

TAA 致慢性肝病内毒素血症大鼠清道夫受体、CD14 表达变化 *

吴金英¹ 张 琪² 高连印² 赵 晖^{2△}

(1 北京中医药大学中药学院 北京 100102 2 首都医科大学中医药学院 北京 100069)

摘要 目的:观察清道夫受体(SR)和脂多糖受体 CD14 在 TAA 介导的慢性肝病内毒素血症大鼠肝组织中的表达。方法:通过大鼠持续灌胃给小剂量(12mg/kg·d)TAA 建立大鼠肝损伤内毒素血症模型,HE 染色光镜观察肝脏病理变化;改良赖氏法检测大鼠血清 ALT、AST;改良过氯酸法测定血清内毒素含量;酶联免疫法检测大鼠血清 CD4⁺ 和 CD8⁺;免疫组化染色方法观察大鼠肝组织清道夫受体和 CD14 的表达。结果:TAA 诱导后,大鼠肝脏出现片状坏死并可见灶性炎症;血清 ALT、AST 及内毒素水平显著升高($P<0.05$ 或 $P<0.01$);血清 CD4⁺、CD8⁺ 细胞明显降低($P<0.01$);肝组织 CD14 表达上调,清道夫受体表达下调,和正常大鼠相比,差异显著($P<0.05$)。结论:肝组织 SR 表达下降和 CD14 表达增强可能是 TAA 介导慢性肝病内毒素血症的重要机制。

关键词 :TAA;内毒素血症;大鼠

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The Expression of Scavenger Receptor and CD14 in Chronic Liver Injury Rats with Endotoxemia Induced by TAA*

WU Jin-ying¹, ZHANG Qi², GAO Lian-yin², ZHAO Hui^{2△}

(1 School of Chinese pharmacy, Beijing University of Traditional Chinese Medicine, Beijing, 100102, China)

2 School of Traditional Chinese Medicine, Capital Medical University, Beijing, 100069, China)

ABSTRACT Objective: To investigate the expression of scavenger receptor and lipopolysaccharide (LPS) receptor CD14 in chronic liver injury rats with endotoxemia induced by TAA. **Methods:** Continuously oral administrating low-dose (12mg/kg.d) TAA to construct liver injury with endotoxemia model in rats. To observe the pathological damage of liver through HE staining, the levels of ALT, AST in blood serum were detected with modified Reit's method, the endotoxin in blood serum were measured by modified perchloric acid method and ELISA was used to detect the CD4⁺ and CD8⁺ in blood serum. The expression of scavenger receptor and CD14 in liver were observed by immunohistochemical staining and then analyzed by imaged analysis system. **Results:** After ten-week attacking by low-dose TAA (12mg/kg·d), patchy necrosis and focus inflammation appeared in rats liver. The content of ALT, AST and endotoxin in blood serum of model significantly increased ($P<0.05$ or $P<0.01$), while CD4⁺, CD8⁺ in serum decreased markedly ($P<0.01$). Compared with normal group, the expression of CD14 in liver of model group obviously increased, while the expression of scavenger receptor was down-regulated ($P<0.05$). **Conclusions:** It may be the important mechanism of chronic liver injury rats with endotoxemia induced by TAA that the lower expression of scavenger receptor and the higher expression of CD14 in liver.

Key words: TAA; Endotoxemia; Rats

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前言

肝硬化、重型及慢性病毒性肝炎等肝病患者多伴有肠源性内毒素血症,其可加重肝损害及促发各种并发症并与肝病互为因果,各型肝炎内毒素血症的发生率分别为:重型肝炎 58%-100%,肝硬化 79%-92%,慢性肝炎 50%-58%,急性肝炎 16%-43%^[1]。

因此建立合理的肝病合并肠源性内毒素血症模型是研究肝病内毒素血症发病机制和临床防治的基础。硫代乙酰胺(thioacetamide, TAA) 诱导肝损伤的同时伴有内毒素血症发生^[2-4]。

目前在实验中常使用大剂量 TAA 短期攻击或将 TAA 加入饮水中长期饮用致肝损伤内毒素血症模型,相关造模方法尚存在不足之处。本实验使用小剂量 TAA(12mg/kg·d)持续灌胃建立慢性肝病内毒素血症动物模型,并观察该模型大鼠肝组织清道夫受体(scavengerreceptor, SR)、CD14 表达变化。

