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·基础研究·

依托咪酯对四氯化碳诱导的大鼠肝损伤的保护作用

李 雯,李玉娟,陈 璐,李双牵,刘俊徽,韩丽丽 (河北北方学院附属第一医院创伤急救外科,河北 张家口 075000)

[摘 要] **目的** 研究依托咪酯对四氯化碳(CCl_4)诱导的大鼠急性肝损伤的保护作用及相关机制。**方法** 将48只SPF级Wistar大鼠随机分为对照组、模型组、依托咪酯0.5 mg/kg组、依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、水飞蓟素(SIL)组(200 mg/kg,阳性对照),每组6只。对照组和模型组静脉注射生理盐水0.2 mL,依托咪酯给药组分别静脉注射0.5 mg/kg、1 mg/kg、2 mg/kg依托咪酯0.2 mL,SIL组静脉注射200 mg/kg SIL 0.2 mL,每天1次,连续给药14 d,然后模型组、依托咪酯给药组和SIL组腹腔注射0.2% CCl_4(10 mL/kg),对照组腹腔注射等量橄榄油,24 h后处死大鼠。测定血清丙氨酸氨基转移酶(ALT)和天冬氨酸氨基转移酶(AST)水平;HE染色评估肝组织病理损伤;ELISA检测肝组织中肿瘤坏死因子-α(TNF-α)和白细胞介素-6(IL-6)水平;检测超氧化物歧化酶(SOD)和丙二醛(MDA)水平;TUNEL染色评估肝组织中细胞凋亡情况;免疫组化检测大鼠肝组织中NF-κB p65阳性表达;Western blot检测相关蛋白的表达。**结果** 与对照组相比,模型组大鼠血清ALT和AST水平明显升高,肝组织病理损伤明显,TNF-α、IL-6、MDA水平显著升高,SOD水平显著降低,肝组织细胞凋亡数量明显增加,Bax/Bcl-2、cleaved caspase-3/caspase-3及p-NF-κB p65/NF-κB p65明显升高,差异均有统计学意义($P<0.05$)。与模型组相比,依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组肝组织病理损伤明显改善,炎症因子释放、氧化应激和肝组织细胞凋亡得到抑制,p-NF-κB p65/NF-κB p65降低。**结论** 依托咪酯对CCl_4诱导的大鼠急性肝损伤具有较好的缓解作用,其机制可能与抑制NF-κB通路有关。

[关键词] 依托咪酯;四氯化碳;肝损伤;白细胞介素-6;丙二醛;NF-κB p65
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Protective effect of etomidate on carbon tetrachloride-induced liver injury in rats

LI Wen, LI Yu-juan, CHEN Lu, LI Shuang-qian, LIU Jun-hui, HAN Li-li (Department of Emergency Trauma Surgery, First Affiliated Hospital of Hebei North University, Zhangjiakou Hebei 075000, China)

Abstract: Objective To investigate the protective effect and related mechanism of etomidate on carbon tetrachloride (CCl_4)-induced acute liver injury in rats. **Methods** A total of 48 SPF grade Wistar rats were randomly divided into the control group, the model group, the etomidate 0.5 mg/kg group, the etomidate 1 mg/kg group, the etomidate 2 mg/kg group and the silymarin (SIL) group (200 mg/kg, as positive control), with 6 rats in each group. The control group and the model group received intravenous injection of 0.2 mL of normal saline, the etomidate groups received intravenous injection of 0.5 mg/kg, 1 mg/kg, and 2 mg/kg of etomidate 0.2 mL, and the SIL group received intravenous injection of 200 mg/kg of SIL 0.2 mL, once a day for 14 consecutive days. Then, the model group, the etomidate groups, and the SIL group received intraperitoneal injection of 0.2% CCl_4 (10 mL/kg), and the control group received intraperitoneal injection of an

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[通信作者] 李 雯,E-mail:ww554006722@163.com

