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小檗碱对肝硬化大鼠肠粘膜及肝脏保护作用的研究*

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摘要 目的:观察小檗碱对肝硬化大鼠肝脏和肠粘膜屏障的保护作用。**方法:**24只Wistar大鼠随机分为小檗碱干预组、肝硬化造模组、正常对照组。小檗碱干预组和肝硬化造模组予以四氯化碳联合酒精进行肝硬化造模。小檗碱干预组造模同时予以小檗碱灌胃,观察大鼠的一般情况、进食量、体重,第8周末处死全部大鼠,检测血清丙氨酸氨基转移酶(ALT)、天冬氨酸氨基转移酶(AST)、内毒素(ET)水平,并取肝组织和回肠进行病理检查。**结果:**肝硬化造模组大鼠和小檗碱干预组大鼠进食量及体重有下降,肝硬化造模组下降大于小檗碱干预组,差别有统计学意义 $P<0.01$ 。小檗碱干预组ALT,AST,ET水平均低于肝硬化造模组,差别有统计学意义 $P<0.01$ 。肝脏病理观察:小檗碱干预组肝小叶结构破坏,假小叶形成,汇管区及小叶内炎症细胞浸润方面明显轻于肝硬化造模组。回盲部病理观察:小檗碱干预组的小肠绒毛缩短、变形、数量减少,上皮细胞排列紊乱方面轻于肝硬化造模组。**结论:**小檗碱对四氯化碳联合酒精所致的肝硬化大鼠有减轻肝损伤和保护肠粘膜的作用。

关键词:小檗碱;肝硬化;肠粘膜;肝脏保护

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Protective Effects of Berberine on the Intestinal Mucosal Barrier and Liver Function in Rats with Liver Cirrhosis*

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ABSTRACT Objective: To explore the protective effect of Berberine on intestinal mucosal barrier and liver function in rats with liver cirrhosis. **Methods:** A total of 24 male Wistar rats were randomly (random number) divided into 3 groups: model group (n=8), berberine group (n=8) and control group (n=8). The rats in the control group were injected intraperitoneally with saline daily. The rats in the model group were injected intraperitoneally with carbon tetrachloride to establish the model of liver cirrhosis. The rats in the berberine group were given berberine respectively based on the model group. The general condition of rats was observed. The body weight and diet intake of the rats in each group were recorded. All rats were sacrificed after 8 weeks and the plasma levels of endotoxin (ET), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured. The pathological changes of liver and ileum tissue were observed by HE staining. **Results:** The rats in the model group and the berberine group had decreased food intake and body weight, and the decline in the model group was more significant than that in the berberine group ($P<0.01$). Compared with the model group, the serum levels of ALT, AST and LPS in the berberine group were significantly decreased ($P<0.01$). The pathological results showed that the structure of small intestinal villi, mucosal space and other structures in the model group were severely damaged, while the structures of villi and mucosal space were improved in the berberine group. Besides, model group presented disordered structure of liver, formation of pseudobulb and inflammatory cell infiltration in hepatic lobule while the structure of liver was improved in the berberine group. **Conclusions:** Berberine plays a protective role on the intestinal barrier and liver function in rats with liver cirrhosis induced by carbon tetrachloride and alcohol.

Key words: Berberine; Liver cirrhosis; Intestinal mucosa; Liver protection

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前言

肝硬化是慢性肝病的晚期状态,病理表现为肝脏的纤维化改变,以及假小叶和再生结节的形成。肝硬化除了肝脏遭受严

重损伤外,还存在肠粘膜屏障的损害和功能紊乱,导致肠道菌群移位、菌血症和内毒素血症^[1,2],极易引起感染导致严重并发症,因此在肝硬化病人中保护肠粘膜屏障,积极预防肠道菌群移位有助于预防感染等并发症的发生。小檗碱(Berberine, BBR)

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也称黄连素,最初应用于治疗肠道细菌感染,现代研究认为小檗碱不仅有抑菌作用,对肠粘膜屏障也有保护作用^[3]。本文对四氯化碳联合酒精所致的肝硬化大鼠予以小檗碱灌胃治疗,观察大鼠的体重,进食量的变化,并比较大鼠回肠粘膜的病理和肝脏病理的变化,探讨小檗碱对肝硬化大鼠肠粘膜及肝脏是否有保护作用,对肝硬化的治疗提供思路和理论基础。