1 材料与方法

1.1 实验材料

1.1.1 动物 清洁级雄性 Wistar 大鼠,体重 180~200g,由北京维通利华实验动物技术有限公司供给,合格证号为 scxk(京)

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作者简介:吴金英(1953-),女,本科,高级实验师,主要研究方向:中药药理,
电话:13021931793, E-mail: wujy@bucm.edu.cn

△通讯作者:赵晖,博士,副教授, E-mail: zhaohui8957@sina.com

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2002-0003。实验条件下自然饮食,适应环境三天后进行实验。

1.1.2 药品及试剂 硫代乙酰胺(TAA)购自北京化学试剂公司;内毒素试剂盒购于上海医学化验所,丙氨酸氨基转移酶(ALT)、天门冬氨酸氨基转移酶测定试剂盒购自中生北控生物科技股份有限公司;大鼠 CD4⁺、CD8⁺ 酶联免疫检测试剂盒均为 Adlitteram Diagnostic laboratories(美国)公司产品。

1.1.3 抗体 Rabbit-CD14、Rabbit-SR 购自美国 Affymetrix 公司,anti-Rabbit-IgG 购自中杉金桥公司,为 Santa Cruz 分装;二步法抗免疫组化检测试剂盒(EnVision+HRP/Rb)、DAB 显色剂均为武汉博士德(Boster)生物工程公司产品。

1.1.4 仪器 752N 型分光光度计,上海精密科学仪器有限公司生产;TGL-16G 型高速台式离心机,上海医用分析仪器厂生产;AEG-220 电子分析天平,日本 Shimadzu 公司;AT-738 半自动生化检测仪,上海安泰分析仪器有限公司。LEICA ASP300 全自动脱水机:德国;LEICA RM2235 轮转式石蜡切片机:德国;LEICA HI1210 摊片机:德国;LEICA EG1150H 包埋机:德国;Nikon 生物显微镜:日本;NIS-Elements Basic Research 图像采集分析系统:日本;酶标仪(芬兰 Thermo BioAnalysis Company 产品, Multiskan MK3 型)。

1.2 实验方法

1.2.1 模型制备 采用随机数字表法将大鼠随机分为正常组和模型组,每组 10 只动物。模型组灌胃给 12mg/kg·d 的 TAA,造模 10 周后,麻醉、取材。正常组给以同等容积的生理盐水灌胃。

1.2.2 取材 各组动物在无菌条件下采集右心室血液,血样放置 4℃ 冰箱中 1 小时,离心 10 分钟(3500rpm),分离血清备用;取血后的大鼠在冰盒上剖腹取肝组织,右叶肝组织浸泡于 10%福尔马林溶液中固定。

1.2.3 血清指标检测 严格按照试剂说明书的要求,赖氏法检测血清 AST、ALT 活性;改良过氯酸法测定内毒素含量;双抗夹心 ELISA 法检测 CD4⁺、CD8⁺T 细胞。

1.2.4 病理学观察及 SR、CD14 免疫组化染色 肝组织常规脱水、石蜡包埋、切片、苏木素-伊红(HE)染色,进行病理观察。石蜡切片机冠状连续切片(片厚 2μm),SP 免疫组织化学染色法检测肝组织 SR、CD14 表达。LEICA 数字显微照相机采集图像,在各组动物肝组织切片各选取 6 个视野利用 NIS-Elements Basic Research 图像采集系统进行图像分析,统计每个视野下 SR、CD14 表达积分光密度(IOD, integrated optical density)反映免疫染色强度,结果取 6 个视野的平均值。

1.2.5 统计方法 运用 SPSS10.0 for windows 进行统计与分析,相关数据分析均采用独立样本 T 检验。

2 结果

2.1 TAA 诱导大鼠血清氨基转移酶及内毒素的变化

TAA(12mg/kg·d)持续灌胃 10 周后,大鼠血清氨基转移酶 ALT、AST 以及内毒素含量均明显高于正常组 ($P<0.05$ 或 $P<0.01$),结果见表 1。

