基础研究 论 著

嗜酸乳杆菌LA-GHB1756对阿司匹林引起的小鼠肠道炎症的影响

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[摘要] **目的** 探讨嗜酸乳杆菌LA-GHB1756对阿司匹林引起的小鼠肠道炎症的影响。**方法** 将40只6~8周龄BALB/c雄性小鼠分为空白对照组、阿司匹林组、LA低剂量组、LA高剂量组等4组。除空白对照组外，其余各组小鼠给予0.5 mg/(100 g·d)的阿司匹林溶液连续灌胃8周引起肠黏膜损伤；LA低剂量组及LA高剂量组在给予阿司匹林的同时给予LA-GHB1756菌液灌胃，LA低剂量组的剂量为2000 cfu/(100 g·d)，LA高剂量组的剂量为10 000 cfu/(100 g·d)，空白对照组及阿司匹林组给予同等体积的生理盐水灌胃。观察各组小鼠的体重、排便情况、毛发色泽等常规指标；测量小鼠结肠长度，观察结肠形态并行病理学观察；ELISA法检测肠组织髓过氧化物酶(MPO)含量、血清肿瘤坏死因子-α(TNF-α)及白细胞介素-6(IL-6)浓度；Western blotting检测肠组织核因子(NF)-κB p65的表达量。**结果** 一般情况观察显示，LA-GHB1756可改善阿司匹林引起的小鼠腹泻及毛发、精神状况改变。在第8周时，阿司匹林组小鼠体重为(21.6 ± 0.5) g，LA低剂量和高剂量组体重明显升高，分别为(22.8 ± 0.4) g和(23.1 ± 0.3) g，差异有统计学意义(P<0.05)。各组小鼠结肠形态及病理学检查结果显示，LA-GHB1756可缓解阿司匹林引起的小鼠肠黏膜水肿及炎症反应，阿司匹林组小鼠结肠长度为(5.80 ± 0.43) cm，LA低剂量和高剂量组小鼠结肠长度分别为(6.17 ± 0.15) cm和(6.50 ± 0.26) cm，均明显长于阿司匹林组，差异有统计学意义(P<0.05)。阿司匹林组小鼠肠组织MPO含量为(95.90 ± 11.34) pg/mg，LA低剂量组及LA高剂量组分别为(76.03 ± 8.72) pg/mg和(51.40 ± 9.12) pg/mg，均低于阿司匹林组，差异有统计学意义(P<0.05)。阿司匹林组小鼠血清TNF-α和IL-6浓度分别为(238.75 ± 17.80) pg/mg和(292.00 ± 15.51) pg/mg，LA低剂量组分别为(207.75 ± 12.04) pg/mg和(250.25 ± 11.50) pg/mg，LA高剂量组分别为(80.25 ± 10.24) pg/mg和(108.50 ± 13.38) pg/mg，均低于阿司匹林组，差异有统计学意义(P<0.05)。阿司匹林组肠组织NF-κB p65表达量是对照组的5.07倍，LA低剂量组及LA高剂量组肠组织NF-κB p65的表达量明显降低，分别降至阿司匹林组的83.74%和82.95%，差异有统计学意义(P<0.05)。**结论** 嗜酸乳杆菌LA-GHB1756可缓解由阿司匹林引起的小鼠肠道炎症，该作用可能与其抑制肠组织MPO、NF-κB p65的表达相关。

[关键词] 嗜酸乳杆菌；肠炎；非甾体类抗炎药；阿司匹林

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Effects of *Lactobacillus acidophilus* LA-GHB1756 on alleviating inflammatory bowel disease in mice caused by aspirin