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equal amount of olive oil. After 24 hours, the rats were killed. The serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were determined. HE staining was used to evaluate the pathological damage of liver tissue. The levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in liver tissue were detected by ELISA. The levels of superoxide dismutase (SOD) and malondialdehyde (MDA) were detected. TUNEL staining was used to evaluate apoptosis in liver tissue. The positive expression of NF-κB p65 in rat liver tissue was detected by immunohistochemistry. The expression of related proteins was detected by Western blot. **Results** Compared with the control group, the levels of serum ALT and AST in the model group were significantly increased, the pathological damage of liver tissue was obvious, the levels of TNF-α and IL-6, and MDA levels were significantly increased, the SOD level was significantly decreased, the number of liver tissue apoptosis was significantly increased, the Bax/Bcl-2, cleaved caspase-3/caspase-3, and p-NF-κB p65/NF-κB p65 were significantly increased, with statistically significant differences (P<0.05). Compared with the model group, the pathological damages of liver tissue in the etomidate 1 mg/kg group, the etomidate 2 mg/kg group and the SIL group was obviously improved, the release of inflammatory factors, oxidative stress, liver tissue apoptosis were inhibited, and the p-NF-κB p65/NF-κB p65 was reduced. **Conclusion** Etomidate has a good alleviating effect on CCl_4-induced acute liver injury in rats, and its mechanism may be related to the inhibition of NF-κB pathway.

Keywords: etomidate; carbon tetrachloride; liver injury; interleukin-6; malondialdehyde; NF-κB p65

急性肝损伤是一种由多种原因引起的肝功能异常,病因包括病毒感染、滥用药物、大量饮酒及摄入有毒物质[1]。持续进行性的肝细胞损伤将导致慢性炎症、纤维化甚至肝硬化[2]。一直以来,人们对肝损伤进行了广泛的研究,但尚未找到有效的治疗措施。依托咪酯是一种临床静脉麻醉剂,具有很强的抗氧化和抗炎作用,可通过减少心功能不全和氧化应激来减轻大鼠的缺血/再灌注损伤[3-4]。依托咪酯对急性肺损伤小鼠具有良好的抗氧化和抗炎作用,并可通过调节核因子E2相关因子2/血红素加氧酶-1信号通路来减轻高氧诱导的肺损伤[5]。但依托咪酯对肝损伤的作用目前尚不清楚。四氯化碳(carbon tetrachloride,CCl_4)是一种经典的肝毒性药物,用于动物模型中急性和慢性肝损伤的诱导[6]。本研究以CCl_4诱导的急性肝损伤大鼠为模型,探讨依托咪酯对肝损伤的影响及相关机制,以期为临床急性肝损伤的治疗提供参考。

1 材料与方法

1.1 主要试剂和仪器

依托咪酯和水飞蓟素(silymarin,SIL)购自美国Sigma公司。HE染色试剂盒、BCA蛋白浓度测定试剂盒、超敏ECL化学发光试剂盒购自上海碧云天公司;肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)和白细胞介素-6(interleukin-6,IL-6)ELISA试剂盒购自上海酶联生物科技有限公司;超氧化物歧化酶(superoxide dismutase,SOD)和丙二醛(malondialdehyde,MDA)测定试剂盒购自南京建成生物工程研究所;蛋白提取试剂盒购自北京Promega公司;试验所用抗体均购自上海艾博抗生物科技有限公司。全自动生化分析仪购自日本日立公司;MultiskanSkyHigh-全波长酶标仪购自美国ThermoFisher公司;BX43光学显微镜购自日本奥林巴斯公司;ChemiDoc XRS+凝胶成像系统购自美国Bio-rad公司。