表 1 各组大鼠血清 ALT、AST 及内毒素的变化

Table 1 The content of ALT, AST and endotoxin of rats in each group (n=10, $\bar{x} \pm s$)

Group	AST(U·L ⁻¹)	ALT(U·L ⁻¹)	内毒素(Eu/mL)
Normal	119.14± 19.06	47.69± 6.57	0.051± 0.005
Model	280.14± 43.27*	178.99± 47.37**	0.179± 0.097*

注:与正常组比较 * $P<0.05$,** $P<0.01$ 。

Note: * $P<0.05$ ** $P<0.01$ compared with normal group.

2.2 TAA 诱导大鼠血清 CD4⁺、CD8⁺ T 细胞变化

与正常组相比,TAA 灌胃 10 周后,大鼠血清 CD4⁺、CD8⁺T 细胞水平明显降低($P<0.01$),见图 1。

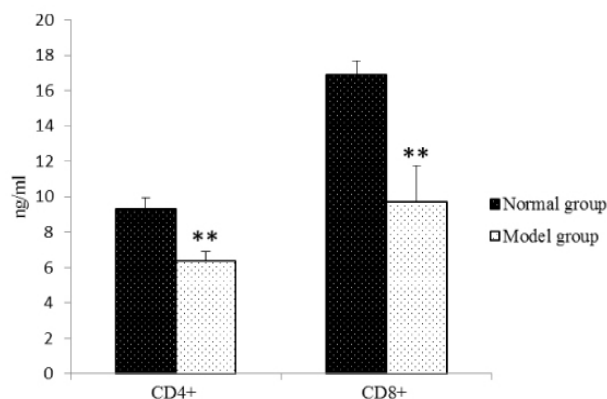


图 1 各组大鼠血清 CD4⁺、CD8⁺ T 细胞变化

注:与正常组比较 ** $P<0.01$

Fig.1 The content of CD4⁺ and CD8⁺ in serum of rats in each group

Note: * $P<0.01$ compared with normal group.

2.3 TAA 诱导大鼠肝脏病理变化

HE 染色显示(见图 2),正常组大鼠肝细胞索以中央静脉为中心向四周呈放射状排列,汇管区无炎细胞浸润,肝小叶结构清晰,肝细胞核大而圆,核膜清晰,核仁明显;模型组肝脏出现片状坏死,肝窦周围有较多淋巴细胞浸润并可见灶性炎症,肝小叶内及汇管区有程度不等的炎性细胞浸润。

2.4 TAA 诱导大鼠肝脏 SR 及 CD14 表达的变化

在正常大鼠肝脏枯否氏细胞可见散在 CD14 阳性产物,而 SR 表达呈弥漫性分布。TAA 诱导后,大鼠肝组织 CD14 阳性产物呈弥漫性分布,SR 表达产物减少;图像分析结果显示,与正常大鼠肝组织 CD14、SR 的表达相比,TAA 诱导大鼠肝脏 CD14 积分光密度值明显增高 ($P<0.05$),SR 积分光密度值明显降低($P<0.05$)(图像分析结果见图 3,免疫组化照片见图 4)。

3 讨论

目前 TAA 致肝损伤模型多为大剂量 TAA(400-600mg/kg)诱发急性肝衰大鼠模型,或将 TAA 加入饮水中,让动物长期饮用致慢性肝损伤模型^[5-7]。然而大剂量 TAA 给药对动物胃肠损

