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姜黄素预处理对干热环境下中暑大鼠肾组织 NF-κB p65 及炎症因子表达的影响 *

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摘要 目的:探讨不同剂量姜黄素对沙漠干热环境下大鼠肾组织炎症因子及 NF-κB p65 表达的影响。**方法:**将 50 只 SD 大鼠随机(随机数字法)分为五组(n=10):常温对照组、干热对照组、姜黄素低浓度组(50 mg/kg)、姜黄素终浓度组(100 mg/kg)、姜黄素高浓度组(200 mg/kg)。常温对照组及干热对照组均给予 0.9 %生理盐水灌胃,姜黄素组大鼠给予不同浓度姜黄素溶液灌胃,连续 7 天。在干热环境中放置 150 分钟后,麻醉处死大鼠,留取血液、肾组织进行分析。观察各组大鼠肾组织形态,检测肾组织中 IL-1β、IL-6、TNF-α 以及 NF-κB p65 表达及血清肌酐、尿素氮以及尿液中肾损伤分子 1(KIM-1)、中性粒细胞明胶酶相关载脂蛋白(NGAL)的水平。**结果:**干热对照组大鼠血清肌酐、尿素以及尿液中 KIM-1、NGAL 水平均较常温对照组明显升高(P<0.05),不同浓度姜黄素预处理组大鼠血清肌酐、尿素以及尿液中 KIM-1、NGAL 均较干热对照组有所下降,且差异具有统计学意义(P<0.05)。干热对照组大鼠肾组织中 IL-1β、IL-6、TNF-α 以及 NF-κB p65、磷酸化 IκB-α 的表达较常温对照组显著增加(P<0.05)。姜黄素处理组大鼠随着姜黄素浓度的升高各指标较干热对照组呈不同程度的下降趋势(P<0.05)。**结论:**姜黄素对于干热环境下大鼠肾损伤的保护作用,可能是与抑制 NF-κB 的表达降低细胞炎症反应水平有关。

关键词:急性肾损伤;干热环境;姜黄素;炎症反应;核因子 -κB

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The Effect of Curcumin on the Expressions of Inflammatory Factors and NF-κB p65 in the of Dry-heat Environment Induced Rats*

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ABSTRACT Objective: To investigate the influence of different doses of curcumin on the inflammatory factors and the expression of NF-κB p65 in kidney tissue of rats in the dry-heat environment. **Methods:** 50 SD rats were randomly divided into five groups (n = 10): normal temperature control group, dry-heat control group and curcumin pretreated groups including low dose (50 mg/kg), moderate dose (100 mg/kg), high dose (200 mg/kg) groups. The two control groups were given 0.9 % saline by gavage, the curcumin group were given different concentrations of curcumin solution by gavage. All the rats were treated for seven consecutive days. The curcumin was dissolved in 0.5% sodium carboxymethylcellulose (CMCNa) solution. The rats were put in the dry-heat environment for 150 min, anaesthetized and sacrificed at 150min. The pathological changes of renal tissue and the changes of the inflammatory factors such as IL-1β, IL-6, TNF-α in the renal tissue and kidney injury molecule 1 (KIM-1), neutrophil gelatinase lipoprotein (NGAL) of urine were observed. Meanwhile, the expression of NF-κB p65 in renal tissue were observed. **Results:** Compared with the normal temperature group, the creatinine, blood urea nitrogen (BUN) in the serum and Kidney Injury Molecule-1 (KIM-1), Neutrophil gelatinase-associated lipocalin (NGAL) in the urine were significantly increased in the dry-heat control group (P<0.05). However, with the pretreatment of different doses of curcumin, the serum BUN, Cr and KIM-1, NGAL in the urine showed downward trend compared with the dry-heat control group (P<0.05). The flammatory factors IL-1β, IL-6, TNF-α in the kidney tissue were also significantly increased in the dry-heat control group compared with the normal control group (P<0.05), with the pretreatment of different dose of curcumin, the IL-1β, IL-6, TNF-α of kidney tissue were decreased compared with the dry-heat control group (P<0.05). Meanwhile, the expressions of NF-κB p65 and phosphorylated IκB-α in kidney tissue were also increased in the normal temperature control group (P<0.05). The expression of NF-κB p65 and phosphorylated IκB-α level were declined in the curcumin pretreated groups (P<0.05). **Conclusion:** Curcumin could obviously reduce the renal inflammation and pathological changes in the rat under dry-heat environment, which might be related to the

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inhibition of the NF-κB p65 expression and inflammatory factors in the kidney.

