

慢性乙醇中毒所致大鼠肝损伤和肝细胞凋亡

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Liver injury and hepatocyte apoptosis induced by chronic alcoholic intoxication in rats

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Abstract

AIM: To investigate the role of hepatocyte apoptosis in the pathogenesis of alcohol-induced liver diseases (ALD) in rats.

METHODS: The rat model of liver injury was induced by combination of drinking and gastric irrigation of ethanol. The morphological changes of the liver were observed by routine HE staining under light microscope. The hepatocyte apoptosis was examined by TUNEL, and the levels of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) were detected by the rate method.

RESULTS: At the end of the 5th week, the light and moderate steatosis appeared in ethanol-treated rat livers, the proportion of fatty degeneration was 40% (8/20); At the end of the 10th week, the proportion

was increased to 85% (17/20), and the morphological changes of alcoholic hepatitis (AH) were found in 45% (9/20) rats. The serum levels of ALT and AST (nkat/L) in ethanol-treated rats were significantly higher than those of the controls (5 wk: $1\ 017 \pm 267$ vs 550 ± 133 , $P < 0.05$; $1\ 350 \pm 333$ vs 967 ± 150 , $P < 0.05$; 10 wk: $1\ 500 \pm 267$ vs 767 ± 250 , $P < 0.05$; $2\ 167 \pm 533$ vs 850 ± 183 , $P < 0.05$), and ALT and AST levels at 10 wk were also higher than those at 5 wk ($P < 0.05$). The TUNEL indexes (%) at 5 and 10 wk were $0.33 \pm 0.49\%$ and $2.03 \pm 1.61\%$ respectively ($P < 0.05$), and the index at 10 wk was significantly different from that of the controls ($0.10 \pm 0.21\%$, $P < 0.05$). Furthermore, the TUNEL index of alcoholic hepatitis was significantly higher than that of alcoholic fatty liver ($3.24 \pm 1.50\%$ vs $1.12 \pm 0.63\%$, $P < 0.05$). Both show the significant difference.

CONCLUSION: Chronic and excessive ethanol consumption can cause liver injury in rats. The amount and time of daily ethanol intake is closely related with the degrees of liver injury. Hepatocyte apoptosis may play an important role in the pathogenesis of ALD.

Key Words: Alcohol; Liver injury; Apoptosis; TUNEL

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摘要

目的: 研究肝细胞凋亡在实验性大鼠乙醇性肝病(ALD)发生、发展中的作用.

方法: 给大鼠饮用220 g/L的乙醇, 并结合540 g/L乙醇分次、少量灌胃的方法建立大鼠肝损伤模型; 常规HE染色, 光镜观察大鼠病理学形态改变, 用TUNEL法检测肝细胞凋亡, 速率法检测血清ALT, AST水平.

结果: 灌乙醇5 wk大鼠肝脏出现轻到中度脂肪变性, 脂滴为以大泡型为主的混合脂滴, 脂变率为40% (8/20); 10 wk, 85% (17/20)大鼠发生肝脂肪变, 45% (9/20)大鼠出现乙醇性肝炎的病理变化. 5, 10 wk大鼠血清ALT, AST均较同期对照组有显著升高 (5 wk: $1\ 017 \pm 267$ vs 550 ± 133 , $P < 0.05$; $1\ 350 \pm 333$ vs 967 ± 150 , $P < 0.05$; 10 wk: $1\ 500 \pm 267$ vs 767 ± 250 , $P < 0.05$; $2\ 167$

± 533 vs 850 ± 183 , $P < 0.05$); 灌乙醇10 wk血清ALT, AST较5 wk升高($P < 0.05$), 有统计学意义. 5, 10 wk大鼠TUNEL指数分别为 $0.33 \pm 0.49\%$ 、 $2.03 \pm 1.61\%$, 与同期对照组相比, 5 wk无显著差异, 10 wk有显著性差异($P < 0.05$); 灌乙醇10 wk TUNEL指数较5 wk高, 有显著性差异($P < 0.05$). 按病理损伤程度, 将实验组分成乙醇性肝炎(AH)组和乙醇性脂肪肝(AFL)组, 结果显示AH组TUNEL指数也较AFL组高($3.24 \pm 1.50\%$ vs $1.12 \pm 0.63\%$, $P < 0.05$), 差异显著.

