

短链脂肪酸对类风湿性关节炎的改善作用及中药的调控

廖明慧, 戴岳*

中国药科大学中药学院, 江苏 南京

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摘要

类风湿性关节炎是一种有“不死的癌症”之称的慢性全身性免疫疾病, 是临床多发且难治的关节运动性疾病之一。短链脂肪酸是肠道菌群的重要代谢产物, 具有抑制炎症和调节免疫等生物活性, 对类风湿性关节炎具有改善作用。此外, 许多中药可通过调控肠道菌群促进短链脂肪酸产生, 呈现抗关节炎效应。本文从短链脂肪酸在类风湿性关节炎疾病状态下的变化, 对疾病的改善作用和机制, 中药调控短链脂肪酸治疗类风湿性关节炎以及短链脂肪酸的应用等方面进行综述, 为认识类风湿性关节炎的病机、促进相关药物的研发及阐明中药的作用机制提供参考。

关键词

短链脂肪酸, 类风湿性关节炎, 肠道菌群, 中药

Ameliorative Effect of Short Chain Fatty Acids on Rheumatoid Arthritis and Regulation of Traditional Chinese Medicines

Minghui Liao, Yue Dai*

School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing Jiangsu

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic immune disease known as “cancer that never”
*通讯作者。

dies". It is one of the most common and refractory joint motor diseases in clinic. Short-chain fatty acids are important metabolites of intestinal flora, which have biological activities such as inhibiting inflammation and regulating immunity, and can improve rheumatoid arthritis. In addition, many traditional Chinese medicines can promote the production of short-chain fatty acids by regulating intestinal flora, showing anti-arthritis effect. In this paper, the changes of short-chain fatty acids in the disease state of rheumatoid arthritis, the improvement effect and mechanism of the disease, the regulation of short-chain fatty acids by Chinese medicines in the treatment of rheumatoid arthritis and the application of short-chain fatty acids were reviewed, so as to provide reference for elucidating the pathogenesis of rheumatoid arthritis, promoting the research and development of related drugs and clarifying the mechanism of action of Chinese medicines.

Keywords

Short-Chain Fatty Acids, Rheumatoid Arthritis, Intestinal Flora, Traditional Chinese Medicines

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1. 引言

类风湿性关节炎(RA)是一种影响关节、软骨和周围组织的慢性自身免疫疾病,不仅会引发关节疼痛、肿胀和僵硬,还会导致关节功能丧失[1] [2]。全球 0.5~1%人口深受 RA 困扰,其中女性患者约为男性患者人数的 3 倍,且患病率具有随年龄增长而升高的趋势[3]。久而不愈的 RA 不仅会对患者的关节造成损害,还会对包括心脏、肾脏、眼睛和皮肤等器官造成伤害,导致患者出现抑郁和焦虑等症状,大幅降低生活质量[4] [5]。目前有许多治疗 RA 的药物,如改善病情抗风湿药(DMARDs)、非甾体类抗炎药(NSAIDs)、糖皮质激素(GCs)和生物制剂等,但因其副作用大和成本高,导致它们的使用范围仍有很大限制[6] [7]。近年来的研究发现,安全经济的短链脂肪酸有望成为治疗 RA 的新手段。短链脂肪酸是由肠道微生物代谢产生的少于六个碳的脂肪酸,包括乙酸、丙酸和丁酸等。短链脂肪酸经由血液循环进入全身发挥广泛的生物学功能,例如调节免疫系统功能、维持肠道黏膜屏障、抑制肠道炎症等[8]。短链脂肪酸可以通过激活 GPR41 受体和抑制组蛋白乙酰化酶(HDAC)活性促进先天淋巴样细胞和 CD4⁺ T 细胞产生 IL-22 以维持肠道稳态[9]。也能促进肠道上皮细胞肠道粘蛋白 2(MUC2)表达,保护肠道粘膜屏障完整性[10]。短链脂肪酸还能抑制单核细胞中 TNF α 和一氧化氮合酶表达,或是抑制内皮细胞中促炎因子 IL-2 和 IL-3 产生,进而发挥抗炎作用[11]。本文综述短链脂肪酸与 RA 发生发展的相关性以及中药的调控,为发掘 RA 治疗策略提供新思路。