1 材料与方法

1.1 材料

Wistar 大鼠购于复旦大学动物房;四氯化碳购自上海阿拉丁生化科技股份有限公司;食用乙醇购自四川绵竹剑南春酒厂有限公司;小檗碱购自美国 sigma 公司;4%多聚甲醛购自赛鸽(上海)生物科技有限公司;东芝全自动生化分析仪(TBA-120FR)购自日本东芝公司;内毒素定量试剂盒购自上海联迈生物工程有限公司;病理切片机购自上海徕卡仪器有限公司;正置光学显微镜购自日本 Olympus 公司;百特酶标仪(Elx800)购自美国 BioTek 公司。

1.2 造模方法及药物

成年健康雄性 Wistar 大鼠 24 只,体重(300 ± 10)g,随机分为 3 组:肝硬化造模组、小檗碱干预组、正常对照组,每组 8 个大鼠。小檗碱干预组和肝硬化造模组予以肝硬化造模。采用四氯化碳联合乙醇法进行肝硬化造模^[4]:按照 0.5 mL/100 g 剂量每周 2 次予以腹腔内注射 40%四氯化碳中性菜籽油溶液,连续 4 周;同时以 10%乙醇溶液为其唯一饮用水。第 5 周起改用 50%四氯化碳中性菜籽油溶液,以 0.5 mL/100 g 剂量每周 2 次予以腹腔内注射,连续 4 周,同时改 30%乙醇溶液为其唯一饮用水。正常对照组予以生理盐水腹腔内注射,饮用水为普通水。小檗碱干预组在造模同时予以小檗碱灌胃,剂量为 200 mg/kg,每天灌胃一次,肝硬化造模组大鼠予以生理盐水灌胃。第 8 周末经腹腔注射 2%戊巴比妥钠后处死全部大鼠。

1.3 观察指标、标本采集与测定方法

造模后每周末分别记录三组大鼠体重、进食量的变化,第

8 周末对各组大鼠麻醉后经下腔静脉采血 10 mL,采血完毕立即使用颈椎脱臼法处死实验大鼠,取肝脏组织及距离回盲部 2 cm 取出部分回肠组织,使用生理盐水冲洗后予 4%多聚甲醛的固定,苏木精-伊红染色法染色后光镜下观察病理变化。血清谷丙转氨酶、谷草转氨酶的测定采用免疫浊度法,由东芝全自动生化分析仪检测。血清内毒素测定采用偶氮显色基法^[5]:取 100 μL 细菌内毒素检查用水及大鼠血清 40 μL 加入无内毒素的试管,再加入 100 μL 鲎试剂溶液,混匀,37℃温育 10 分钟。温育结束后加入 100 μL 显色液,混匀后再次 37℃温育 6 分钟。温育结束后加入 500 μL 1 号偶氮化试剂溶液,混匀后加入 500 μL 2 号偶氮化试剂溶液,再次混匀后加入 500 μL 3 号偶氮化试剂溶液。混匀后室温下静置 5 分钟,全自动酶标仪于 545 nm 波长处读取吸光度值。

1.4 统计学方法

采用 SPSS 19.0 统计软件分析,数据用均数 ± 标准差($\bar{x} \pm s$)表示,所有多组间比较采用单因素方差(AVONA)分析,组间比较采用 LSD 法检验样本间两两差异,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般情况观察

三组大鼠均无死亡,正常组大鼠一般状态良好,皮毛色泽良好,反应迅速,行动敏捷;肝硬化造模组大鼠渐出现皮毛色泽发暗无光泽,体型消瘦,反应变慢。小檗碱干预组大鼠皮毛色泽及反应情况介于两组之间。

2.2 三组大鼠每周进食量比较

观察期间,肝硬化造模组大鼠和小檗碱干预组大鼠进食量下降,肝硬化造模组大鼠下降大于小檗碱干预组,第四周末起两组进食量差异具有统计学意义 $P < 0.01$ 。正常对照组和肝硬化造模组比较,第三周末起肝硬化造模组进食量下降明显,差异有统计学意义 $P < 0.01$ 。见表 1。