结论: 过量饮用乙醇可以引起中毒性肝脏疾病, 饮用乙醇及持续时间与肝损伤的发生有密切关系. 细胞凋亡在乙醇诱发肝损伤时可能起着重要作用.

关键词: 乙醇; 肝损伤; 凋亡; TUNEL

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0 引言

乙醇性肝病 (alcoholic liver disease, ALD) 是因长期过量饮酒引起的中毒性肝脏疾病, 主要有3种, 即: 乙醇性脂肪肝 (alcoholic fatty liver, AFL)、乙醇性肝炎 (alcoholic hepatitis, AH)和乙醇性肝硬化(alcoholic liver cirrhosis, ALC), 三者可单独出现, 也可同时并存或先后移行^[1], 重度乙醇中毒造成的肝损伤往往威胁到患者的生命^[2]. 西方国家ALD发病率较高, 酗酒者患肝硬化是正常人的6.8倍, 在美国城市25-64岁人群中, 乙醇性肝硬化的死亡率居第三位^[3]. 北京协和医院1982-1991报告ALD的病死率为1.1%, 1996年报告达9.1%^[4]. 随着乙醇饮品消耗量的增多, ALD的发病率也随之上升. 关于ALD的发病机制, 目前尚未完全阐明. 过去只注意研究乙醇本身或其代谢产物对肝细胞的直接毒性作用以及营养失调、肝脏代谢异常及脂质过氧化等变化在ALD发病学中的作用^[5]. 近年来, 发现免疫反应和细胞基因异常调控及凋亡机制参与ALD的病理损伤过程, 认为细胞凋亡是造成ALD的主要因素^[6].

1 材料和方法

1.1 材料 雌性Wistar大鼠60只, 质量90-110 g, 本院动物实验科提供. 原位细胞凋亡检测试剂盒 (terminal deoxynucleotidyl transferase nick end labeling, TUNEL), 为德国Boehringer Mannheim公司产品. 浓缩缓冲液、DAB溶液和浓缩过氧化氢溶液, 购自北京中山生物技术有限公司. 丙氨酸氨基转移酶 (ALT)、天门冬氨酸氨基转移酶 (AST)、血清总胆红素 (T BiLi) 检测试剂购自上海张江生物技术有限公司.

1.2 方法 雌性Wistar大鼠60只正常喂养1 wk后, 随机分为2组, 对照组10只/笼, 共20只; 实验组10只/笼, 共40只. 造模方法为: 先给大鼠随意饮用50 g/L的乙醇3 d, 第4天换成100 g/L, 以后每隔1 wk增加20 g/L直至180 g/L, 然后在每周增加10 g/L直至终浓度为220 g/L; 从饮用220 g/L的乙醇开始, 以540 g/L乙醇1.5 mL每日分3次灌胃至5 wk末; 以540 g/L乙醇1.2 mL每日分3次灌胃至10 wk末. 对照组饮用自来水, 灌胃时采用生理盐水, 灌胃方法及时间同上. 于开始灌胃5 wk末、10 wk末分别处死实验组各20只及对照组各10只, 腔静脉取血, 剖腹取肝脏. 细胞凋亡检测采用TUNEL法, 操作按说明书进行. TUNEL阳性计数选择标记效果较好的区域, 在400×视野中计数阳性细胞数, 阳性细胞数除以肝细胞总数作为细胞凋亡指数 (TUNEL指数), 每例计数5个视野, 取均值以百分数表示, $< 1.5\%$ 属于低凋亡指数, $\geq 1.5\%$ 属于高凋亡指数.

