泌导致的膳食脂肪吸收。在一项多中心、随机对照试验中[19]，对 52 名活检证实的 NASH 患者，将 GLP-1 激动剂利拉鲁肽皮下注射 48 周。结果显示利拉鲁肽治疗的患者达到 NASH 组织学缓解，利拉鲁肽能显著降低肝纤维化进展[优势比(OR) 4.3；95%置信区间(CI) 1.0~17.7；p = 0019]，但与安慰组相比，利拉鲁肽会引起腹泻、便秘和食欲不振等胃肠道不良反应。利拉鲁肽独特的组织学疗效和代谢综合征的改善使其成为 NAFLD 具有良好前景的治疗方法，值得在更大规模的研究中进一步研究。

2.4. 维生素 E

氧化应激可能导致 NASH 患者肝细胞损伤和疾病进展，目前认为是关键机制之一。维生素 E 作为抗氧化剂已用于治疗 NASH [20]。由于研究的标准不同，维生素 E 的剂量不同，使用的维生素 E 配方不明确等多方因素，可以总结认为维生素 E 可降低 NASH 患者的氨基转移酶，非糖尿病 NASH 患者的脂肪变性、组织炎症和气球样变得到改善，并使 NASH 消退，但维生素 E 无法逆转或延缓肝纤维化。有研究指出[21] [22]，维生素 E 可能会增加致死率、前列腺癌、遗传变异等风险。因此，在缺乏有效性数据之前，维生素 E 不推荐用于治疗糖尿病患者的 NAFLD。

2.5. 熊脱氧胆酸、 ω-3 脂肪酸

相关研究表明[23] [24]，熊去氧胆酸能改善 NAFLD 患者的转氨酶和脂肪变性，改善 NASH 患者肝组织学特征。但在一项多中心、随机对照试验中，熊去氧胆酸与安慰剂在治疗 NASH 患者的组织学改变上并无明显差异[25]。Masterton 等[26]发现在 NAFLD 患者中使用 ω-3 脂肪酸能改善肝病进展。然而，也有报道称 ω-3 脂肪酸对 NAFLD 或 NASH 患者治疗效果并不满意[27]。因此，UCDA 及 ω-3 脂肪酸是否能常规治疗 NAFLD 或 NASH，未来还需进一步研究。

2.6. 伊马替尼

伊马替尼为酪氨酸激酶抑制剂，最开始用于靶向治疗慢性粒细胞白血病[28]。关研究表明，伊马替尼的抗炎作用能显著减少急性肝损伤和肥胖小鼠的脂肪组织炎症，降低腹腔和肝脏巨噬细胞的 TNFα 基因表达以及全身脂质水平，对减少肝脏脂肪变性、组织炎症，增加胰岛素敏感性等方面具有重要作用[29] [30]。最近，伊马替尼被证明能抑制 PPARγ21 的翻译后磷酸化，而 PPARγ21 是巨噬细胞极化的重要调节因子[31]。因此，伊马替尼靶向作用于巨噬细胞和肝脏中炎症和脂肪生成途径可能是 NAFLD 患者一种新型治疗策略。

2.7. 非诺贝特、苯扎贝特

过氧化物酶体增殖物激活受体(PPARs)是调节脂质代谢、能量平衡和炎症相关基因表达的转录因子，PPAR-α 激动剂可通过增加线粒体 β-氧化引起肝脏脂肪变性的表达降低，而 PPAR-β/δ 通过降低餐后阶段的肝脏糖异生改善肝脏胰岛素抵抗[32]。非诺贝特激活 PPAR-α 可通过上调果糖喂养小鼠中 β-氧化相关酶和 DNL 表达减少显著改善肝脏胰岛素抵抗，苯扎贝特激活泛 PPAR 可对来自 PPARα、PPAR-β/δ 活化引起肝细胞中与 β-氧化和脂质转运相关的基因表达增加，同时与炎症相关的基因水平降低[33] [34]。因此，过氧化物酶体增殖物激活受体可作为治疗非酒精性脂肪肝的靶点。

2.8. 肠道菌群

通过给予益生菌调节肠道菌群被认为是 NAFLD 治疗的潜在策略[35]。动物研究的数据表明[36]，益

生菌和益生元已被证明可以改变微生物群的成分，并影响食物消化，调节食欲和体重。它们的有益作用可以影响葡萄糖和脂肪代谢，改善胰岛素敏感性，减轻慢性全身炎症。在国外一项双盲单中心随机安慰剂随机对照试验中，48 例患者被随机分配接受添加益生菌生联合 ω-3 脂肪酸或安慰剂治疗 8 周，通过瞬时弹性成像(SWE)测量的脂肪肝指数(FLI)和肝脏硬度(LS)的变化，结果发现，肝脏脂肪变性和纤维化减少程度显著大于安慰剂组。因此，益生菌与 ω-3 脂肪酸在 NAFLD 中能降低肝脏脂肪，改善血脂代谢，减轻全身慢性炎症[37]。王薇等[38]研究表明，益生菌可通过调节 NAFLD 患者肠道菌群，帮助降低 TNF-α，使血脂联素水平升高，进而调控血糖、血脂代谢，减轻 NAFLD 的肝脏损伤。

2.9. 奥替普拉(Oltipraz)