表 1 三组大鼠每周进食量改变的比较(单位:g, $\bar{x} \pm s$)

Table 1 Comparison of weekly food intake changes among three groups of rats(g, $\bar{x} \pm s$)

	BBR group (n=8)	Model group (n=8)	Control group (n=8)
First week	461.62 ± 7.23	460.50 ± 6.65	464.5 ± 6.70
Second week	457.62 ± 7.21	455.25 ± 7.78	463.62 ± 5.97
Third week	447.12 ± 8.13	442.50 ± 9.25 ^b	464.37 ± 6.78 ^b
Fourth week	439.75 ± 9.73 ^a	423.85 ± 14.93 ^{ab}	465.50 ± 6.04 ^b
Fifth week	426.62 ± 14.13 ^a	408.12 ± 16.05 ^{ab}	467.37 ± 5.99 ^b
Sixth week	411.25 ± 13.82 ^a	382.87 ± 15.08 ^{ab}	473.62 ± 8.50 ^b
Seventh week	395.10 ± 17.11 ^a	366.21 ± 12.32 ^{ab}	476.13 ± 10.23 ^b
Eighth week	380.62 ± 14.99 ^a	343.12 ± 9.97 ^{ab}	480.32 ± 9.25 ^b

Note: compared with model group ^a $P < 0.01$, compared with control group ^b $P < 0.01$.

2.3 三组大鼠每周体重改变的比较

观察期间,肝硬化造模组大鼠和小檗碱干预组大鼠体重下降,肝硬化造模组大鼠体重下降大于小檗碱干预组,第八周末

起差异明显,差别具有统计学意义 $P < 0.01$ 。正常对照组和肝硬化造模组比较,第四周末起肝硬化造模组体重下降差别具有统计学意义 $P < 0.01$ 。见表 2。

表 2 三组大鼠每周体重变化的比较(单位:g, $\bar{x}\pm s$)

Table 2 Comparison of weekly body weight changes among three groups of rats($\bar{x}\pm s$)

	BBR group (n=8)	Model group (n=8)	Control group (n=8)
First week	307.75± 6.84	308.00± 9.70	305.00± 10.8
Second week	307.42± 7.02	304.87± 8.39	309.75± 10.51
Third week	306.87± 7.40	303.87± 8.37	313.37± 11.16
Fourth week	304.75± 7.30	300.75± 7.98 ^b	316.25± 11.80 ^b
Fifth week	302.62± 7.27	297.5± 8.01 ^b	322.50± 12.55 ^b
Sixth week	299.50± 7.41	293.01± 7.74 ^b	327.87± 12.51 ^b
Seventh week	296.13± 6.40	288.62± 7.41 ^b	335.75± 12.38 ^b
Eigth week	293.5± 6.57 ^a	283.12± 7.52 ^{ab}	346.75± 12.65 ^b

Note: compared with model group ^a $P<0.01$, compared with control group ^b $P<0.01$.

2.4 各组血液生化及内毒素比较

与正常对照组相比,肝硬化造模组和小檗碱干预组两组大鼠血清 ALT,AST,ET 水平均明显升高($P<0.01$)。与肝硬化造模组相比,小檗碱干预组大鼠血清 ALT,AST,ET 水平明显降低($P<0.01$)。见表 3。

表 3 三组大鼠血液学指标的比较($\bar{x}\pm s$)

Table 3 Comparison of peripheral blood levels of ALT, AST and ET in rats from three groups($\bar{x}\pm s$)

	BBR group (n=8)	Model group (n=8)	Control group (n=8)
ALT(U/L)	49.81± 4.74 ^{ab}	64.27± 8.69 ^a	32.13± 3.42 ^b
AST(U/L)	98.71± 12.33 ^{ab}	119.42± 10.71 ^a	49.73± 7.72 ^b
ET(EU/mL)	0.72± 0.04 ^{ab}	0.87± 0.09 ^a	0.52± 0.07 ^b

Note: compared with model group ^a $P<0.01$, compared with control group ^b $P<0.01$.