1.2 动物模型建立

动物实验经河北北方学院附属第一医院伦理委员会审核批准(2021041),符合3R原则。48只SPF级健康雄性Wistar大鼠(6周龄,180~200 g)购自河北省实验动物中心[动物生产许可证号:SCXK(冀)2018-004],饲养于25 ℃、50%~70%湿度环境中,12 h光照/黑暗循环,自由获取食物和水,适应性饲养1周。将大鼠随机分为对照组、模型组(CCl_4)、依托咪酯0.5 mg/kg组、依托咪酯1 mg/kg组、依托咪酯2 mg/kg组和SIL组(200 mg/kg SIL,阳性对照),每组8只。对照组和模型组静脉注射0.2 mL生理盐水,依托咪酯给药组参考文献[4]分别静脉注射0.5 mg/kg、1 mg/kg、2 mg/kg依托咪酯0.2 mL,SIL组静脉注射200 mg/kg SIL 0.2 mL,每天1次,连续给药14 d。末次给药1 h后模型组、依托咪酯给药组和SIL组均腹腔注射0.2% CCl_4溶液(10 mL/kg),对照组腹腔注射等量橄榄油。24 h后,使用苯巴比妥对大鼠实施安乐死,通过心脏穿刺采集血样;取出肝组织,并制备肝组织切片,其余于液氮中冷冻,用于后续实验。

1.3 血清肝功能指标检测

采集血液后于4 ℃以3 000 r/min离心30 min分离血清,使用全自动生化分析仪测定各组大鼠血清丙氨酸氨基转移酶(alanine aminotransferase,ALT)和天冬氨酸氨基转移酶(aspartate aminotransferase,AST)水平。

1.4 HE染色

取部分肝组织置于4%多聚甲醛中固定24 h,随后对肝组织进行脱钙并用石蜡包埋,制成5 μm厚的切片,于室温下苏木素染色5 min,随后用伊红染色2 min。光学显微镜下观察肝组织病理学变化。

1.5 ELISA测定大鼠肝组织中TNF-α和IL-6水平

将大鼠肝组织加入适量生理盐水捣碎,3 000 r/min离心10 min,取上清液。分别将标本或不同浓度标准品加入到相应孔中(每孔50 μL),立即加入50 μL生物素化抗体37 ℃孵育30 min。甩去孔内液体,每孔加入80 μL的亲和链酶素-HRP,轻轻振荡混匀,37 ℃孵育30 min。洗涤3次后,每孔加入底物A、B各50 μL,轻轻振荡混匀,37 ℃避光孵育10 min。加入50 μL终止液,立即使用酶标仪测量450 nm波长处的吸光度。

1.6 SOD和MDA水平检测

按试剂盒说明书操作,采用羟胺法测定SOD水平,TBA法测定MDA水平。

1.7 TUNEL染色

对制备的石蜡切片进行脱蜡、再水化和洗涤。然后,根据说明书用TUNEL反应混合物培养切片。光学显微镜下选择5个随机视野观察肝组织细胞凋亡情况。

1.8 免疫组化

肝组织用4%福尔马林固定,石蜡包埋,切成3 μm厚的切片。将切片置于二甲苯中常规脱蜡并在梯度乙醇中再水化。用5%正常山羊血清封闭1 h,与原代抗体NF-κB p65(1∶500)共孵育过夜。PBS清洗3次后,室温下与二抗孵育30 min,光学显微镜下分析切片。

1.9 Western blot

从肝组织中提取总蛋白并用BCA试剂盒检测。将每个样品中的总蛋白(20 μg)上样到10%十二烷基硫酸钠聚丙烯酰胺凝胶中电泳分离,然后转移到聚偏二氟乙烯膜上。5%脱脂牛奶室温封闭膜1 h,并与Bcl-2(1∶500)、Bax(ab32502,1∶1 000)、cleaved caspase-3(1∶500)、caspase-3(1∶500)、NF-κB p65(1∶500)、p-NF-κB p65(1∶500)、β-actin(1∶1 000)一抗在4 ℃下孵育过夜。第2天取膜,用TBST洗涤3次,室温下与HRP标记的山羊抗兔IgG二抗孵育1 h,然后用TBST洗涤3次。ECL显色曝光,采用Image J分析条带的灰度值。