2. RA 状态下短链脂肪酸的变化

RA 的病程可分为未进展为关节炎和临床关节炎两个阶段,分别指抗瓜氨酸蛋白抗体(ACPA)呈阳性但无临床症状和出现明显临床症状阶段[12]。研究人员对未进展为关节炎受试者的血清短链脂肪酸水平进行检测,发现短链脂肪酸水平与关节炎进展呈负相关性,其中降低的短链脂肪酸主要为乙酸盐和丁酸盐[13]。在临床早期(患病小于一年),对患者的粪便进行检测发现仅有丙酸水平显著降低[14]。RA 发展至临床阶段,患者粪便中丁酸盐和丙酸盐显著减少,但乙酸盐没有显著差异[15]。但另一研究结果显示,与健康对照相比,RA 患者粪便中乙酸盐、丙酸盐、丁酸盐和戊酸盐均明显降低[16]。二者结果存在差异可能

是由于样本量较少和地域差异, 前者样本来自英国的 20 名健康志愿者和 19 名 RA 患者, 后者来自我国 10 名健康志愿者和 16 名 RA 患者。此外, 也有研究发现 RA 患者血清和粪便中丁酸水平均显著降低[17]。对佐剂诱导关节炎小鼠的粪便样品进行分析, 与关节发生病变前相比, 关节炎急性期和缓解期乙酸盐和丁酸盐明显降低, 而丙酸盐只在缓解期降低[12]。短链脂肪酸中乙酸、丙酸、丁酸等在 RA 疾病状态下不同程度降低, 提示补充短链脂肪酸可能是改善 RA 的有效途径。

3. 短链脂肪酸对 RA 的改善作用

3.1. 短链脂肪酸改善 RA

近几年研究表明, 短链脂肪酸的补充与 RA 疾病进程减缓有关。在胶原诱导关节炎模型小鼠饮用水中单独补充乙酸盐、丙酸盐或丁酸盐都能显著改善小鼠疾病症状, 三者联用治疗效果更佳[15] [18]。此外, 短链脂肪酸的不同给药方式会产生类似的改善效果, 如将丁酸盐酯化高直链淀粉喂食、均匀混合在饲料中喂食以及丁酸盐自由饮水, 都能明显减轻胶原诱导关节炎小鼠的疾病症状[14] [19]。

3.2. 短链脂肪酸改善 RA 的机制

短链脂肪酸可以通过多种途径改善 RA。在胶原诱导的小鼠关节炎中, 提前给予短链脂肪酸(乙酸盐、丙酸盐和丁酸盐联合使用), 可通过激活 GPR43 受体, 增加调节性 B 细胞数目, 降低过渡性 B 细胞和滤泡 B 细胞数目, 发挥抗关节炎作用[13]。

其次, 丙酸钠自由饮水能够通过促进脾脏 Treg 细胞扩增和 IL-10 产生, 在缓解胶原诱导关节炎小鼠的疾病症状中起关键作用[17]。另有研究表明, 丙酸钠通过促进 miR-140-5p 表达, 抑制成纤维细胞样滑膜细胞的存活素表达和细胞活力, 进而降低胶原诱导关节炎大鼠炎症反应[20]。

此外, 丁酸钠通过增加 5-羟基吲哚-3-乙酸(5-HIAA, 一种血清素衍生代谢物), 直接激活芳烃受体(AhR), 提高调节性 B 细胞抑制能力, 限制生发中心的 B 细胞(GC B 细胞)和浆母细胞的分化, 进而改善佐剂诱导小鼠关节炎[10]。丁酸钠也能通过抑制去乙酰化酶(HDACs)活性, 进而抑制恒定型自然杀伤 T 细胞(iNKT)细胞产生细胞因子, 减轻佐剂诱导的大鼠关节炎[21]。其他研究表明, 丁酸盐通过直接增强 Treg 细胞分化, 上调 IL-10 产生, 从而影响 Th17 细胞功能, 抑制炎症细胞因子表达, 缓解胶原诱导的小鼠关节炎[19]。丁酸盐膳食补充剂通过增强 Cxcr5、Bcl6 及 Tcf7 的启动子区域高度乙酰化, 促进滤泡调节性 T 细胞分化, 进而改善胶原诱导小鼠关节炎[22]。

4. 短链脂肪酸的应用

尽管目前没有临床证据显示直接补充短链脂肪酸可以改善 RA 患者疾病症状, 但仍有许多通过其他方式提高短链脂肪酸水平改善 RA 等疾病的尝试, 包括饮食干预、益生菌补充以及粪菌移植等。

有关饮食干预, 研究者评估了以高直链淀粉或传统小麦为基础的饮食是否可以增加人体内短链脂肪酸的浓度。经过 80 名受试者 4 周对照饮食, 高直链淀粉膳食组粪便中丁酸水平显著上升, 粪便短链脂肪酸产生菌高于原始水平。因此, RA 患者也许可以通过增加饮食中高直链淀粉比例, 从而延缓 RA 的疾病进程[23]。

