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短链脂肪酸在肠道中生理作用的研究进展

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摘　要

短链脂肪酸是肠道菌群的主要代谢产物，其在人体的消化、免疫、内分泌、心血管、神经等多个系统中起着重要作用，因其产生及转运主要发生在肠道中，故其在肠道中的生理作用十分重要。故本文将就短链脂肪酸在肠道中的生理作用作一综述。

关键词

短链脂肪酸，肠道菌群，炎症，新生儿坏死性小肠结肠炎，肿瘤

Research Progress of Physiological Function of Short-Chain Fatty Acids in the Intestine

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Abstract

Short-chain fatty acids are the main metabolites of the intestinal flora. They play an important role in the digestion, immunity, endocrine, cardiovascular, and nervous systems of the human body. Because their production and transport mainly occur in the intestine, the physiological role in the intestine is very important. Therefore, this article will review the physiological role of short-chain fatty acids in the intestinal tract.

Keywords

Short-Chain Fatty Acids, Intestinal Flora, Inflammation, Neonatal Necrotizing Enterocolitis, Tumor

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1. 引言

短链脂肪酸是含 1~6 碳原子的有机酸，包含乙酸(C2)、丙酸(C3)、丁酸(C4)、异丁酸(C4)、戊酸(C5)和异戊酸(C5)等。人体中的短链脂肪酸以乙酸、丙酸、丁酸含量最多(多达 95%)，在结肠和粪便中的比例大约为 60:20:20，它们同时也是目前肠道短链脂肪酸研究的热点[1] [2] [3]。目前发现短链脂肪酸与人体多个系统疾病如消化系统、内分泌系统、免疫系统、心血管系统、神经系统等密切相关[4] [5] [6]。

2. 短链脂肪酸的产生

人体中的短链脂肪酸主要由肠道菌群产生，肠道菌群将肠道内不易消化的碳水化合物如低聚果糖、糖醇、抗性淀粉、菊粉和植物细胞壁中的多糖等[4] [7]水解成寡糖，然后水解成单糖，并在肠道的厌氧环境中发酵，通过 Embden-Meyerhof Parnas 途径(糖酵解，六碳糖)和磷酸戊糖途径(五碳糖)、Wood-Ljungdahl 途径等将单糖转化为磷酸烯醇丙酮酸(PEP)。随后，将 PEP 转化为短链脂肪酸[3] [8]。肠道中生产短链脂肪酸细菌主要有双歧杆菌、拟杆菌、厚壁菌等厌氧菌[8]。短链脂肪酸产生常受到宿主基因型、饮食、年龄、健康状况的影响[9] [10] [11] [12]，而在婴儿肠道短链脂肪酸的产生则常常与早产、分娩方式、喂养方式、早期广谱抗生素治疗等密切相关[11] [13] [14] [15]。短链脂肪酸在肠道中产生后大多数经肠道上皮吸收，部分与粪便混合排出[8]。有研究表明可以通过测定粪便中的短链脂肪酸水平来诊断鉴别肠道疾病，如乳糜泻、炎症性肠病、结直肠癌、新生儿坏死性小肠结肠炎[9]。

3. 短链脂肪酸的生理作用

短链脂肪酸在肠道中产生后在肠道能量代谢、抗炎、肠粘膜屏障保护、肠道动力等方面起着重要作用[16]。其生理作用主要通过抑制组蛋白去乙酰化酶(histone deacetylase, HDACs)或激活短链脂肪酸受体等信号通路实现[17] [18] [19]。短链脂肪酸可通过抑制组蛋白去乙酰化酶，激活组蛋白乙酰转移酶发挥进而发挥作用，丁酸盐是最重要的 HDAC 抑制剂。目前发现在肠道上皮细胞及免疫细胞上有三种 G 蛋白偶联受体高表达，分别为 GPR43 (游离脂肪酸受体 2，FFAR2)，GPR41 (游离脂肪酸受体 3，FFAR3)，及 GPR109A (羟基羧酸受体 2，HCAR2)，他们是目前发现最主要的短链脂肪酸受体[3] [16] [17] [20]。接下来，我们将具体探讨短链脂肪酸的生理作用。