Key words: Acute renal injury; Dry-heat environment; Curcumin; Inflammatory reaction

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前言

中暑是以核心体温升高以及中枢神经系统症状为特征的致命性疾病[1,2],常表现为谵妄、惊厥、昏迷以及核心体温≥ 40 ℃等。早在 2002 年,中暑被重新定义为因热细胞毒性、全身炎症反应综合征 (systemic inflammatory response syndrome,SIRS)以及凝血障碍导致的多器官功能障碍 (multiple organ dysfunction syndrome,MODS)[3]。中暑常发生于高温环境中,而沙漠干热环境具有气温高、湿度低以及紫外线强等特点,沙漠地区的特殊工作人员、战士以及旅行者等一旦发生中暑常因体液丢失过多等造成严重后果。中暑时全身有效循环血量减少,机体为保证重要脏器的血流供应会相应减少外周组织及肾脏血流,肠道损伤造成细菌入血而引发全身炎症反应综合征(SIRS)[4]。急性肾损伤(acute kidney injury,AKI)是中暑的并发症之一。肾脏处于缺血缺氧状态引发细胞内的氧化应激以及炎症反应,另外热应激对细胞的直接毒性也造成肾细胞进一步损伤。

姜黄素是一种广泛应用的膳食色素,根据现阶段的研究普遍认为姜黄素具有抗炎抗氧化的药理作用。姜黄素对各种急慢性炎症反应均具有抗炎作用[5]。研究表明姜黄素可抑制 NF-κB 的表达以及炎性细胞前炎症细胞因子(TNF-α、IL-β 和 IL-8)的产生,减轻由同型半胱氨酸诱导的内皮细胞损伤 [6]。我们前期研究表明干热环境下肾脏的损伤随着干热环境持续时间延长而加重,并且姜黄素可提高干热环境下大鼠的生存率[7,8]。因此,我们推测姜黄素对于干热环境下大鼠肾损伤有保护作用。本研究通过复制干热环境大鼠中暑模型,并在造模前给予不同浓度姜黄素进行预处理,以探讨姜黄素对干热环境下大鼠肾损伤的保护足以及其可能的机制。

1 材料与方法

1.1 实验动物

50 只成年雄性 SD 大鼠(180~220 g)购自新疆医科大学实验动物中心,饲养温度(22± 1)℃,各 12h 白天与黑夜循环的房子中,饲料与水随意供应。

1.2 实验分组与处理

50 只雄性 SD 大鼠随机分为 5 组(n=10):常温对照组、干热对照组、姜黄素 50 mg/kg 组、姜黄素 100 mg/kg 组、姜黄素 200 mg/kg 组。常温对照组及干热对照组大鼠给予 0.9 %生理盐水灌胃,姜黄素组分别给予不同浓度的姜黄素溶液灌胃,连续灌胃 7 天。

1.3 主要药品和试剂

姜黄素由东京化成工业株式会社生产, 溶解于 0.5%羧甲基纤维素钠(CMCNa)中使用。大鼠肾损伤分子 -1(kidney injury molecule-1,KIM-1)、中性粒细胞明胶酶相关脂质运载蛋白(neutrophil gelatinase associated lipocalin,NGAL)、白介素 IL-1β、白介素 IL-6、肿瘤坏死因子 TNF-α ELISA 试剂盒购自安徽巧伊科技有限公司;核因子 NF-κB p65 抗体购自于 Abcam 公司。