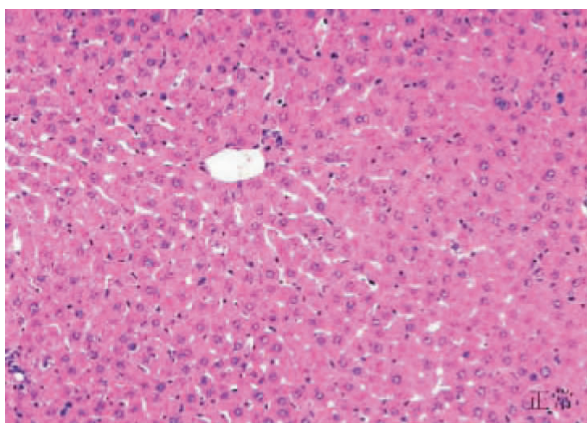


图 2-1 正常组
Fig.2-1 Normal group

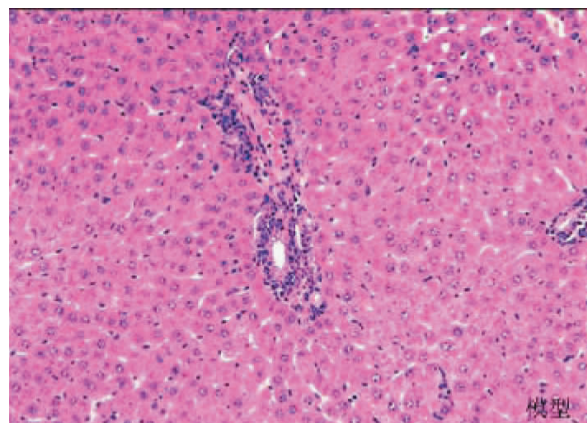


图 2-2 模型组
Fig.2-2 Model group

图 2 各组大鼠肝脏病理变化

Fig.2 The pathological damage of rat liver in each group (HE stain× 200)

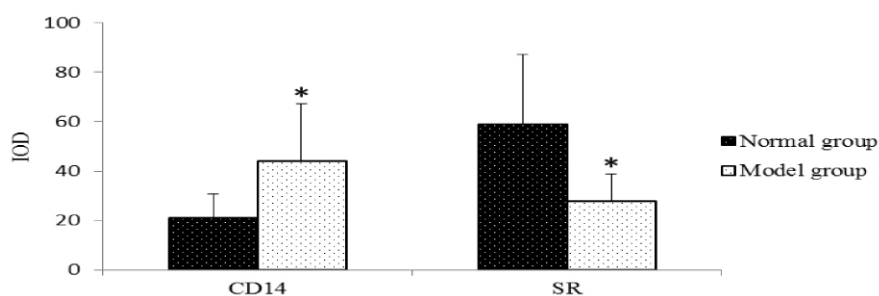


图 3 各组大鼠肝脏 SR、CD14 表达的变化

注:与正常组相比,*P<0.05

Fig.3 The expression of CD14、SR of rat liver in each group

Note: *P<0.05 compared with normal group.