3.1. 抗炎作用

短链脂肪酸通过调节免疫细胞趋化、活性氧(ROS)及细胞因子释放来发挥抗炎作用。研究表明，在结肠中短链脂肪酸，如丁酸、丙酸可诱导 cTreg 及 CD4+ T 细胞数目增多，但对结肠 Th1 或 Th17 细胞数无明显影响，并且进一步上调 Foxp3 和 IL-10 表达，而 TGF 水平保持不变[15] [17]。戊酸可以强烈上调对 Bregs 和 CD4+ T 细胞产生 IL-10，减少 IL-17A 作用，而且强烈抑制致病性 Th17 细胞表型增殖[21]。短链脂肪酸抑制 IL-1β 对未成熟肠细胞 HDAC3 和 HDAC5 基因的诱导，进一步抑制 IL-8 的分泌[22]。并且经丁酸处理的巨噬细胞分泌 IL-6、IL-8、TNFα 减少[8] [23]。在单核细胞中，丁酸盐和丙酸盐抑制了 LPS 诱导的 TNFα 和一氧化氮的表达[24]，并且可降低 NF-κB 的活性[25]。当短链脂肪酸作用于小鼠中性粒细胞上时，可通过激活 GPR43 促进 ROS 的释放[26]，而活性氧(ROS)是清除病原体的有效杀菌因子，以此起到抗炎作用。

研究表明，短链脂肪酸与肠道炎症性疾病如炎症性肠病、新生儿坏死性小肠结肠炎等疾病密切相关。在体外实验中，予以不同浓度丁酸对肠上皮细胞进行处理后发现。高浓度丁酸(8 mM，15 mM)会对肠上皮细胞造成严重损害，造成肠上皮细胞死亡增多，而低浓度丁酸(1 mM)处理被 H_2O_2 损伤后的肠上皮细胞后却发现活细胞增多，对受损细胞有保护作用[27]。与健康人相比，炎症性肠病患者粪便中乙酸盐、戊酸盐和总短链脂肪酸水平均显著下降，但丙酸盐则无显著差异[28] [29]。并且目前发现丁酸在治疗溃疡性结肠炎方面有着显著作用。有研究认为过量的短链脂肪酸聚集可诱发新生儿坏死性小肠结肠炎[30]，予以仔猪添加了从 NEC 患儿粪便中分离的大肠杆菌的配方奶喂养后，可诱导仔猪肠道短链脂肪酸尤其乙酸和丙酸增多，并进一步导致仔猪发生 NEC [31]。但是也有研究发现用丁酸处理 NEC 小鼠处理后小鼠肠道病理损伤减轻。

3.2. 抗菌作用

短链脂肪酸常通过破坏肠道渗透压和 pH 平衡、促进宿主抗菌肽的表达、影响致病菌养分吸收和能量产生起到抗菌作用保护肠道，并且由于其工作浓度远低于对宿主细胞的毒性阈值[32] [33]，故而较为安全，已被应用于食品中的抗菌剂[34] [35]。亦有研究将丁酸盐活体给药用于控制沙门氏菌感染[36]。短链脂肪酸可通过降低肠道 pH 值，直接促进共生菌的生长，另一方面抑制致病菌的生长[37]。

3.3. 调节肠道完整性

肠道完整性是维持肠道粘膜动态平衡的重要因素。肠道完整性破坏常常引起如炎症性肠病，乳糜泻、肠易激综合征、新生儿坏死性小肠结肠炎等肠道疾病，故维持肠道完整性至关重要[8] [38]。短链脂肪酸可能是促进肠道完整性的关键细菌产物。丁酸或丙酸都可以诱导人杯状细黏蛋白 2 (MUC2) mRNA 的表达和促进 MUC2 的分泌[39]，能有效将机体与肠道病原菌、食源性抗原隔离，增强肠道化学屏障。在体外实验中向 Caco-2 细胞添加丁酸可以加速依赖于 AMPK (AMP-激活蛋白激酶)激活的紧密连接蛋白 ZO-1、occludin 的组装，并且增强紧密连接蛋白 Claudin-7、claudin-1 表达，增强跨膜电阻(TER)，并且同时加强细胞紧密连接，降低肠道通透性，维持肠道完整性，增强上皮屏障功能[27] [40] [41]，保护肠道完整性。