统计学处理 采用SPSS11.0统计分析软件, 数据以mean \pm SD表示, 各组间比较采用两样本均数的 t 检验.

2 结果

灌乙醇前实验组大鼠烦躁易激怒, 好斗; 灌乙醇5 wk后大鼠行动不稳, 步态蹒跚, 嗜睡, 鼠毛较乱, 晦暗无光泽, 进食量平均约为对照组的2/3, 灌乙醇10 wk后以上症状进一步加重, 对照组未见异常. 试验组大鼠体质量比同期对照组轻, 差异显著; 试验组大鼠肝质量较同期对照组有所升高, 经统计学分析无显著性差异 (表1).

2.1 HE染色观察 灌乙醇5 wk 40% (8/20) 大鼠发生脂肪肝变性, 脂滴为以大泡型为主的混合脂滴, 少数大鼠肝脂变程度较为严重 (图1A); 灌乙醇10 wk, 肝损伤进一步加重, 脂变率上升达85% (17/20), 45% (9/20)大鼠出现乙醇性肝炎的病理变化: 肝细胞脂肪变性, 伴有不同程度炎性细胞的浸润和点状坏死 (图1B). 试验组大鼠ALT, AST均比同期对照组高, 差异显著; 灌乙醇10 wk ALT, AST较灌乙醇5 wk升高, 有显著性差异, T BiLi在各组中变化不大, 无显著性差异 (表1).

2.2 乙醇诱发肝损伤时大鼠肝细胞凋亡指数的变化 TUNEL阳性表达为胞核棕色或棕褐色 (图1C), 灌乙醇 5 wk及10 wk肝细胞试验组大鼠TUNEL指数均比同期对照组高, 灌乙醇5 wk差异不显著, 灌乙醇10 wk有显著性差异; 灌乙醇10 wk TUNEL指数比灌乙醇5 wk高, 差异显著 (表1). 将实验组 (灌乙醇5 wk, 灌乙醇10 wk)按肝组织损伤程度分为AFL组和AH组, 比较二者的TUNEL指数及血清ALT, AST水平, 结果AH组TUNEL指数较AFL组升高, 有显著性差异; AH组的血清ALT, AST水平均较AFL组高, 差异显著, 提示AH损伤较AFL更为严重 (表2).

表1 乙醇诱发肝损伤时大鼠体质量、肝质量和肝功能的变化

t/wk	分组	n	体质量 (g)	肝质量 (g)	ALT (nkat/L)	AST (nkat/L)	T BiLi (μmol/L)	TUNEL指数 (%)
5	对照	10	214.7 ± 14.2	8.8 ± 0.8	550 ± 133	967 ± 150	6.4 ± 2.4	0.00
	实验	20	198.5 ± 10.4 ^a	9.0 ± 0.9	1 017 ± 267 ^a	1 350 ± 333 ^a	6.8 ± 2.2	0.33 ± 0.49
10	对照	10	248.2 ± 18.2	9.3 ± 0.9	767 ± 250	850 ± 183	6.5 ± 2.2	0.10 ± 0.21
	实验	20	227.3 ± 10.8 ^a	9.7 ± 1.1	1 500 ± 267 ^c	2 167 ± 533 ^c	6.5 ± 2.3	2.03 ± 1.61 ^{ac}

^a*P* < 0.05 vs 对照组; ^c*P* < 0.05 vs 5 wk.

表2 AFL组与AH组TUNEL指数及血清ALT、AST水平的比较

分组	n	TUNEL指数 (%)	ALT (nkat/L)	AST (nkat/L)
AFL	16	1.12 ± 0.63	1 234 ± 183	1 467 ± 317
AH	9	3.24 ± 1.50 ^a	1 600 ± 167 ^a	2 600 ± 450 ^a

^a*P* < 0.05 vs AFL.