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[**Abstract**] **Objective** Use aspirin to induce mouse inflammatory bowel disease model, and investigate whether *Lactobacillus acidophilus* LA-GHB1756 can alleviate this type of enteritis injury. **Methods** A total of 40 male BALB/c mice (6-8 weeks old) was randomized into four groups: control group, aspirin group, LA low-dose group, and LA high-dose group. Except for the control group, the remaining groups were given 0.5 mg/(100 g·d) aspirin solution by gavage for eight weeks to induce inflammatory bowel disease. The LA low-dose and high-dose groups received an additional 2000 cfu/(100 g·d) and 10 000 cfu/(100 g·d) of LA-GHB1756 bacterial liquid, respectively. Accordingly, the control and aspirin groups received the same volume of normal saline through gavage. We then monitored the mouse's body weight, defecation status, hair color, and other conventional indicators, colon macroscopic and pathological staining. We used ELISA to detect intestinal tissue MPO content, serum tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) expression. We employed Western blotting to detect intestinal tissue NF-κB p65 expression levels. **Results** The general observation of mice in each group showed that LA-GHB1756 could improve the diarrhea, hair, and mental status of aspirin-induced mice. In the 8th week, the body weight of mice in the aspirin group was (21.6 ± 0.5) g. The body weight was statistically significantly improved in the LA low-dose and high-dose groups, which were (22.8 ± 0.4) g and (23.1 ± 0.3) g, respectively (P<0.05). The colon morphology and pathological results showed that LA-GHB1756 could alleviate intestinal mucosal edema and inflammation caused by aspirin in mice. The colon length of mice in the aspirin group was (5.80 ± 0.43) cm, and the colon length of low-dose and high-dose LA groups was (6.17 ± 0.15) cm and (6.50 ± 0.26) cm, respectively. This length improvement was statistically significant (P<0.05). The results of MPO content in intestinal tissues showed that aspirin group was (95.90 ± 11.34) pg/mg, the MPO content in LA low-dose group and LA high-dose group were (76.03 ± 8.72) pg/mg and (51.40 ± 9.12) pg/mg respectively, which was significantly decreased compared with aspirin group, the difference was statistically significant (P<0.05). The results of serum TNF-α and IL-6 expression showed that the concentrations of TNF-α and IL-6 in aspirin group were (238.75 ± 17.80) pg/mg and (292.00 ± 15.51) pg/mg, respectively, while those in LA low-dose group were (207.75 ± 12.04) pg/mg and (250.25 ± 11.50) pg/mg, respectively, LA high-dose group were (80.25 ± 10.24) pg/mg and (108.50 ± 13.38) pg/mg, respectively. Compared with aspirin group, TNF-α and IL-6 contents in LA low-dose group and LA high-dose group were statistically significantly decreased (P<0.05). The expression of NF-κB p65 was increased up to 5.07 fold in aspirin group when compared with control group. This level was statistically significantly decreased to 83.74% and 82.95% in LA low-dose and high-dose groups, respectively (P<0.05). **Conclusion** LA-GHB1756 can relieve intestinal inflammation in mice caused by aspirin, this effect may be related to the inhibition of MPO and NF-κB p65 expression in intestinal tissue.

[**Key words**] *Lactobacillus acidophilus*; enteritis; non-steroidal anti-inflammatory drugs; aspirin

非甾体抗炎药(non-steroidal anti-inflammatory drugs，NSAIDs)具有解热、镇痛、抗炎等作用，在临床上被广泛用于心脑血管疾病、风湿免疫性疾病、骨关节疼痛、发热等的治疗[1-2]。但大量研究表明，长期应用NSAIDs会导致肠道黏膜损伤[3]，其机制是NSAIDs抑制环氧合酶(cyclooxygenase，COXs)，进而阻断前列腺素(prostaglandin，PGs)这类具有胃肠道黏膜保护作用的局部激素的生成。长期的肠道黏膜损伤可导致小肠、结肠部位出现溃疡、出血、穿孔及慢性缺铁性贫血等并发症。有研究表明，服用NSAIDs的人群中50%以上出现不同程度的肠黏膜损伤，可导致溃疡(发生率为4.5%)、溃疡性出血(发生率为1%)等[4-7]。目前尚无针对这类不良反应的有效预防及处理措施。