1.10 统计学分析

采用SPSS 21.0软件分析数据,结果用均数±标准差($\bar{x}\pm s$)表示,多组差异比较采用单因素方差分析,组间两两比较采用t检验,P<0.05为差异有统计学意义。

2 结果

2.1 依托咪酯对CCl_4诱导的急性肝损伤大鼠肝功能的影响

与对照组相比,模型组大鼠血清AST和ALT水平均显著升高(P<0.05);与模型组相比,依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组血清AST和ALT水平显著降低(P<0.05)。依托咪酯2 mg/kg组与SIL组血清AST和ALT水平比较差异无统计学意义(P>0.05),见表1。

表1 各组大鼠肝功能指标比较($\bar{x}\pm s$,IU/L)

组别	AST	ALT
对照组	148.61±27.05	36.59±11.97
模型组	373.52±43.35*	154.38±22.42*
依托咪酯0.5 mg/kg组	365.13±38.42	148.32±26.94
依托咪酯1 mg/kg组	276.71±28.74#	108.46±15.48#
依托咪酯2 mg/kg组	198.39±36.13#	78.06±18.73#
SIL组	176.14±47.35#	67.02±13.54#

*:与对照组相比,P<0.05;#:与模型组相比,P<0.05

2.2 依托咪酯对CCl_4诱导的急性肝损伤大鼠肝组织病理损伤的影响

与对照组相比,模型组大鼠肝细胞结构紊乱,可见大量中性粒细胞浸润;与模型组相比,依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组肝组织病理损伤程度显著改善。依托咪酯2 mg/kg组与SIL组肝组织病理损伤无明显变化,见图1。

2.3 依托咪酯对CCl_4诱导的急性肝损伤大鼠炎症因子和氧化应激的影响

与对照组相比,模型组大鼠肝组织中TNF-α、IL-6、MDA水平显著升高(P<0.05),SOD水平显著降低(P<0.05);与模型组相比,依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组中TNF-α、IL-6、MDA水平显著降低(P<0.05),SOD水平显著升高(P<0.05),见表2。

2.4 依托咪酯对CCl_4诱导的急性肝损伤大鼠肝组织细胞凋亡的影响

与对照组相比,模型组肝组织细胞凋亡数目显著增加;依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组肝组织细胞凋亡现象显著缓解。Western blot结果显示,与对照组比较,模型组肝组织中Bax/Bcl-2和cleaved caspase-3/caspase-3显著升高(P<0.05);与模型组比较,依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组Bax/Bcl-2和cleaved caspase-3/caspase-3显著降低(P<0.05),见图2。

2.5 依托咪酯对CCl_4诱导的急性肝损伤大鼠肝组织中NF-κB p65表达的影响

免疫组化结果显示,与对照组相比,模型组大鼠肝组织中NF-κB p65阳性表达显著增加;与模型组比较,依托咪酯1 mg/kg组、依托咪酯2 mg/kg组大鼠肝组织中NF-κB p65阳性表达降低,见图3a。Western blot