3.4. 抗癌作用

目前研究表明短链脂肪酸与多种人类肿瘤，如结直肠癌、肝癌、膀胱癌、胃癌、乳腺癌、肺癌等密切相关[42] [43]。肿瘤细胞主要依靠葡萄糖而不是丁酸作为其主要能源物质。有研究发现，在结直肠癌患者粪便中的总短链脂肪酸水平明显低于健康人[9]。也有人发现与健康人相比，结肠癌患者的粪便乙酸含量较高，而丁酸含量较低[44] [45]。研究表明通过增加纤维素摄入增加短链脂肪酸产生，可降低癌症，特别是结直肠癌风险。短链脂肪酸抑制 HDAC 降低端粒酶活性，增加细胞周期抑制基因表达，降低肿瘤细胞的恶性增殖，诱导肿瘤细胞程序性死亡，起到抗癌作用[46]。丁酸可能通过直接诱导人结肠癌细胞 GPR 109a 表达直接增加肿瘤细胞凋亡[47]，有研究报道人结肠恶性腺腺癌组织中 FFAR2 表达的显着降低。该受体在 CRC 细胞中的重新表达和激活抑制增殖和诱导的细胞凋亡和细胞周期骤停，提供了 FFAR2 作为肿瘤抑制剂的证据[48]，也可能通过增加丁酸转运体如单羧酸转运蛋白(MCT)、钠偶联转运蛋白(SMCT) 1/2 等的表达而间接起作用[49]。同时 SMCT-1 在人结肠癌细胞中表达下调，进一步强调了 SMCT-1 在结肠癌中的作用。丁酸盐增强 p21wafl 和 bax 表达、上调 miR-203 表达，下调 miR-92a 表达，上调 Endocan 基因表达，抑制 SP1 (特异性蛋白质 1)的转移，促进结直肠癌肿瘤细胞凋亡[43]。

3.5. 调节肠道动力

短链脂肪酸在肠道中可起到降低或增强肠道动力的作用，并且受到其种类及浓度的影响。短链脂肪

酸可通过结合 FFAR2、FFAR3 促进 PYY (肠肽 YY)的分泌并降低肠道动力，增强饱腹感[16]。无菌动物的肠道动力降低，通过在结肠腔内输注 SCFA 可以部分恢复肠道动力，其中丁酸盐的效果最好[43]。丁酸盐可通过增加肠道胆碱神经元的比例来影响肠道神经元，进而提高肠道蠕动能力[50]，而丙酸盐能够降低肠道蠕动能力[51]。短链脂肪酸亦可作用于肠嗜铬细胞进而调节 5-HT 的合成和分泌，促进 5-HT 的释放，诱导肠道蠕动反射增强，加快肠道传输速度[52]。

3.6. 能量代谢

短链脂肪酸在肠道产生后可被结肠上皮吸收，为结肠细胞提供能量或进一步进入血液在调节机体脂肪酸，葡萄糖和胆固醇的代谢中发挥相关作用[9]。丁酸盐是结肠细胞的主要和首选代谢底物，提供了其增殖和分化所需的至少 60%~70%的能量需求[18]。短链脂肪酸可促进 B 细胞、T 细胞对葡萄糖的摄取，并提高 B 细胞的糖酵解和糖酵解能力，增加 B 细胞效应[9]。

4. 展望

短链脂肪酸是肠道菌群的重要代谢产物，具有十分丰富的生理作用，并且目前发现短链脂肪酸在多种疾病的发生、诊断及治疗中扮演者重要角色。但目前对于短链脂肪酸的研究依然存在许多空白，尤其缺乏真正的人体试验数据，使其应用多局限于实验室研究。希望随着医学研究的进一步深入，短链脂肪酸可以尽早应用于临床，为疾病的预防及诊治提供新的思路。

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