嗜酸乳杆菌(*Lactobacillus acidophilus*，LA)属于乳杆菌属，为人体肠道的一种益生菌，可定植于肠道细胞表面，维持肠道菌群的微生态平衡，参与营养物质的消化、吸收及代谢等过程[8-10]。LA具有改善肠道功能、抑制病原微生物入侵、免疫增强、抗肿瘤等作用，已被广泛应用于肠道微生物感染、肠易激综合征(irritable bowel syndrome，IBS)及溃疡性肠病等疾病的预防和治疗[11-14]。NSAIDs在损伤肠道黏膜的同时，也能影响肠道菌群构成，导致炎症应答失调，从而增加病原微生物感染的风险，加

重IBS症状，诱发溃疡性肠病[15]。本研究采用嗜酸乳杆菌LA-GHB1756干预长期大量应用NSAIDs诱导的小鼠肠炎，探讨LA-GHB1756对肠黏膜的保护作用，以期为LA-GHB1756的应用提供依据。

1 材料与方法

1.1 材料 嗜酸乳杆菌LA-GHB1756由本实验室保存。40只6~8周龄BALB/c雄性小鼠购自本校动物实验中心，体重18~22 g。阿司匹林(货号：A2093，美国Sigma公司)；髓过氧化物酶(MPO)检测试剂盒(货号：A0441-1-1，南京建成生物工程研究所)。肿瘤坏死因子(tumor necrosis factor，TNF)-α检测试剂盒(货号：PT512)、白细胞介素-6(interleukin-6，IL-6)检测试剂盒(货号：PI326)、细胞裂解液(货号：P0013)、细胞核蛋白与细胞质蛋白抽提试剂盒(货号：P0027)、二喹啉甲酸(BCA)蛋白浓度测定试剂盒(货号：P0012S)、增殖细胞核抗原(proliferating cell nuclear antigen，PCNA)一抗(货号：AF0261)、核转录因子-κB(nuclear transcription factor-κB，NF-κB p65)一抗(货号：AF1234)均购自上海碧云天生物技术有限公司。其他试剂均为国产分析纯。

1.2 实验方法

1.2.1 动物分组及给药 将小鼠适应性喂养1周，随机分为4组，分别为空白对照组、阿司匹林组、LA低剂量组、LA高剂量组，每组10只。除空白对照组外，其余各组小鼠给予0.5 mg/(100 g·d)的阿司匹林溶液连续灌胃8周引起肠黏膜损伤；LA低剂量组及LA高剂量组在给予阿司匹林的同时给予LA-GHB1756菌液灌胃，LA低剂量组的剂量为2000菌落形成单位(cfu)/(100 g·d)，LA高剂量组的剂量为10 000 cfu/(100 g·d)，给药时间与阿司匹林相同，空白对照组及阿司匹林组给予同等体积的生理盐水灌胃。8周后取血并处死小鼠，摘取小鼠结肠，生理盐水冲洗，横切一半放入4%甲醛溶液浸泡，其余组织存于液氮中冷冻保存备用。实验过程符合国家和单位有关实验动物的管理和使用规定。

1.2.2 一般情况观察 每周观察并记录小鼠体重、排便情况及毛发色泽等一般情况。

1.2.3 结肠形态及病理学观察 取小鼠结肠，格尺拍照，记录长度。截取1 cm长的组织，冲洗内壁，4%甲醛溶液固定，脱水，石蜡包埋，切片，HE染色，放置二甲苯中浸泡3次，每次10 min脱蜡，将切片分别在无水乙醇、90%乙醇、80%乙醇中各浸泡2 min，纯净水冲洗2 min。用苏木精染色3 min，浸泡于0.2%的盐酸乙醇中分化5 s，纯净水冲洗，伊红染色2 min。切片分别在80%乙醇、90%乙醇、无水乙醇中各浸泡5 min，二甲苯浸泡2次，每次10 min。切片滴加中性树脂封片，盖上盖玻片，晾干后于400倍显微镜下观察并拍照。