2.5 肝脏病理观察

正常对照组:肝小叶轮廓清晰,肝细胞体积正常,细胞界限清楚,胞浆红染,胞核位于中央,未见有炎细胞浸润(图 1a)。肝硬化造模组:肝小叶结构严重破坏,假小叶形成,汇管区及小叶内淋巴细胞大量浸润(图 1b)。小檗碱干预组:肝小叶结构部分破坏,远离中央静脉的肝细胞发生脂肪变性,汇管区淋巴细胞轻度浸润(图 1c)。

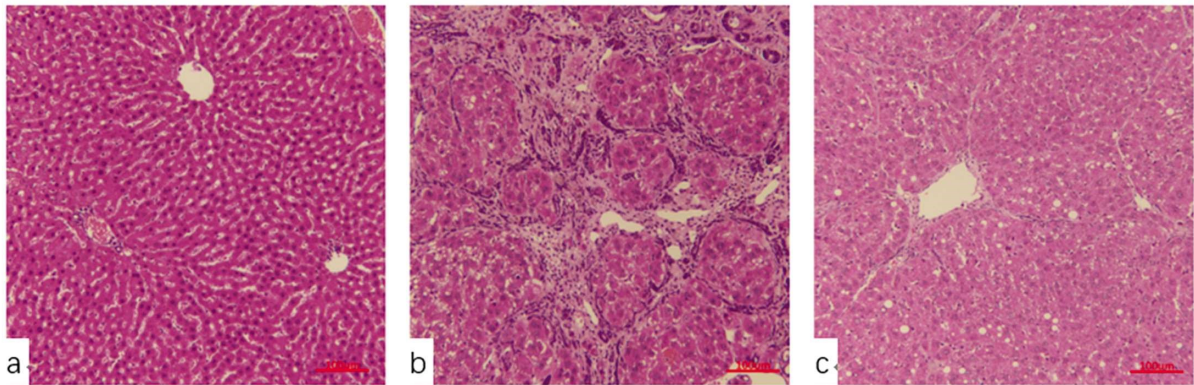


图 1 各组大鼠肝脏组织病理改变(HE, × 100)

Fig. 1 Histopathological changes of liver in different groups of rats (HE, × 100)

注:a:正常对照组,b:肝硬化造模组,c:小檗碱干预组

Note: a: control group, b: model group, c: berberine group

2.6 肠粘膜病理观察

肝硬化模型组与正常组相比可见小肠绒毛缩短、变形、数量减少、间距变宽,上皮细胞排列不规则等现象,小檗碱干预组和肝硬化造模组比较,可见小肠绒毛轻度缩短、变形、数量略有减少,上皮细胞排列呈现轻度不规则(具体见图 2)。

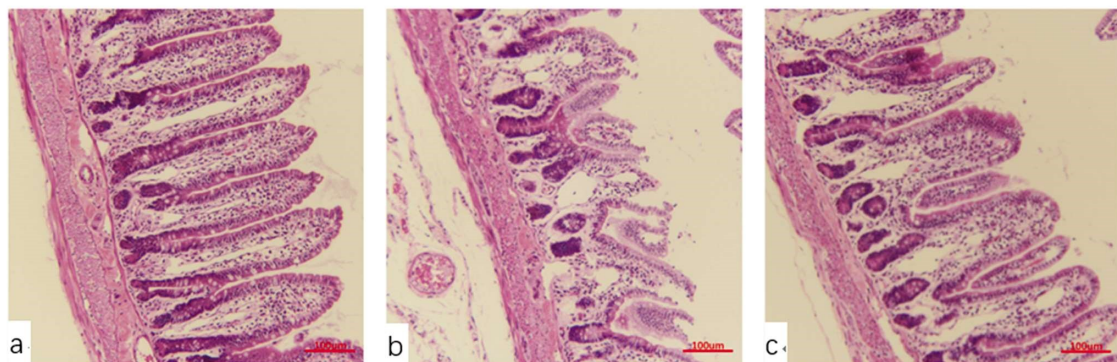


图2 各组大鼠小肠组织病理改变(HE, × 100)

Fig. 2 Histopathological changes of intestine in different groups of rats (HE, × 100)