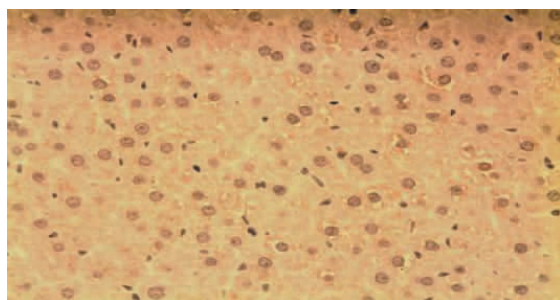


图 4-1 正常大鼠肝脏 CD14 表达
Fig.4-1 The expression of CD14 of rat liver in normal group

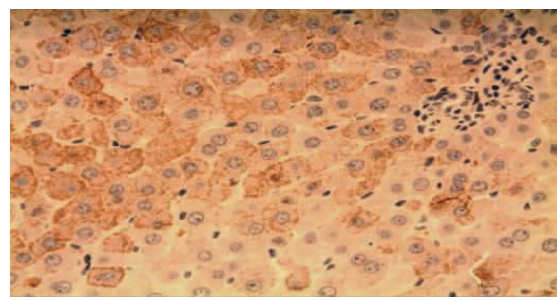


图 4-2 模型大鼠肝脏 CD14 表达
Fig.4-2 The expression of CD14 of rat liver in model group

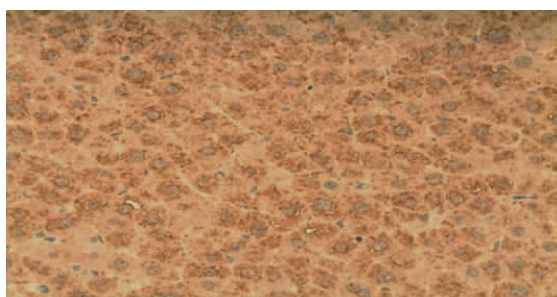


图 4-3 正常大鼠肝脏 SR 表达
Fig.4-3 The expression of SR of rat liver in normal group

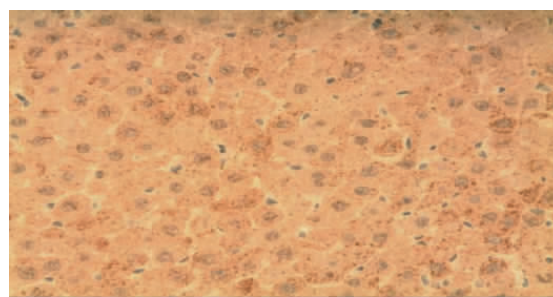


图 4-4 模型大鼠肝脏 SR 表达
Fig.4-4 The expression of SR of rat liver in model group

图 4 各组大鼠肝组织 CD14、SR 的表达

Fig.4 The expression of CD14、SR of rat liver in each group immuno-histochemical stain (SP× 200)

伤严重,动物死亡率较高,长期饮用 TAA 致肝损伤的方法不能保证每只动物 TAA 摄入量一致,且由于动物吸收能力不一,因此动物肝损伤程度的个体差异较大。本实验对 TAA 诱导大鼠肝损伤模型的方法进行改进,采用小剂量 TAA(12mg/kg·d)长期灌胃,既降低了对动物胃肠道的直接刺激作用,又保证了每只动物 TAA 的摄入量。结果表明,TAA 小剂量诱导 10 周后,动物肝脏出现片状坏死,中央静脉周围有大量的炎性细胞浸润,肝窦明显扩张充血,血清转氨酶及内毒素水平显著升高,CD4⁺/CD8⁺T 细胞数量明显降低,说明 TAA 长期低剂量可诱导肝细胞损伤及肠源性内毒素血症形成,同时可降低动物细胞免疫功能。

随着肝脏疾病与肠源性内毒素血症关系研究的深入,肝病时存在程度不等的肠源性内毒素血症已得到公认,肠源性内毒素血症在肝脏疾病发生、发展中的作用被进一步明确^[9-11]。TAA 是一种弱的致癌物,在肝内代谢成硫氢化合物,与肝大分子物质结合,引起肝损伤,同时还能激活磷脂酶 A2,引起肝细胞膜损害。由于肝功能障碍,可引起肠道菌群失调,肠道内的革兰阴性菌细胞壁脂多糖(LPS)成分增多,内毒素可直接损害肝细胞,还可以通过激活库普弗细胞(Kupffer cells, KCs)、单核细胞释放促炎介质如 TNF(肿瘤坏死因子)、IL-1、IL-6、NO、白三烯而间接损害肝细胞,同时破坏肠道屏障结构,内毒素过量易位,由此形成肝损伤-肠道菌群失调-肠源性内毒素血症的恶性循环,最终导致肠源性内毒素血症^[12-13]。

KCs 是位于肝血窦内的巨噬细胞,是机体拮抗内、外源性感染的主要防御细胞。内毒素作用于肝脏后,首先与 LPS 结合蛋白(LBP)结合,被运输到靶细胞后,再与 CD14 受体结合,激活核因子- κ B(NF- κ B),启动促炎基因转录、表达、诱发肝损伤^[14-16]。在 LPS 信息传递中起启动作用的激活性细胞受体为 CD14。而调控巨噬细胞清除、灭活内毒素的受体为清道夫受体(SR),SR 是近年发现的介导巨噬细胞吞噬降解细菌脂多糖的受体,可与多种带有负电荷的大分子(包括脂多糖)结合,并将之转移到细胞内降解^[17,18]。因此,SR 和 CD14 作为 KCs 表面对 LPS 具有高亲和力的糖蛋白受体,在内毒素血症时的表达变化必然会影响肝损伤的发生和发展^[19-20]。

本次实验结果显示,TAA 致肝损伤过程中,血中内毒素含量明显增高,肝细胞出现变性、坏死等病理改变,肝组织 SR 的表达下降,CD14 的表达增加。因此,我们认为 TAA 可以通过直接途径和间接途径对肝细胞造成损伤,KCs 活化是 TAA 诱导肝损害并发肠源性内毒素血症的病理关键。