1.2.4 ELISA法检测肠组织MPO含量 精密称定100 mg肠组织样品，液氮冷冻研磨，10 000 r/min离心10 min，加入细胞裂解液提取总蛋白，BCA法测定蛋白浓度。按MPO试剂盒说明书操作，每50 mg组织加入960 μl缓冲液混匀制备成5%的组织匀浆液。吸取900 μl组织匀浆液，加100 μl反应试剂一，于37 ℃反应15 min得到样品，吸取200 μl样品加200 μl反应试剂四，加3 ml显色剂，于37 ℃反应30 min，加50 μl试剂七60 ℃反应10 min，终止反应，于460 nm波长处测定光密度(OD)值，以纯净水为空白对照。按以下公式计算MPO含量：MPO含量=(测量OD值－空白OD值)/11.3×取样量。

1.2.5 ELISA法检测血清TNF-α及IL-6浓度 将全血室温放置2 h，于4 ℃下2000 r/min离心10 min得到血清，吸取100 μl血清加入待测孔内，用封板膜封住反应孔，室温孵育2 h，洗板5次，最后一次置于厚吸水纸拍干，每孔加入100 μl生物素化抗体，封板室温孵育1 h，洗板5次，吸水纸拍干。每孔加入100 μl辣根过氧化物酶标记的链霉亲和素，封板室温孵育20 min，洗板5次，吸水纸拍干。每孔加入100 μl的3,3',5,5'-四甲基联苯胺(3,3',5,5'-tetramethylbenzidine，TMB)显色剂，封板室温孵育20 min，每孔加入50 μl终止液，于460 nm波长处测定OD值。以纯净水为空白对照，以标准品制作标准曲线，根据标准曲线计算TNF-α及IL-6浓度。

1.2.6 Western blotting检测肠组织NF-κB p65表达量 精密称定500 mg肠组织样品，剪成细小的碎片，按20:1的比例混合抽提试剂A和试剂B，得到组织匀浆液，将500 mg肠组织加入1667 μl组织匀浆液中，冰浴15 min，于4 ℃下1500 r/min离心5 min，吸取上清液，沉淀加1 ml含苯甲基磺酰氟(phenylmethanesulfonyl fluoride，PMSF)的抽提试剂A，剧烈震荡5 s，冰浴15 min，加入50 μl抽提试剂B，剧烈震荡5 s，冰浴1 min，再次剧烈震荡5 s，于4 ℃下15 000 r/min离心5 min，吸去上清液。将沉淀加入250 μl含PMSF的核蛋白抽提试剂，剧烈震荡30 s，放置冰浴，每隔2 min剧烈震荡30 s，共30 min，于4 ℃下15 000 r/min离心10 min，吸取上清液即为细胞核蛋白。将细胞核蛋白加入SDS-PAGE蛋白上样缓冲液，100 ℃水浴加热5 min变性。将10 μl样品加到胶孔内，浓缩胶电压100 V，样品进入分离胶后，设置电压150 V进至溴酚蓝到底部。切除浓缩胶，分离胶转膜，400 mA恒流转膜40 min。使用Western快速封闭液浸泡膜封闭

30 min，4 ℃一抗孵育过夜，洗涤3次，每次5 min，二抗室温孵育1 h，洗涤3次，每次5 min。ECL法显色，以PCNA为内参计算蛋白的相对表达量。

1.3 统计学处理 采用SPSS 17.0软件进行统计分析。实验数据以$\bar{x}\pm s$表示，组间比较采用单因素方差分析，进一步两两比较方差齐时采用LSD-t检验，方差不齐时采用Tamhane's T_2法。P<0.05为差异有统计学意义。