短链脂肪酸的产生与肠道微生物息息相关, 通过补充益生菌增加短链脂肪酸似乎也是一条可行策略。已有研究将 46 名 RA 患者分为两组, 分别服用干酪乳杆菌补充剂和安慰剂, 八周后前者的多种炎症标志物显著降低, 而干酪乳杆菌已被证实其抗关节炎作用与短链脂肪酸水平上升有关, 提示益生菌或许可以作为 RA 患者的一种补充治疗方法[24] [25]。

此外, 粪菌移植(FMT)的关键点是将肠道菌群从健康供体移植到患病受体中, 从而调节肠道菌群稳

态, 恢复短链脂肪酸的产生[26]。粪菌移植目前已经成功治疗炎症性肠病和特发性血小板减少性紫癜等多种自身免疫疾病[27]。在一项关于粪菌移植治疗 RA 的研究中, 一名没有基础病但有 5 年 RA 病史的女性接受了一名 8 岁健康女孩的粪菌移植, 移植后该患者没有身体不适且关节炎症状明显改善[28]。虽然该研究没有测定粪菌移植后患者粪便短链脂肪酸水平变化, 但在另一项粪菌移植治疗自身免疫性疾病系统性红斑狼疮的研究中, 粪菌移植显著提高系统性红斑狼疮患者粪便中短链脂肪酸水平[29]。因此, 粪菌移植调控肠道菌群, 有可能恢复短链脂肪酸水平, 进而改善 RA。

尽管可以通过多种途径上调短链脂肪酸发挥抗关节炎作用, 但需要注意的是, 目前关于短链脂肪酸治疗 RA 的临床试验尚处于初步阶段, 需要更多研究确定其最佳治疗方案。

5. 中药调控短链脂肪酸呈现抗 RA 作用

随着 16S rRNA 基因测序技术的不断进步和代谢组学方法的普及应用, 近年来发现多种中药抗 RA 效应与调控短链脂肪酸相关。例如, 乌头汤治疗 RA 已有一千年的历史, 佐剂诱导关节炎大鼠灌胃给予乌头汤, 其肠道拟杆菌、普雷沃氏菌等丰富度上升, 乙酸和丁酸等短链脂肪酸浓度明显上调, 大鼠关节炎症状减轻[30]。枸杞多糖灌胃给药上调了关节炎大鼠短链脂肪酸中丙酸和丁酸含量, 进而改善胶原诱导大鼠关节炎[31]。祖师麻片在我国用于治疗 RA 也有数十年历史, 在佐剂诱导关节炎大鼠中灌胃给予祖师麻片研磨制成的混悬液, 关节炎大鼠粪便中的厚壁菌和拟杆菌数量上升, 丙酸盐和丁酸盐水平显著提高[32]。此外, 本室前期研究发现小檗碱灌胃给药显著下调胶原诱导关节炎大鼠肠道普雷沃氏菌的丰度, 增加丁酸盐浓度, 发挥抗关节炎效应[33]。灌胃给予苍术提取物改善大鼠胶原诱导关节炎时, 大鼠肠道中厚壁菌和拟杆菌丰度呈现回调趋势, 短链脂肪酸水平明显上调[34]。灌胃给予羟基积雪草苷通过扩大丁酸球菌和拉式丁酸球菌等细菌丰富度, 上调肠道丁酸水平, 诱导 Treg 细胞分化和 IL-10 表达, 发挥改善关节炎作用[35]。这些研究提示, 许多中药治疗 RA 可能依赖于肠道短链脂肪酸的产生。

6. 结论及展望

短链脂肪酸为人体自然代谢产物, 摄入后不会产生明显的毒副作用, 安全性较高, 具有防治 RA 的潜力和应用前景。此外, 其具有抑制炎症介质合成和炎症反应、减轻关节炎疼痛以及调节免疫系统功能的多样生物活性, 可全面增强 RA 治疗剂的效果[36]。但短链脂肪酸在治疗 RA 方面的应用仍存在局限性。与传统药物相比, 短链脂肪酸治疗时间较长, 需要持续的摄入和使用, 否则难以达到预期效果, 不适用于需要迅速缓解症状的患者; 通过饮食摄入的短链脂肪酸剂量难以达到治疗要求, 仅能作为改善 RA 的辅助措施; 目前尚缺乏大规模临床研究证明其疗效。如何使短链脂肪酸更加安全有效地用于 RA 的防治, 是目前和今后相当时期内面临的挑战。

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