参考文献(References)

- [1] 李夏青,韩德五,陈贤明.肝硬化大鼠肠源性内毒素血症的程度及肝组织中内毒素的分布[J].山西医科大学学报,2000,31(3):195-196
Li Xia-qing, Han De-wu, Chen Xian-ming. Severity of gut-originated endotoxemia and endotoxin distribution in the cirrhotic hepatic tissue [J]. Journal of Shanxi Medical University, 2000, 31(3):195-196
- [2] 高连印,付修文,谭勇等.清毒汤治疗急性肝损伤大鼠肠源性内毒素血症的实验研究[J].时珍国医国药,2009,20(4):984-985
Gao Lian-yin, Fu Xiu-wen, Tan Yong, et al. Experimental study of effect of Qingdu decoction on intestinal endotoxemia in acute liver injury rats [J]. Lishizhen Medicine and Materia Medica Research, 2009, 20(4):984-985
- [3] 武希润,赵元昌,闫晋平,等.暴发性肝衰竭动物模型的实验研究[J].山西临床医药,1996,5(4):308
Wu Xi-run, Zhao Yuan-chang, Yan Jin-ping, et al. Experimental study on Animal Models of Fulminant hepatic Failure [J]. Shanxi Clinical Medicine, 1996, 5(4):308
- [4] 陈锋,何生松,朱清静,等.大黄对硫代乙酰胺致急性肝衰竭大鼠 IL-6 及 c-met 蛋白的表达影响[J].辽宁中医杂志,2008,35(9):1423-1425
Chen Feng, He Sheng-song, Zhu Qing-jing, et al. Effect of Rhubarb on IL-6 and c-met's Expression in Thioacetamide-Induced Acute Hepatic Failure in Rats [J]. Liaoning Journal of Traditional Chinese Medicine, 2008, 35(9):1423-1425
- [5] 高连印,杜宇琼,付修文,等.清毒汤对大鼠实验性肝损伤内毒素血症的治疗作用[J].中西医结合肝病杂志,2006,16(6):347-349
Gao Lian-yin, Du Yu-qiong, Fu Xiu-wen, et al. Experimental study of effect of Qingdu decoction on hepatic injuries by endotoxin in rats [J]. Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases, 2006, 16(6):347-349
- [6] 姜树民,刘冰,王宝柱,等.保肝益胃合剂对硫代乙酰胺所致大鼠急性肝损伤的保护作用[J].中华中医药学刊,2008,26(10):2124-2125
Jiang Shu-min, Liu Bing, Wang Bao-zhu, et al. Guarantees Liver Profit Stomach Mixture to Be Result of Big Mouse Acute Liver Damage Protective Function to Thioacetamide [J]. Chinese Archives of Traditional Chinese Medicine, 2008, 26(10):2124-2125
- [7] 朱清静,陈锋,盛国光.丹黄方对硫代乙酰胺所致大鼠急性肝衰竭的防治作用[J].中西医结合肝病杂志,2007,17(1):35-37
Zhu Qing-jing, Chen Feng, Sheng Guo-guang. Prevention and cure effect of Danhuangfang on acute hepatic failure rats thioacetamide-induced [J]. Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases, 2007, 17(1):35-37
- [8] 余林中,江爱达,陈育尧等.凉膈散对内毒素血症小鼠的肝脏库普弗细胞 CD14 和清道夫受体表达的影响 [J]. 中国中药杂志,2006,31(3):220-223
Yu Lin-zhong, Jiang Ai-da, Cheng Yu-yao, et al. Liangge San effects the expression of CD14 and scavenger receptor in the kupffer cells of liver of endotoxemia mice [J]. China Journal of Chinese Materia Medica, 2006, 31(3):220-223
- [9] 毛卫林,俞炯,陈月美.肝衰竭患者外周血 CD4⁺/CD8⁺T 细胞比值的变化与人工肝疗效的相关性研究 [J]. 浙江检验医学,2008,6(3):11-13
Mao Wei-lin, Yu Jiong, Chen Yue-mei. A Study of Relationship between the change of CD4⁺/CD8⁺ in the peripheral blood and curative effect in patients with liver failure [J]. Zhejiang Journal of Laboratory Medicine, 2008, 6(3):11-13
- [10] Hoebe KH, Witkamp RF, Fink Gremmels J, et al. Direct cell-to-cell contact between Kupffer cells and hepatocytes augments endotoxin-induced hepatic injury [J]. Am J Physiol Gastrointest Liver Physiol, 2001, 280(4):G720-728
- [11] Tsujimoto T, Kuriyama S, Yamazaki M, et al. Augmented hepatocellular carcinoma progression and depressed Kupffer cell activity in rat cirrhotic livers [J]. Int J Oncol, 2001, 18(1): 41-47