2 结 果

2.1 各组小鼠一般情况比较 对照组小鼠体重平稳增长，饮食情况良好，毛发较润泽，大便呈颗粒状，精神状况良好，第8周的体重为(24.1 ± 0.6) g。阿司匹林组小鼠在第6~8周出现腹泻，毛发稀疏无光泽，黏液样便，精神萎靡，活动减少，第8周的体重为(21.6 ± 0.5) g，明显低于对照组，差异有统计学意义(P<0.05)。LA低剂量组小鼠饮食情况有所改善，大便逐渐成形，精神状况有所改善，第8周的体重为(22.8 ± 0.4) g，高于阿司匹林组，差异有统计学意义(P<0.05)。LA高剂量组小鼠饮食情况明显改善，大便逐渐成形，精神状况有所改善，第8周体重为(23.1 ± 0.3) g，明显高于阿司匹林组，差异有统计学意义(P<0.05，图1)。

2.2 各组小鼠结肠形态及病理学检查结果 对照组小鼠结肠形态正常，长度(7.87 ± 0.06) cm，其余组小鼠结肠明显缩短变粗，且伴有炎症、充血现象(图2A)。阿司匹林组小鼠结肠长度为(5.80 ± 0.43) cm，小于对照组，差异有统计学意义(P<0.05)；LA低剂量组小鼠结肠长度为(6.17 ± 0.15) cm，与阿司匹林组比较无明显差异(P>0.05)；LA高剂量组小鼠结肠长度为(6.50 ± 0.26) cm，明显长于阿司匹林组，差异有统计学意义(P<0.05，图2B)。小鼠结肠HE染色结果显示，在第8周时对照组小鼠肠黏膜结构完整；阿司匹林组小鼠肠黏膜明显水肿、炎症，伴有大量空泡；LA干预组肠黏膜水肿程度、炎症程度明显减轻，空泡减少，且随着给药剂量的加大，炎症的缓解程度更加明显(图2C)。

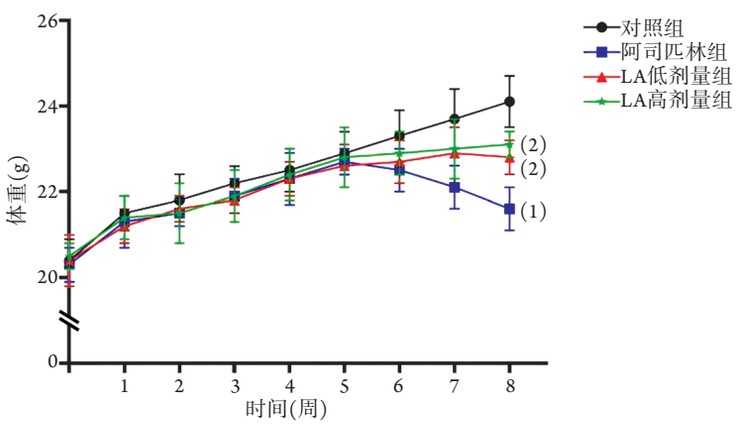

图1 各组小鼠体重变化情况

Fig.1 Weight change of mice in each group

与对照组比较，(1)P<0.05；与阿司匹林组比较，(2)P<0.05

2.3 各组小鼠肠组织MPO含量比较 对照组小鼠肠组织MPO含量为(15.01 ± 2.57) pg/mg，阿司匹林组为(95.90 ± 11.34) pg/mg，阿司匹林组高于对照组，差异有统计学意义(P<0.05)。LA低剂量组及LA高剂量组小鼠肠组织的MPO含量分别为(76.03 ± 8.72) pg/mg和(51.40 ± 9.12) pg/mg，均低于阿司匹林组，差异有统计学意义(P<0.05，图3A)。

2.4 各组小鼠血清TNF-α及IL-6浓度比较 对照组小鼠血清TNF-α、IL-6浓度分别为(43.5 ± 6.56) pg/mg、(66.25 ± 9.81) pg/mg，阿司匹林组分别为(238.75 ± 17.80) pg/mg、(292.00 ± 15.51) pg/mg，均高于对照组，差异有统计学意义(P<0.05)。LA低剂量组TNF-α和IL-6浓度分别为(207.75 ± 12.04) pg/mg、(250.25 ± 11.50) pg/mg，LA高剂量组分别为(80.25 ± 10.24) pg/mg、(108.50 ± 13.38) pg/mg，均低于阿司匹林组，差异有统计学意义(P<0.05，图3B)。