注:a:正常对照组,b:肝硬化造模组,c:小檗碱干预组

Note: a: control group, b: model group, c: berberine group

3 讨论

肝硬化的发病机制中,肠粘膜屏障功能的改变有重要作用^[6,7]。肠粘膜屏障是人类自身所有屏障中功能中最为复杂的一个屏障,它阻止了肠腔内有害物质进入血液循环和体内其他组织器官,因此对于维护肠道正常功能,防止细菌移位有着重大的意义。而在肝硬化门脉高压时,由于肠道粘膜的淤血、水肿、缺血,造成微绒毛损害,使肠粘膜的清除能力下降,易发生细菌过度生长及外来菌的定植^[8-10],尤其在重症肝炎或晚期失代偿肝硬化病程中^[11],肠上皮的完整性和功能受到严重破坏,肠道屏障几乎丧失,肠道病原菌移位产生的大量代谢产物以及内毒素通过受损的肠粘膜屏障进入肝脏,同时由于肝脏解毒功能的下降,这些有害物质入血,引发肠源性感染、肝性脑病及肝损害加重等一系列反应^[12]。文献记载^[13,14],约有半数的肝硬化患者死于合并的细菌感染,其主要病原菌为来源于肠道的革兰阴性菌。因此如何有效保护肠粘膜屏障,维护肠道的功能,减缓肝硬化的发展,成为肝硬化治疗的关键。

小檗碱作为一种肠道抑菌药物在我国的应用历史悠久,现有研究发现小檗碱有肝脏保护作用。小檗碱可以通过抑制炎症细胞的趋化作用,减少氧自由基的生成及肿瘤坏死因子- α 的产生和释放,同时增强肝脏网状内皮系统的吞噬能力,加快清除血清内毒素,从而减轻肝脏的炎症损伤^[15-17]。有实验^[18-20]证实小檗碱在脂肪肝大鼠模型中能抑制与脂肪生成、炎症、纤维化和血管生成相关的基因的表达。Han等^[21]实验发现小檗碱能通过调节 Nrf 2-Keap 1-ARE 和 p53 信号通路改善四氯化碳诱导的大鼠肝损伤;吴晓艳等^[22]对非酒精性脂肪性肝病大鼠予盐酸小檗碱治疗 4 周后,发现肝组织病理得到明显改善,肝细胞脂肪变性减轻,证明小檗碱有一定的保护肝细胞作用。多项研究^[23-25]证实 BBR 能改善四氯化碳诱导的肝纤维化,抑制肝星状细胞的增殖。因此 BBR 能预防肝纤维化,是预防慢性肝病新策略。此外,小檗碱对肠粘膜屏障的保护作用越来越受到重视。口服小檗碱能够减轻脓毒血症以及放疗、非甾体类抗炎药引起的肠粘膜损伤^[26,27]。小檗碱能减轻尿毒症相关的肠粘膜功能损害^[28],通过维持肠粘膜屏障的完整性和减轻肠道炎症从而对溃疡性结肠炎的肠粘膜有保护作用^[29]。许建慧^[30]等实验证实,小檗碱能

显著提高结肠粘膜紧密连接蛋白 claudin-1, ZO-1 mRNA 的表达水平,降低 MLCK mRNA 的表达水平,同时能抑制 claudin-2 从粘膜表面向隐窝的移位,保护肠粘膜屏障的结构和功能的完整,减少内毒素血症水平。本试验中,肝硬化大鼠造模时予以小檗碱干预,可以观察到干预组大鼠进食量明显优于肝硬化造模组,而体重下降则相反,小檗碱干预组的 ALT, AST 及 ET 水平明显低于肝硬化组,肝脏病理上干预组肝小叶结构破坏,假小叶的形成,炎性细胞的浸润明显好于肝硬化组,肠粘膜病理上干预组小肠绒毛缩短、变形、数量减少、间距的变宽,上皮细胞排列不规则等现象均好于肝硬化造模组,提示小檗碱对四氯化碳联合酒精所致的肝硬化大鼠有减轻肝损伤和肠粘膜保护的作用。

综上所述,小檗碱对肝硬化大鼠的肝脏和肠粘膜有保护作用,作用机理可能与小檗碱的抗炎作用和保护肠粘膜的机械屏障有关。小檗碱在临床应用中具有毒副作用少,价格低廉等优点,值得推广。

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