1.4 干热环境大鼠中暑模型的复制、血液、尿液、肾组织的收集

常温对照组大鼠置于常温环境中 (温度 20± 2℃, 湿度 40-50 %)。其余各组大鼠参照本课题组已建立的干热环境下大鼠中暑模型进行复制[9],将大鼠置于模拟沙漠干热环境中(西北特殊环境人工实验舱,中国人民解放军乌鲁木齐总医院研制),设置温度 41± 0.5 ℃,湿度 10± 1 %,每 30 min 监测大鼠核心体温。150 min 取出大鼠,3 %戊巴比妥麻醉各组大鼠,采集大鼠下腔静脉血液进行血液指标分析,穿刺膀胱收集尿液进行肾损伤指标分析,处死大鼠分离肾组织进行后续分析。

1.5 检测方法

1.5.1 **肌酐**(creatinine,CREAT)、**尿素**(urea) 血液标本 3000 rpm 离心 10 min,取上清液 -20 ℃保存,肌酐以及尿素由全自动生化分析仪检。

1.5.2 **肾损伤分子** -1(KIM-1)、**中性粒细胞明胶酶相关载脂蛋白**(NGAL) ELISA 法检测尿液中肾损伤分子 -1(KIM-1)、中性粒细胞明胶酶相关载脂蛋白(NGAL),试剂盒由安徽巧伊公司提供,根据说明书操作。

1.5.3 **组织病理学** 肾组织于 10 %中性甲醛中固定,脱水、石蜡包埋,切片,脱蜡,HE 染色,并在双盲的条件下拍摄照片。

1.5.4 **肾组织中** IL-1β、IL-6、TNF-α **水平的测定** 取 0.1 g(± 0.05 g)肾组织置于玻璃匀浆器中,剪刀剪碎组织,加入 200 μL 磷酸盐缓冲液研磨至无块状组织, 加入 700 μL磷酸盐缓冲液使组织匀浆的终浓度为 10 %,3500 rpm 离心 10 min 取上清液于 -20 ℃保存。ELISA 法测定肾组织中 IL-1β、IL-6、TNF-α 的水平,根据说明书操作。试剂盒由安徽巧伊公司提供。

1.5.5 **蛋白质印迹法检测肾组织中** NF-κB p65 **的表达** 取 0.1 g(± 0.05 g)冻存肾组织液氮研磨至无块状,加入 1 mL 裂解液冰上裂解 2 h,离心取上清,按照 1:1 比例加入 2× 上样缓冲液沸水中煮沸 8 min,离心取上清液 -80 ℃保存。由 BCA 方法检测进行蛋白定量(Pierce™ BCA Protein Assay Kit, Thermo Fisher Scientific),Western Blot 法检测肾组织匀浆 NF-κB p65 表达,β-actin 为内参,蛋白上样量为 120 ng,电泳电压为 80 V 转 120 V,电泳完成后转印 20 min,电流 0.25 A。5 %脱脂奶粉封闭 2 h,4 ℃一抗孵育过夜。洗膜 5 次,二抗孵育 2 h,洗膜 5 次。化学发光法进行图像采集,进一步进行灰度分析。

1.6 统计学处理

数据采用 SPSS 21.0 统计软件进行统计。计量资料用均数± 标准差表示,使用单因素方差分析比较各组大鼠之间均数的差异,进一步两组间比较采用 SNK-q 检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 各组血清肌酐、尿素、及尿液中 KIM-1、NGAL 水平的比较

图 1 所示,与常温对照组血清中肌酐(25.7± 4.37)、尿素

(5.38± 0.48) 含量相比，干热对照组大鼠血清肌酐 (85.67± 4.08)、尿素(12.63± 0.68)水平明显上升，差异具有统计学意义(P<0.05)，不同浓度姜黄素预处理大鼠血清中肌酐以及尿素含量较干热对照组均有所下降且差异具有统计学意义(P<0.05)。常温对照组大鼠尿液中 KIM-1 (147.30± 37.63) 及 NGAL (121.86± 38.34) 呈低表达，干热对照组尿液中 KIM-1 (1090.50± 84.00)、NGAL(2203.25± 169.06)水平均较常温对照组明显升高(P<0.05)，而姜黄素预处理组尿液中 KIM-1 以及 NGAL 水平较干热对照组均有下降(P<0.05)。