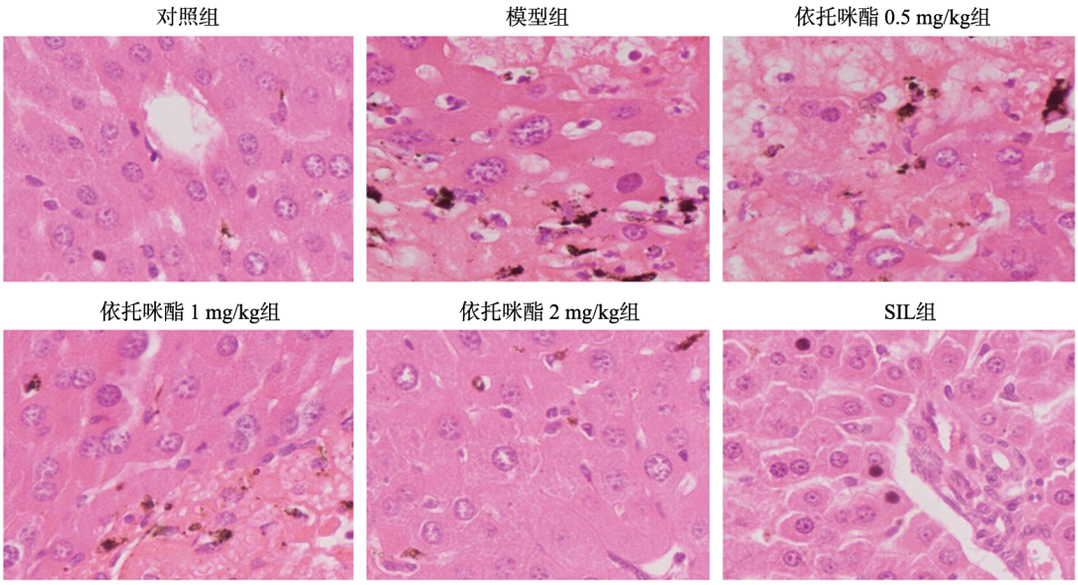
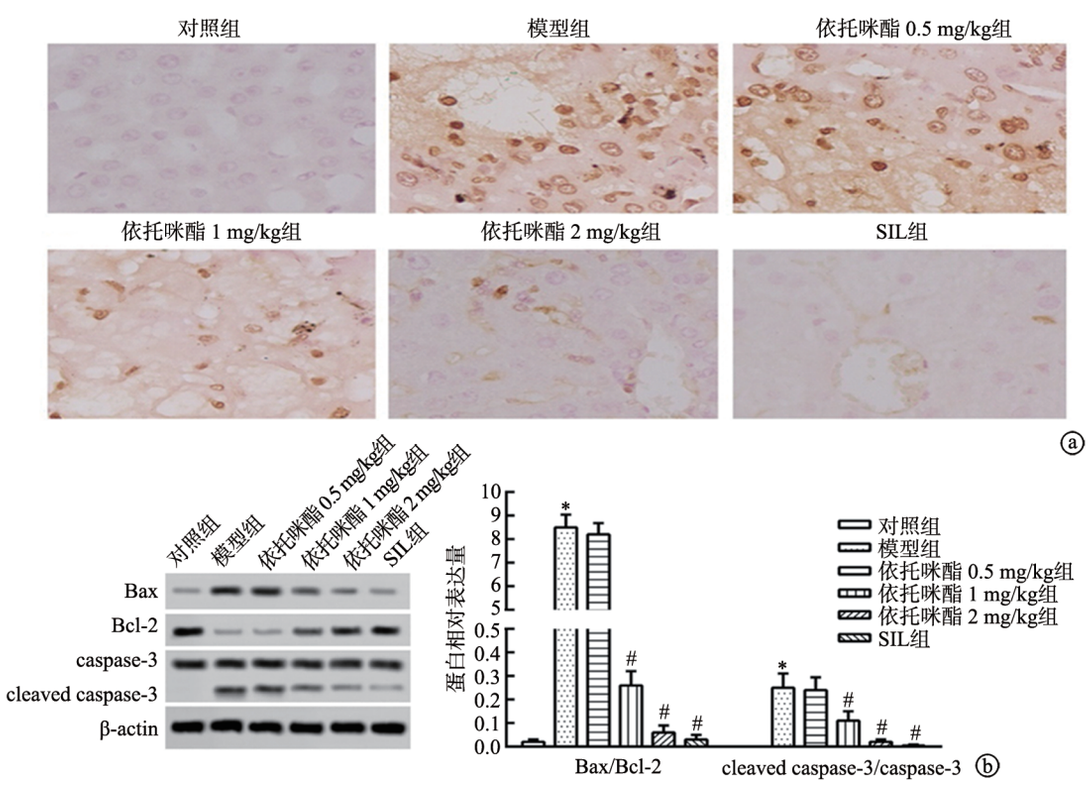


图1　HE染色观察各组大鼠肝组织病理损伤(×400)