3 讨论

建立乙醇性肝损伤的动物模型可模仿人体ALD的病理变化,在ALD的研究中具有重要的作用。Tsudamoto-French大鼠ALD模型是国外通用的ALD动物模型,该模型的肝脏病变基本上接近人类ALD病理变化,但是由于价格昂贵,在国内尚未得到应用^[7-9]。国内有人采用乙醇灌胃法,我们重复的结果显示大鼠的死亡率很高,实验难以进行。我们采用给大鼠饮用220 g/L乙醇,并结合540 g/L乙醇分次,少量灌胃的方法成功地复制出了大鼠ALD的部分病变。我们认为制备ALD动物模型时,必须保持动物血液中高乙醇含量,使其肝脏长期处于持续高氧化代谢状态,才能造成乙醇肝损伤^[10]。此外,我们选择雌性大鼠进行实验,主要是因为雌性大鼠较雄性大鼠更易于发生乙醇性肝损伤^[11],从而缩短造模时间。在本研究中,灌乙醇5 wk大鼠肝脏即可出现轻到中度脂肪变性,脂变率为40% (8/20),脂滴为以大泡型为主的混合脂滴,未见明显的气球样变性;血清ALT,

AST均有不同程度升高,与对照组比,有显著性差异,血清T BiLi水平变化不大;肝脏轻度肿大,与同期对照组比较无显著性差异,体质量较同期对照组轻。灌乙醇10 wk,脂肪变性进一步加重,85%大鼠发生脂肪肝变,45%大鼠肝组织损伤更严重,出现AH的病理变化,血清ALT、AST升高更为显著,与同期对照组比有显著性差异。上述变化表明,过量饮用乙醇可引起中毒性肝脏疾病,同时也表明饮用乙醇量及持续时间与肝损伤的发生有密切关系^[12-16]。

关于ALD的发病机制,目前尚未完全阐明。过去只注意研究乙醇本身或其代谢产物对肝细胞的直接毒性作用以及营养失调^[17],肝脏代谢异常及脂质过氧化等变化在ALD发病学中的作用^[18,19]。近年来,发现细胞凋亡机制参与ALD的病理损伤过程,认为细胞凋亡是造成ALD的主要因素。细胞凋亡 (cell apoptosis) 或程序化细胞死亡 (programmed cell death, PCD) 是多细胞有机体为调控机体发育,维护内环境稳定,由基因控制的细胞主动死亡过程。凋亡是正常细胞现象,但也可被许多外部因素激发,提示激活凋亡控制基因的机制可以不同。肝细胞凋亡发生在肝发育和成人肝的肝细胞更新时,也发生在各种病毒、免疫、肿瘤和药物引起的肝脏疾病^[20-23]。检测凋亡细胞是利用细胞凋亡时产生特征性DNA片段,以TdT介导的dUTP缺口末端标记技术原位显示凋亡细胞的形态和分布。实验中

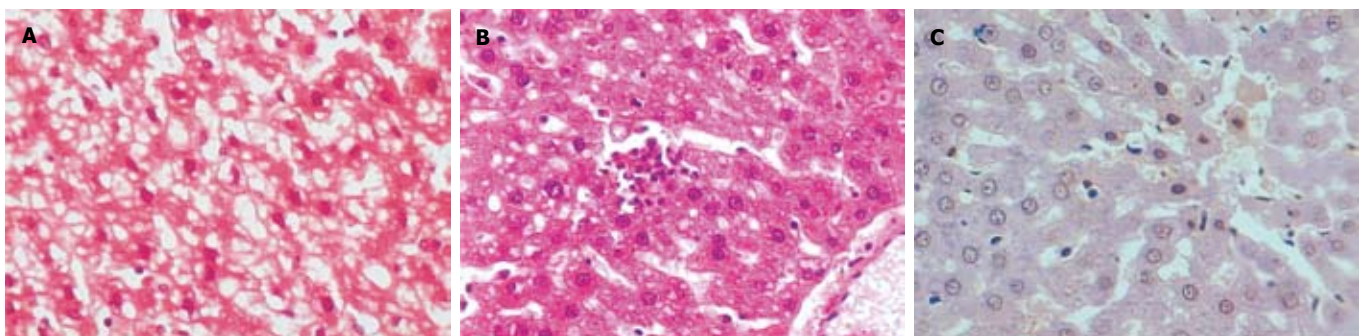


图1 大鼠肝脏组织学 (×200)。A: 灌胃5 wk HE大量以大泡型为主的混合脂滴; B: 灌胃10 wk HE肝实质内有点状坏死区; C: 灌胃10 wk TUNEL染色显示凋亡细胞。