表 1 血清中肌酐、尿素与尿液中 KIM-1、NGAL 含量的变化

Table 1 The changes of creatinine and urea in serum and the concentrations of NGAL and KIM - 1 in urine

	NT control	DH control	50 mg/kg	100 mg/kg	200 mg/kg
Creatinine(μmol/L)	27.5± 4.37#	85.67± 4.08*	81.67± 1.75*#	74.33± 2.88*#	60.83± 3.43*#
BUN(mmol/L)	5.38± 0.48#	12.63± 0.68*	10.70± 0.61*#	10.37± 1.06*#	9.43± 0.47*#
KIM-1(pg/mL)	147.30± 37.63#	1090.50± 84.00*	945.73± 48.07*#	639.17± 44.71*#	592.67± 34.39*#
NGAL(ng/mL)	121.86± 38.34#	2203.25± 169.06*	1678.07± 322.32*#	1212.51± 134.16*#	526.07± 53.79*#

Note: Data were expressed as ± SD, n=10;#: Significantly different compared to DH control groups(P<0.05),

*: Significantly different compared to NT control groups(P<0.05).

2.2 各组肾脏形态学的比较

常温对照组肾脏组织未见明显病理变化，肾小球与肾小管形态均正常。干热对照组肾组织可见明显病理变化，肾小囊变窄，近曲小管上皮细胞水肿，肾小管管腔变窄，近曲小管部分含蛋白管型。与干热对照组相比，姜黄素 100 mg/kg 组与 200 mg/kg 组肾组织病理变化明显减轻，可见肾小管内管型消失，仅有肾小管上皮肿胀，管腔内有脱落的上皮细胞。

2.3 各组肾组织 IL-1、IL-6、TNF-α 的表达的比较

干热对照组大鼠肾组织中 IL-1(46.82± 0.99)、IL-6(43.06± 5.77)、TNF-α(46.88± 0.99)的表达较常温对照组肾组织中 IL-1 (29.49± 1.06)、IL-6(21.72± 3.15)、TNF-α(29.52± 1.07)的表达明显上升，差异具有统计学意义(P<0.05)。不同剂量姜黄素预处理组肾组织中 IL-1、IL-6、TNF-α 的表达均较干热对照组有所下降(P<0.05)，其中姜黄素预处理 200mg/kg 的大鼠肾组织内 IL-1(41.60± 0.95)、IL-6(30.08± 3.04)、TNF-α(36.71± 1.20)的表达下降最明显(P<0.05)。IL-6 的表达在姜黄素 50 mg/kg 组(37.26± 6.63)与姜黄素 100 mg/kg(34.64± 4.99)组之间无统计学差异(P>0.05)。

2.4 各组肾组织中 NF-κB p65 表达的比较

干热对照组大鼠肾组织中 IκB 与 NF-κB p65 的表达显著高于常温对照组，经姜黄素预处理 100 mg/kg 组与 200 mg/kg 组的大鼠肾组织中磷酸化的 IκB-α 与 NF-κB p65 的表达量较干热对照组大鼠明显下降(P<0.05)，见图 2。