2.5 各组小鼠肠组织NF-κB p65表达量比较 与对照组(1.00)比较，阿司匹林组小鼠肠组织NF-κB p65的相对表达量明显增高，是对照组的5.07倍，差异有统计学意义(P<0.05)。使用LA干预后，LA低剂量组及LA高剂量组中NF-κB p65的表达量分别降低至阿司匹林组的83.74%和82.95%，与阿司匹林组比较，差异有统计学意义(P<0.05，图4)。

3 讨 论

长期服用NSAIDs可引起肠道疾病如肠炎、肠

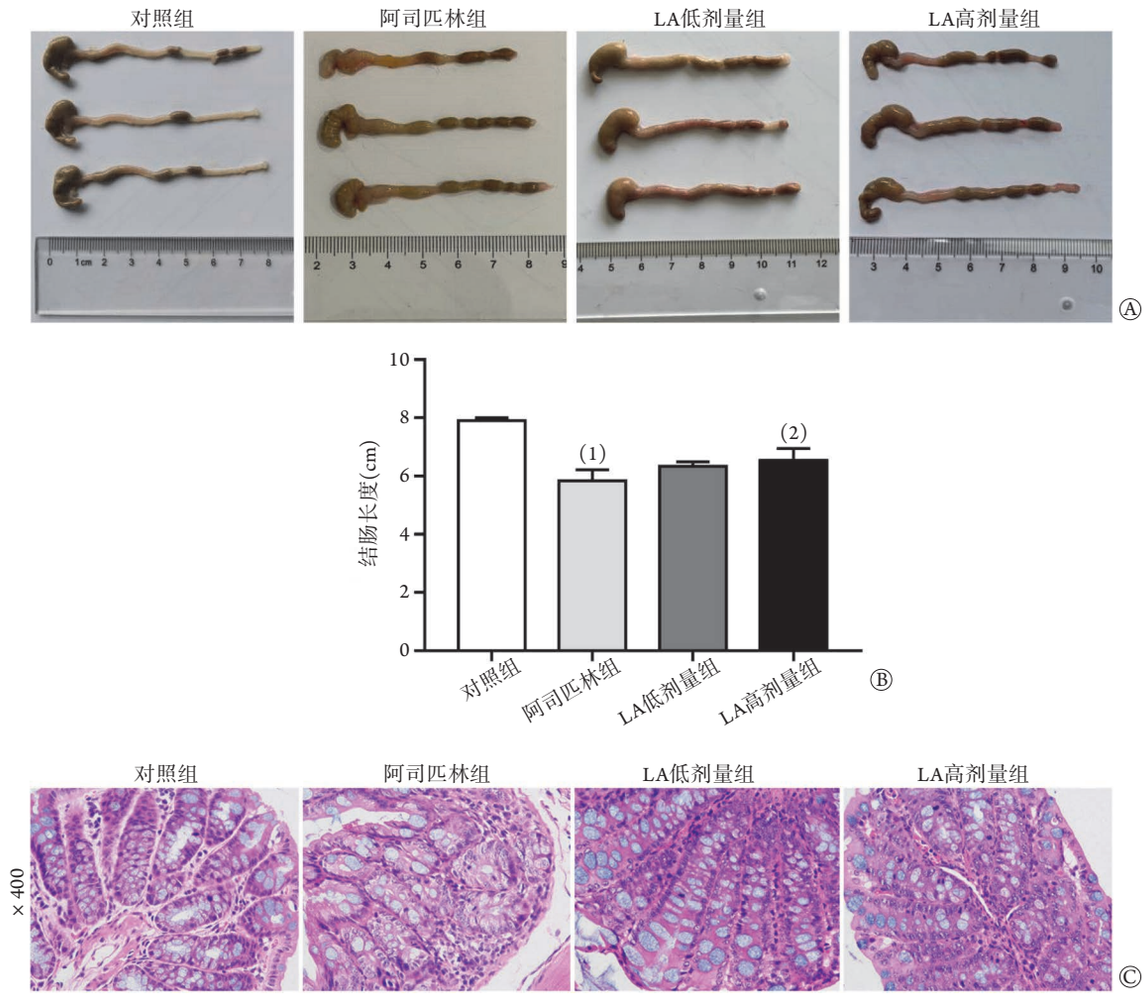

图2 各组小鼠结肠形态(A)、长度(B)及病理学变化(C)