可见TUNEL阳性细胞核染成棕色, 与周围肝细胞比, 体积缩小、核固缩明显. 本研究中, 对照组、灌乙醇5 wk、灌乙醇10 wk肝细胞平均TUNEL指数(%)分别为 0.10 ± 0.21 , 0.33 ± 0.49 , 2.03 ± 1.61 , 尤其灌乙醇10 wk, TUNEL指数 $>1.5\%$, 属于高凋亡指数. 表明长期过量饮用乙醇的大鼠肝细胞凋亡指数明显高于正常大鼠, 提示乙醇诱发大鼠肝细胞凋亡与乙醇的作用时间和量均有关系. 我们同时比较了AFL组与AH组, AH组TUNEL指数为 $3.24 \pm 1.50\%$, 也属高凋亡指数, 与文献[24]报道基本一致. AH组血清ALT为 $1\ 600 \pm 167$ nkat/L, AST为 $2\ 600 \pm 450$ nkat/L, 与AFL组比较, 差异显著, 表明AH肝组织损伤程度较AFL更为严重, 并且此种损伤伴有肝细胞高凋亡指数的出现, 进一步表明肝细胞凋亡在乙醇诱发肝损伤时可能起着极其重要的作用^[25]. 关于在ALD中肝细胞发生凋亡的机制尚无统一认识, 目前认为与以下因素密切相关: 细胞色素P450IIE1 (cytochrome P450IIE1, CYP1IIE1) 的活化^[26]; Fas及其配体的作用^[27-29]; 肿瘤坏死因子(TNF- α)和受体(TNFR1)活性增高^[30]等. 这将是今后研究的方向.

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• 消息 •

更正与说明专栏

本刊讯 《世界华人消化杂志》为了对同行评议、编辑、校对、审读、文章价值等质量进行跟踪报道，特设“更正与说明”固定专栏，包括“事实纠错”、“文字更正”、“解释说明”三个子栏目，不仅对前一期或近期出现的文字差错和事实错误进行更正、就引发歧义或晦涩难懂之处做解释说明，而且针对文章的学术水平等进行讨论。在此，我们热烈欢迎读者、作者、编委等积极审读《世界华人消化杂志》，给更正与说明栏目投稿。投稿者凭文章的编号，可免费注册(<http://www.wjgnet.com/1009-3079/new/39.doc>)使用中国生物医学基金论文摘要库3 a。中国生物医学基金论文摘要库(<http://www.wjgnet.com/cmfa/index.jsp>)收录了1994-2005年国内发表在1 204种生物医学类期刊总计20万以上的论文摘要。这些论文受国家、军队和省部级自然科学基金、杰出青年基金、重大计划项目基金资助，内容丰富、数据准确，体现了我国生物医学的发展历程、脉络和方向，可为相关领域大学者和研究人员了解并掌握当前研究动态、开辟新的研究领域提供思路。(世界胃肠病学杂志社 2005-10-10)

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技法与经验

本刊讯 《世界华人消化杂志》2006年设置“技法与经验”专栏，及时报道微创、内镜下治疗消化病新的技术和方法及成熟的经验。我们热烈欢迎各位作者踊跃投稿，免费刊登彩色照片。写作格式如下：

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0 引言

1 技术方法 1.1 原理；1.2 适应证；1.3 器材准备；1.4 步骤；1.5 实例

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0 引言；1 诊断；2 治疗；3 特色；4 门诊时间