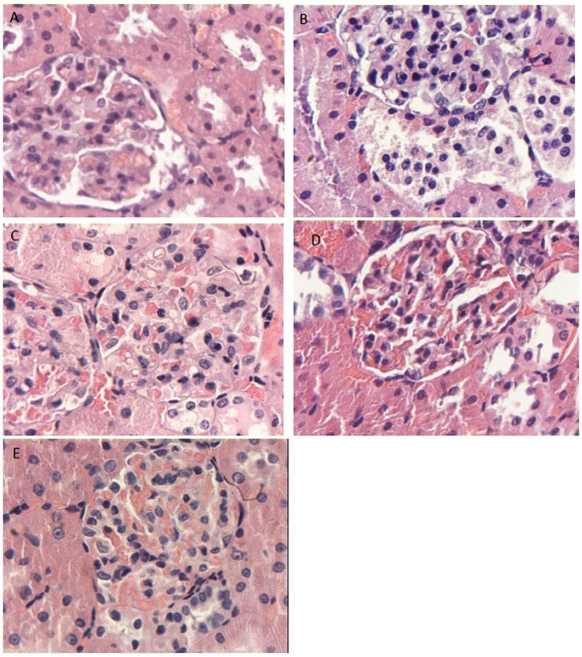

图 1 各组大鼠肾组织形态比较

Fig 1 Comparison of the morphology of kidney tissue between different groups

Note: A was the normal temperature control group, the glomerular and tubular structures were clear, and the arrangement of cells were rule. B was the dry-heat control group, glomerular cell showed vacuolation, the surrounding renal tubular epithelial cell swelling, shedding,and a large number of renal tubules in the medulla contained cast. C was the curcumin 50 mg/kg group, the glomerular cells were swollen, the glomerular capsule cavity was narrow, and renal tubules in the medulla contained cast. D was the curcumin 100 mg/kg group, the renal tubular cells were found swell, but no shedding, and the epithelial cells of renal tubular epithelial cells in medulla had fell off. E was the curcumin 200 mg/kg group, which showed that the glomerular capsule was narrow, and the epithelial cells were swollen and partly detached.

3 讨论

干热环境下，随着体液大量丢失以及核心体温升高，机体血液重新分布，肾脏血供减少，肾脏细胞处于缺血缺氧状态，同时高温可对细胞有直接的热细胞毒性[4]。本研究结果显示将大鼠置于干热环境中 150 分钟之后，肾组织可见明显病理变化以及血清中肌酐和尿素的明显升高，尤其是反应肾小管早期损伤的 KIM-1 与 NGAL 呈现倍数增长。同时，干热对照组大鼠肾组织中 IL-1β、IL-6、TNF-α 的含量呈上升趋势，肾组织中 NF-kB p65 的表达增加。有研究显示在中暑动物血清 IL-1β、IL-6、TNF-α 等炎症因子的含量显著升高[10]。因此，干热环境下的急性肾损伤可能与机体内失控的炎症反应以及热应激激活

表 2 姜黄素对肾组织中炎症因子含量的影响

Table 2 The effects of curcumin on inflammatory factors in the kidney tissues

	NT control	DH control	50 mg/kg	100 mg/kg	200 mg/kg
IL-1β(pg/mL)	29.49± 1.06#	46.82± 0.99*	43.26± 0.96*#	41.60± 0.93*#	36.11± 0.78*#
IL-6(pg/mL)	21.72± 3.15#	43.06± 5.77*	37.26± 6.63*#	34.64± 4.99*#	30.08± 3.04*#
TNF-α(pg/mL)	29.52± 1.07#	46.88± 0.95*	43.18± 0.95*#	41.51± 0.78*#	36.71± 1.20*#

Note: Data were expressed as ± SD, n=10; ;#: Significantly different compared to DH control groups(P<0.05), *: Significantly different compared to NT control groups(P<0.05).