表2　各组大鼠肝组织中TNF-α、IL-6、SOD、MDA水平比较($\bar{x}\pm s$)

组别	TNF-α(pg/mg)	IL-6(pg/mg)	SOD(U/mg)	MDA(nmol/mg)
对照组	31.78±2.17	8.26±0.53	8.37±0.17	0.22±0.03
模型组	83.14±5.20*	33.98±1.81*	4.18±0.11*	0.73±0.05*
依托咪酯0.5 mg/kg组	80.74±4.98	30.79±1.64	4.02±0.14	0.69±0.07
依托咪酯1 mg/kg组	61.02±6.87#	21.32±1.30#	5.96±0.09#	0.52±0.04#
依托咪酯2 mg/kg组	47.82±4.67#	11.28±1.12#	6.05±0.20#	0.34±0.05#
SIL组	44.54±7.53#	10.97±1.47#	6.11±0.18#	0.29±0.08#

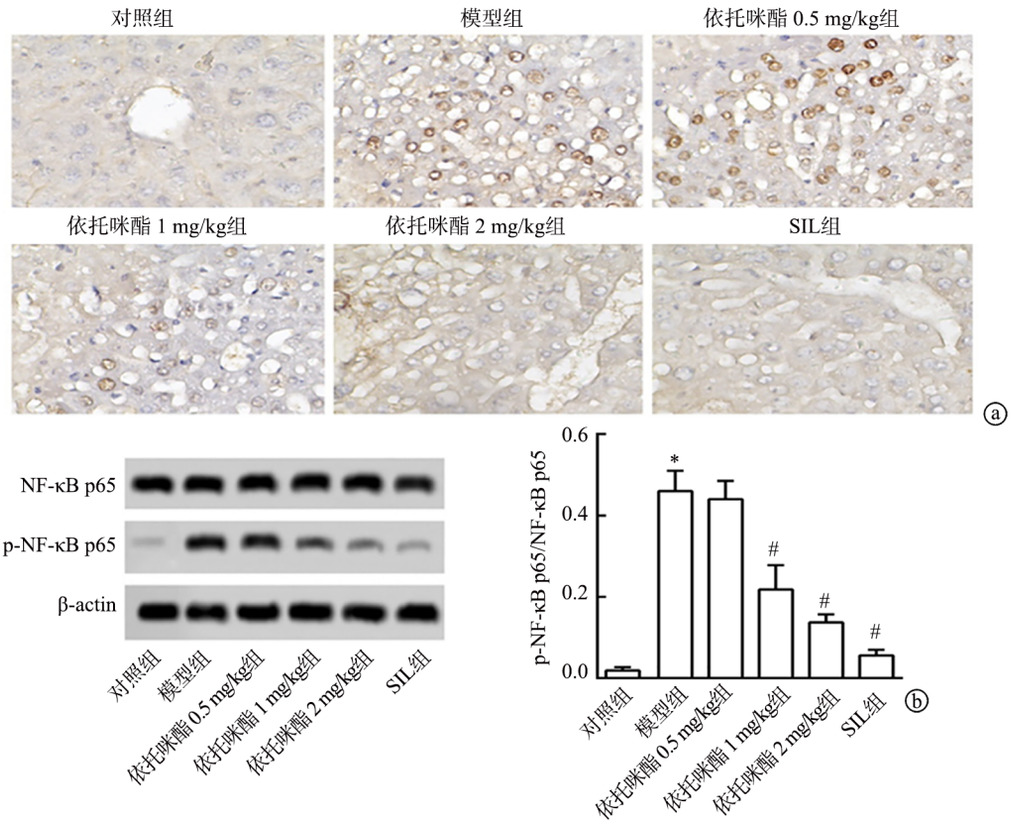
*:与对照组相比,$P<0.05$;#:与模型组相比,$P<0.05$



a:TUNEL染色图(×400);b:Western blot检测凋亡相关蛋白的表达　*:与对照组相比,$P<0.05$;#:与模型组相比,$P<0.05$

图2　各组大鼠肝组织细胞凋亡情况

结果显示，与模型组比较，模型组肝组织中p-NF-κB p65/NF-κB p65显著增加（$P<0.05$）；与模型组比较，依托咪酯1 mg/kg组、依托咪酯2 mg/kg组、SIL组中NF-κB p65的磷酸化被逆转（$P<0.05$），见图3b。