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凋亡而且可以通过激活 Beclin-1 来激活自噬^[14,15]。实验研究也表明通过使缺血再灌注心肌过度表达 Bcl-2 而抑制了再灌注过程中心肌细胞凋亡及自噬性细胞死亡,从而减少了心肌损伤^[16,17]。最新的文献报道,短暂的脊髓缺血再灌注损伤同样可以诱导自噬现象的发生^[18]。我们的研究也显示高压氧预处理可以下调 Bcl-2 的表达^[9]。

实验研究表明脊髓缺血再灌注期, HBO 预处理可能通过调节自噬体形成及活性减轻缺血再灌注损伤。但是自噬体形成的相关分子 Beclin-1、PI3K 与凋亡信号通路相关分子 Bcl-2、caspase-3 的相互作用及其调节关系仍然需要进行深入的研究探讨。

参考文献(References)

- [1] Li Q, Li J, Zhang L, et al. Preconditioning with hyperbaric oxygen induces tolerance against oxidative injury via increased expression of heme oxygenase-1 in primary cultured spinal cord neurons[J]. Life Sci, 2007, 80: 1087-1093
- [2] Nie H, Xiong L, Lao N, et al. Hyperbaric oxygen preconditioning induces tolerance against spinal cord ischemia by upregulation of antioxidant enzymes in rabbits[J]. J Cereb Blood Flow Metab, 2006, 26: 666-674
- [3] Dong H, Xiong L, Zhu Z, et al. Preconditioning with hyperbaric oxygen and hyperoxia induces tolerance against spinal cord ischemia in rabbits[J]. Anesthesiology, 2002, 96: 907-912
- [4] Baba H, Sakurai M, Abe K, et al. Autophagy-mediated stress response in motor neuron after transient ischemia in rabbits [J]. J Vasc Surg, 2009, 50: 381-387
- [5] Yan W, Zhang H, Bai X, et al. Autophagy activation is involved in neuroprotection induced by hyperbaric oxygen preconditioning against focal cerebral ischemia in rats[J]. Brain Res, 2011, 1402: 109-121
- [6] Itakura E, Mizushima N. Atg14 and UVRAG: mutually exclusive subunits of mammalian Beclin 1-PI3K complexes[J]. Autophagy, 2009, 5: 534-536
- [7] Rothfuss A, Stahl W, Radermacher P, et al. Evaluation of mutagenic effects of hyperbaric oxygen (HBO) in vitro[J]. Environ Mol Mutagen, 1999, 34: 291-296
- [8] Garber K. Autophagy. Explaining exercise[J]. Science, 2012, 335: 281
- [9] He C, Bassik MC, Moresi V, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis [J]. Nature, 2012, 481: 511-515
- [10] Shi CS, Shenderov K, Huang NN, et al. Activation of autophagy by inflammatory signals limits IL-1beta production by targeting ubiquitinated inflammasomes for destruction [J]. Nat Immunol, 2012, 13: 255-263
- [11] Swanson MS, Molofsky AB. Autophagy and inflammatory cell death, partners of innate immunity[J]. Autophagy, 2005, 1: 174-176
- [12] Vlodavsky E, Palzur E, Feinsod M, et al. Evaluation of the apoptosis-related proteins of the BCL-2 family in the traumatic penumbra area of the rat model of cerebral contusion, treated by hyperbaric oxygen therapy: a quantitative immunohistochemical study[J]. Acta Neuropathol, 2005, 110: 120-126
- [13] Luo S, Rubinstein DC. Apoptosis blocks Beclin 1-dependent autophagosome synthesis: an effect rescued by Bcl-xL[J]. Cell Death Differ, 2010, 17: 268-277