Fig.2 Colon macroscopic (A), length (B) and pathological changes (C) of mice in each group

与对照组比较，(1)$P<0.05$；与阿司匹林组比较，(2)$P<0.05$

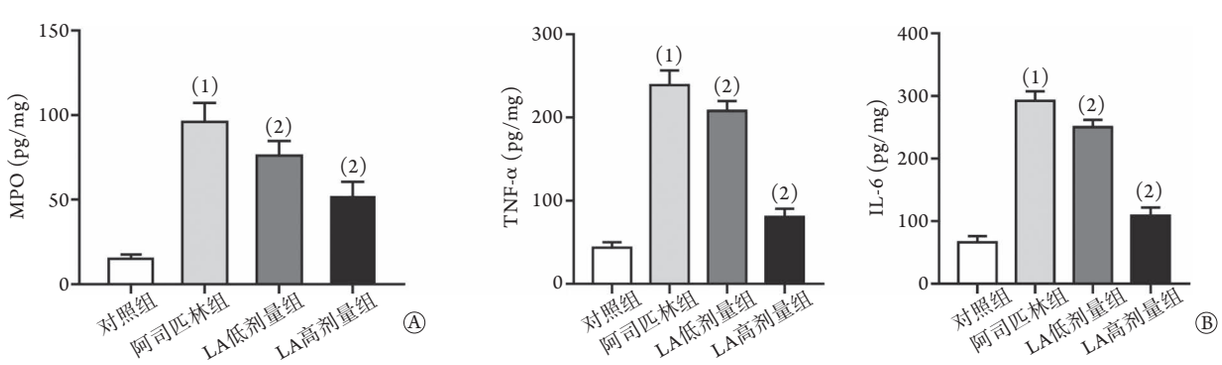

图3 各组小鼠肠组织MPO含量(A)及血清TNF-α和IL-6浓度(B)比较

Fig.3 Comparison of MPO content in intestinal tissue (A) and TNF-α and IL-6 expression in serum (B) of mice in each group

与对照组比较，(1)$P<0.05$；与阿司匹林组比较，(2)$P<0.05$

黏膜溃疡等，并增加了贫血的发生风险。NSAIDs可与COXs的活性中心结合，抑制COXs的活性，并阻止PGs的生成，生理浓度的PGs对于细胞增殖、血管新生及黏膜修复具有重要作用，因此NSAIDs可能通过阻止PGs的生成而破坏肠道黏膜。本研究使用阿司匹林灌胃小鼠8周建立NSAIDs诱导肠炎模型，结果发现模型小鼠出现体重减轻、黏液样便等情况；结肠长度变短、发生炎症并充血，病理学检查结果显示结肠出现黏膜水肿、炎症现象；肠组织中MPO含量升高；血清TNF-α及IL-6水平升高；肠组织NF-κB p65表达升高。该结果提示阿司匹林可引起肠炎，与文献报道NSAIDs可引起下消化道炎