a：免疫组化图（×400）；b：Western blot检测p-NF-κB p65/NF-κB p65水平 *：与对照组相比，$P<0.05$；#：与模型组相比，$P<0.05$

图3 各组大鼠肝组织中NF-κB p65表达情况

3 讨论

CCl_4诱导的肝损伤动物模型是研究药物保肝作用的常用方法。肝损伤可通过测定血清AST和ALT水平来评估[7]。本研究结果显示，依托咪酯治疗可显著降低AST和ALT水平；HE染色显示，CCl_4诱导的急性肝损伤大鼠肝细胞损伤伴有中性粒细胞浸润，而依托咪酯可明显改善肝损伤。以上结果表明，依托咪酯对CCl_4诱导的肝毒性具有改善作用。

TNF-α、IL-1β和IL-6是炎症反应中的重要细胞因子，随着肝损伤的进展，其水平不断升高[8]。Kupffer细胞产生的TNF-α可通过激活T细胞和巨噬细胞来诱导免疫应答，进而刺激其他炎症细胞因子的分泌和NO的产生[6]。IL-6刺激肝细胞产生各种急性期蛋白，保护肝细胞免受损伤[9]。本研究结果显示，依托咪酯可显著降低CCl_4诱导的大鼠血清中的TNF-α和IL-6水平，提示依托咪酯可抑制肝损伤引起的炎症因子释放。MDA是脂质过氧化的终产物，由自由基攻击质膜形成，常被用作脂质过氧化损伤的标志物[10]。MDA水平的增加表明脂质过氧化增强，从而导致肝损伤和抗氧化防御系统的失活[11]。SOD是重要的抗氧化酶，可以阻断脂质过氧化链[12]。本研究结果表明，CCl_4显著增强大鼠的氧化应激反应，而依托咪酯可使MDA水平降低，SOD水平升高，提示依托咪酯可抑制CCl_4引起的氧化应激。说明依托咪酯可通过降低炎症因子水平，增加肝抗氧化活性，从而保护肝免受肝毒性损伤。

细胞凋亡发生受促凋亡蛋白Bax和抗凋亡蛋白Bcl-2之间的平衡调节[13]。线粒体应激导致细胞色素C释放到细胞质中，进而导致caspase-9和caspase-3的激活，引发细胞凋亡[14]。本研究结果显示，CCl_4可导致肝细胞凋亡数量和促凋亡标志物cleaved caspase-3和Bax显著增加，这与其他研究的结果一致[15]；依托咪酯的预防性给药导致Bax/Bcl-2和cleaved caspase-3/caspase-3降低以及肝细胞凋亡数量的减少，表明依托咪酯可通过抑制细胞凋亡减轻CCl_4诱导的肝损伤。肝损伤后，NF-κB及其下游信号被激活，促进TNF-α、

IL-6和IL-1β等多种炎症细胞因子水平升高[16]。有研究表明,合欢皮乙醇提取物通过调控NF-κB通路减轻CCl_4诱导的小鼠急性肝损伤[17]。本研究结果显示,CCl_4诱导肝组织细胞中p-NF-κB p65/NF-κB p65水平升高,依托咪酯治疗可显著降低p-NF-κB p65/NF-κB p65的水平,提示依托咪酯可通过NF-κB通路显著减轻炎症反应以及降低肝细胞损伤的程度,但其机制需要进一步证实。

综上所述,依托咪酯对CCl_4诱导的大鼠急性肝损伤具有较好的缓解作用,其机制可能与抑制NF-κB通路有关。

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