- [14] Liu L, Fang YQ, Xue ZF, et al. Beta-asarone attenuates ischemia-reperfusion-induced autophagy in rat brains via modulating JNK, p-JNK, Bcl-2 and Beclin 1[J]. Eur J Pharmacol, 2012, 680: 34-40
- [15] Grishchuk Y, Ginot V, Truttmann AC, et al. Beclin 1-independent autophagy contributes to apoptosis in cortical neurons[J]. Autophagy, 2011, 7: 1115-1131
- [16] Dong Y, Undyala VV, Gottlieb RA, et al. Autophagy: definition, molecular machinery, and potential role in myocardial ischemia-reperfusion injury[J]. J Cardiovasc Pharmacol Ther, 2010, 15: 220-230
- [17] Gustafsson AB, Gottlieb RA. Eat your heart out: Role of autophagy in myocardial ischemia/reperfusion[J]. Autophagy, 2008, 4: 416-421
- [18] Chen HC, Fong TH, Lee AW, et al. Autophagy is activated in injured neurons and inhibited by methylprednisolone after experimental spinal cord injury[J]. Spine (Phila Pa 1976), 2012, 37(6):470-475
- [12] 郭花,薛辉.肝硬化动物模型研究进展[J].中国比较医学杂志, 2006, 16(8):499-501
Guo Hua, Xue Hui. Progress in Research on Animal Models of Hepatic Cirrhosis [J]. Chinese Journal of Comparative Medicine, 2006, 16(8):499-501
- [13] 朱宁川,陈宁.肝病肠道菌群失调与肠源性内毒素血症[J].中国微生物生态学杂志, 2006, 16(1):61
Zhu ning-chuan, Chen ning. Intestinal Microflora Dysregulation and Intestinal Endotoxemia [J]. Chinese Journal of Microecology, 2006, 16(1):61
- [14] 谢国旗,蒋建新,陈永华.肝星形细胞 CD 14 表达变化在内毒素肝损伤中的作用[J].中华医院感染学杂志, 2002, 12(5):344-346
Xie Guo-qi, Jiang Jian-xin, Chen Yong-hua, et al. Dynamic Expression of CD14 on Kupffer Cells in Endotoxin-induced Hepatic Injury [J]. Chinese Journal of Nosocomiology, 2002, 12(5):344-346
- [15] Ivan Zanoni, Renato Ostuni, Giusy Capuano, et al. CD14 regulates the dendritic cell life cycle after LPS exposure through NFAT activation [J]. Nature, 2009, 9: 264-268
- [16] Oikawa K, Ohkohchi N, Sato M, et al. Elimination of Kupffer cells suppresses activation of nuclear factor kappa B and production of cytokines and eicosanoids in non-heart-beating donors[J]. Transplant Proc, 2001, 33:839-840
- [17] Lee YG, Lee SH, Lee SM. Role of Kupffer cells in cold/worm ischemia reperfusion injury of rat liver [J]. Arch Pharm Res, 2000, 23(6): 620-625
- [18] Ivan Zanoni, Renato Ostuni, Lorri R. Marek, et al. CD14 Controls the LPS-Induced Endocytosis of Toll-like Receptor 4[J]. Cell, 2011, 147(11):868-880
- [19] 王春妍,杨世忠,江海艳.急性肝损伤大鼠肠源性内毒素血症形成机理及其作用的实验研究 [J].临床肝胆病杂志, 2007, 23(2): 109-111
Wang Chun-yan, Yang Shi-zhong, Jiang Hai-yan. Study on formation mechanism and effect of intestinal endotoxemia in the rats with experimental acute liver injury [J]. Chinese Journal of Clinical Hepatology, 2007, 23(2):109-111
- [20] Urata K, Brault A, Rocheleau B, et al. Role of Kupffer cells in survival after rat liver transplantation with long portal vein clamping times [J]. Transpl Int, 2000, 13(6):420-427

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