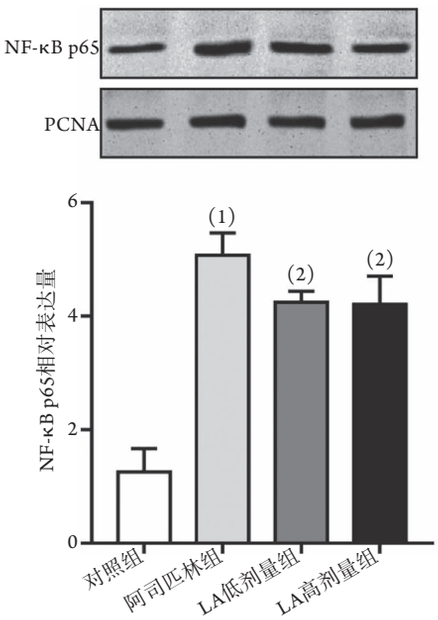

图4 各组小鼠肠组织NF-κB p65表达量比较

Fig.4 Comparison of NF-κB expression in intestinal tissues

与对照组比较，(1)P<0.05；与阿司匹林组比较，(2)P<0.05

症一致[16]。

目前尚无有效手段可缓解这种类型的炎症。有研究表明，益生菌可修复溃疡性结肠炎患者的肠黏膜屏障[17-18]，并可有效降低其血清TNF-α、γ干扰素(interferon-γ，IFN-γ)及IL-6水平[19-21]；通过抑制烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate，NADPH)氧化酶的表达，减轻肠组织的氧化应激损伤[22]；激活辅助性T细胞17(Th17)等免疫细胞，促进免疫球蛋白A(immunoglobulin A，IgA)的产生；使IL-22、α防御素等细胞因子表达升高，抵御病原微生物的入侵；刺激肠道上皮细胞分泌黏蛋白(MUC)，使肠上皮细胞与肠道内容物之间形成屏障，促进肠黏膜的修复[23-26]。嗜酸乳杆菌LA作为人体重要的一类益生菌，在进入人体肠道后可产生大量的乳酸，降低肠道内pH值，有效阻止病原菌的增殖，且LA可黏附于肠道上皮细胞，阻止病原菌对肠上皮细胞的入侵，竞争病原菌的生长空间，有效调节肠道微生态系统的平衡[27-29]。本实验使用阿司匹林灌胃导致小鼠肠炎，并采用LA-GHB1756进行干预，结果发现，小鼠饮食情况、精神状况、体重降低、结肠缩短等均有不同程度的改善，病理学检查结果表明，LA-GHB1756可有效缓解肠道炎症。

MPO是一种血红素过氧化物酶，当发生炎症时，MPO能生成过量的强氧化剂次氯酸(HOCl)，其生成量超过机体的抗氧化能力后，则会导致氧化应激损伤[30]。研究表明，结肠炎患者及葡聚糖硫酸钠(DSS)诱导的肠炎动物模型均可导致MPO明显升高[31-32]。乳酸菌可明显降低MPO水平，缓解由MPO引起的氧化应激损伤[33]。NF-κB是在炎症刺激下发生核移位的转录因子，被激活后引起细胞核NF-κB p65的表达升高，诱导TNF-α、IL-6及IL-1β等炎性因子的大量表达，这些细胞因子又会促进NF-κB的核移位，形成正反馈通路；乳酸菌可通过下调NF-κB p65抑制炎性因子的表达，起到减轻肠道炎症的作用[34]。本研究结果表明，LA-GHB1756可降低由阿司匹林引起的肠组织MPO高表达，缓解由炎症引起的氧化应激损伤，同时降低血清TNF-α、IL-6的表达，减少炎性因子的分泌，降低肠组织NF-κB p65的表达，减轻肠道炎症反应，且呈一定的剂量依赖性。

LA是具有多种功能的益生菌。赵琳等[35]的研究表明，LA85能够通过提高小鼠淋巴细胞增殖分化能力、巨噬细胞吞噬能力及NK细胞的活性而提升小鼠的免疫功能；孔庆敏等[36]报道LA28可缓解由丙戊酸引起的子代大鼠外周炎症及肝损伤。本研究结果显示LA-GHB1756可缓解阿司匹林所致的小鼠肠炎，其机制可能与抑制肠组织MPO、NF-κB p65的表达相关，然而LA-GHB1756作用于肠上皮细胞的具体靶点尚不明确，其对肠道菌群的调节作用及肠免疫细胞的影响也有待进一步研究。

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