奥替普拉是一种人工合成的二硫乙酮，通过交替激活 AMPK 和失活 S6K1 改善脂肪变性，同时减少脂肪酸的合成，通过抑制 LXR-a 活性和降低肝脏内 SREBP-1c 的表达加速脂质氧化[39]。在一项多中心对照实验中[40]，将肝脏脂肪 > 20%和高转氨酶血症的受试者随机分配至 3 组：安慰剂(n = 22)、30 mg oltipraz (n = 22)或 60 mg oltipraz (n = 24)，每日两次，持续 24 周。研究发现，实验组肝脏脂肪含量减少百分比显著大于安慰剂组，实验组肝脏脂肪含量的绝对变化呈剂量依赖性增加，体重指数也显著降低。因此，奥替普拉对显著降低 NAFLD 患者的肝脂肪含量具有重大作用。

2.10. Aramchol

Aramchol 通过稳定的酰胺键结合 2 种天然组分胆汁酸和花生四烯酸获得，是一种新型合成的脂质分子[41]。硬脂酰辅酶 A 去饱和酶 1 (SCD1)是调节肝脏脂肪酸代谢的关键酶。SCD1 抑制可减少脂肪酸的合成并增加脂肪酸的 β 氧化，导致甘油三酯和脂肪酸酯的肝脏储存减少。而 Aramchol 对硬脂酰辅酶 A 去饱和酶 1 (SCD1)活性的抑制率为 70%~83% [42]。在一项对照试验中[43]，给予 NAFLD 患者 Aramchol 治疗 3 个月后发现，NAFLD 患者肝脏脂肪含量水平通过 Aramchol 治疗而降低，且与降低水平呈剂量反应关系。这使得 Aramchol 成为脂肪肝相关疾病治疗的候选药物，但目前尚未满足的医疗需求，需要在代谢和组织学上进一步研究。

2.11. 吡非尼酮

吡非尼酮是一种抗纤维化药物，可抑制 T 细胞和巨噬细胞的肺内流来治疗肺纤维化[44]。吡非尼酮可抑制肝星状细胞增殖、降低了炎性细胞因子的表达，通过降低大鼠肝脏转氨酶水平，减弱氧化应激，预防脂多糖诱导的肝毒性[45] [46] [47]。最近一项研究中，Chen 等[48]发现吡非尼酮通过减轻脂质蓄积和氧化应激，在饮食诱导的 NASH 脂毒性模型中限制并逆转了肝脏脂肪变性和胰岛素抵抗，通过抑制 TGF-β通路和星状细胞活化来减弱肝纤维化。因此，吡非尼酮未来可能是 NASH 的治疗靶点。

2.12. Emricasan

脂肪变性肝细胞可通过死亡配体 Fas 和肿瘤坏死因子相关凋亡诱导配体(TRAIL)激活的外源性途径或通过内源性途径激活发生凋亡，而两种凋亡途径均聚集在半胱天冬酶活化上，半胱天冬氨酸特异性蛋白酶，在细胞凋亡中起着重要作用[49] [50]。这一机制可能使得 Emricasan 成为脂肪肝相关疾病治疗的候选药物。Barreyro 等[51]研究泛半胱天冬酶抑制剂 Emricasan 是否可改善 NASH 小鼠模型的肝损伤和纤维化中发现，喂食高脂食物的小鼠的肝细胞凋亡增加了 5 倍，caspase-3 和-8 活性分别增加了 1.5 倍和 1.3 倍；在喂食高脂食物 + Emricasan 的小鼠中，这种细胞凋亡增加显著减弱。通过抑制肝细胞凋亡抑制肝损伤和纤维化，表明 Emricasan 可能是 NASH 中有效抗纤维化治疗方法。

2.13. 司维拉姆

胆汁酸螯合剂是一种不可吸收的阳离子聚合物，可结合胆汁酸以及肠道中的大量分子，阻止其重吸收，常用于治疗血脂异常和高磷血症[52] [53]。除了能够阻止胆汁酸和磷酸盐在肠道中的吸收外，还报告了胆汁酸螯合剂通过激活 TGR5 (一种结合胆汁酸的 G 蛋白偶联受体)调节脂肪和葡萄糖代谢[54] [55]。相关研究发现，胆汁酸螯合剂还可提高人和小鼠的胰岛素敏感性，减轻肥胖和肝脏脂肪变性[55]。在一项评估司维拉姆治疗非酒精性脂肪性肝病(NAFLD)小鼠的疗效中，研究显示司维拉姆治疗显著减少了肝脏脂肪变性和小叶炎症，NAFLD 肝脏中促炎性浸润巨噬细胞显著减少，活化的 Kupffer 细胞分数显著增加，司维拉姆改善了 NAFLD，并对抗了肝脏中的先天性免疫细胞失调。因此，胆汁酸螯合剂-司维拉姆可能也是治疗 NAFLD 一种有效药物。

3. 结语

NAFLD 发病率逐年升高，但目前尚缺乏有效的药物。本文系统性综述了既往针对 NAFLD 治疗的相关药物和机制，为开展新的研究，寻求 NAFLD 治疗方案提供新的思路及依据。在目前治疗 NAFLD 药物中，主要是通过降低氧化应激、抑制胰岛素抵抗、减轻组织炎症、抗纤维化、调节脂肪和葡萄糖代谢等机制改善肝脂肪样变性，延缓或逆转肝纤维化达到治疗目的，但类似于 Oltipraz、Aramchol 等药物目前尚未真正应用于临床，未来还需进一步开展更多研究评估药物的安全性及有效性。同时，中医药专家对 NAFLD 兴趣浓厚，且有很多中药治疗 NAFLD 的报道，并付诸于临床实践。因此，未来中西医结合治疗也为 NAFLD 患者提供了选择的可能。

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