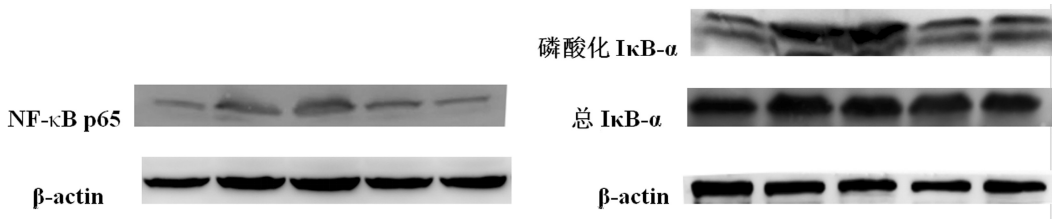

图 2 各组大鼠肾组织中 NF-κB p65 以及 IκB-α 表达的比较

Fig 2 Comparison of the NF-kappa B p65and I kappa B alpha expressions in the kidney tissues between different groups

表 3 各组大鼠肾组织中 NF-κB p65 以及 IκB-α 表达的比较

Table 3 Comparison of the NF-kappa B p65and I kappa B - alpha expressions in the kidney tissues between different groups

	NT control	DH control	50 mg/kg	100 mg/kg	200 mg/kg
Relative density of NF-κB	0.187± 0.0057#	0.258± 0.0067*	0.151± 0.0062*#	0.115± 0.0058*#	0.121± 0.0036*#
Relative density of phosphorylated IκB-α	0.0508± 0.0023#	0.147± 0.0056*	0.124± 0.0070*#	0.108± 0.0053*#	0.099± 0.0056*#
Ratio of IκB-α/total IκB	0.713± 0.0064#	0.179± 0.0076*	0.160± 0.0076*#	0.142± 0.0063*#	0.133± 0.0034*#

Note: a was the change of expression of NF-κB p65 and b was the change of expression of IκB, Data were expressed as ± SD, n=10; # : Significantly different compared to DH control groups(P<0.05), *: Significantly different compared to NT control groups(P<0.05).

NF-κB 进一步加剧细胞内的炎症反应有关。NF-κB 作为核转录因子家族中重要成员在调控炎症因子的表达、细胞周期、细胞分化等方面有重要作用 [11-15]。有功能活性的 NF-κB 主要作为 Rel 家族的亚基组成的异源二聚体存在，通常在胞浆中与抑制蛋白 Ikb 结合形成无活性的复合体。当细胞细胞暴露于外部刺激时，引起 IκB 快速磷酸化随后被蛋白酶体降解。IκB 解离后 NF-κB 二聚体转位到细胞核，通过结合顺式作用元件 κB 而诱导大量的靶基因表达、转录、合成细胞因子，细胞粘附分子，生长因子等等[16]。实验中发现干热环境下胞浆中磷酸化的 IκB-α 表达大量增加，从而使 NF-κB p65 向核内转移增多，引起炎症因子的合成及释放。

现阶段中暑尚无特效的治疗方案，中暑患者常常遗留严重后遗症，因此中暑防重于治。姜黄素作为传统药物，具有安全性高、副作用小等特点。近年来，姜黄素已显著转变为前瞻性多能的候选药物，主要进行治疗中的应用研究[17]。大量的实验研究证明姜黄素对多种病因及毒物药物诱导急性肾损伤的保护作用。一些动物实验研究显示姜黄素对人为诱导的急性肾损伤具有保护作用，Liyu He 等[18]用 100 mg/kg 剂量的姜黄素灌胃干预庆大霉素诱导的肾损伤大鼠模型，结果显示姜黄素可降低庆大霉素诱导的肾损伤大鼠的血清 BUN 和 Cr 的水平，明显改善结果损伤，说明姜黄素可减轻药物诱导的急性肾损伤。另外，有实验证明在毒物引导的急性肾损伤肾损伤中，姜黄素同样对急性肾损伤具有保护作用，如铅诱导的肾损伤[19]以及 CCl_4 诱导的肾损伤模型[20]。

本实验首次将姜黄素应用于干热环境下的大鼠中暑模型，发现姜黄素预处理对干热环境下大鼠的急性肾损伤具有保护作用，可明显降低血清中肌酐、尿素以及尿液中肾损伤分子 -1 (KIM-1)、NGAL 的含量，同时降低肾组织中 NF-κB p65 的表达。因此，姜黄素对于干热环境下大鼠肾损伤的保护作用，可能是与抑制 NF-κB 的表达降低细胞炎症反应水平有关。

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