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姜黄素预处理对沙漠干热环境中暑大鼠心肌细胞凋亡和 Caspase-3 活性的影响 *

张 立¹ 刘江伟^{2Δ} 康 燕^{3Δ} 马 娜² 唐 军² 高晓康² 沈才福² 董 翔²

(1 乌鲁木齐市第一人民医院门诊部 新疆 乌鲁木齐 830000;

2 新疆军区总医院新疆特殊环境医学重点实验室 新疆 乌鲁木齐 830000; 3 解放军 69240 部队医院 新疆 乌鲁木齐 830000)

摘要 目的:研究姜黄素预处理对沙漠干热环境不同阶段中暑大鼠心肌损伤、细胞凋亡及半胱天冬氨酸蛋白酶-3(Caspase-3)活性的影响。**方法:**选择雄性健康 SD 大鼠 80 只,将其随机分为 2 组(n=40):盐水对照组以及姜黄素预处理组。每组再分为 4 个亚组(n=10):干热 0 min 组(即常温组),干热 50 min 组(轻度中暑组),干热 100 min 组(中度中暑组),干热 150 min 组(重度中暑组)。盐水组大鼠给予 0.9%生理盐水灌胃,姜黄素组大鼠给予剂量为 100 mg/kg 姜黄素灌胃,各组大鼠均连续灌胃 7 天。0 min 组置于常温环境中,其余组放置在西北特殊环境人工实验舱内,设置干热环境:温度(41± 0.5)℃,湿度(10± 1)%,并在相应时间点麻醉大鼠,取血液以及心脏组织。检测血液心肌酶谱磷酸肌酸激酶(CK)、磷酸肌酸激酶同工酶(CK-MB)及乳酸脱氢酶(LDH)水平,用 TUNEL 法检测心肌细胞凋亡率,Caspase-3 比色试剂盒检测 Caspase-3 活性。**结果:**随着干热环境时间的延长,大鼠血清 CK、CK-MB、LDH 水平、心肌细胞凋亡率及心肌组织 Caspase-3 活性均逐渐升高,而姜黄素预处理组在干热环境放置 50 min、100 min 和 150 min 时的血清 CK、CK-MB、LDH 水平、心肌细胞凋亡率及心肌组织 Caspase-3 活性均明显低于对照组(P<0.01)。**结论:**姜黄素预处理可通过减少心肌细胞凋亡、增加 Caspase-3 活性,保护沙漠干热环境中暑大鼠心肌损伤。

关键词:姜黄素;干热环境;心肌损伤;凋亡;半胱天冬氨酸蛋白酶-3

中图分类号:R-33;R135.3;R594.1 **文献标识码:**A **文章编号:**1673-6273(2018)21-4022-05

The Effects of Curcumin Pretreatment on Myocardial Apoptosis and Caspase-3 Activity of Heatstroke Rats in Dry-heat Environment of Desert*

ZHANG Li¹, LIU Jiang-we^{2Δ}, KANG Yan^{3Δ}, MA Na², TANG Jun², GAO Xiao-kang², SHEN Cai-fu², DONG Xiang²

(1 Department of Outpatient, Urumqi Municipal First People's Hospital, Urumqi, Xinjiang, 830000, China;

2 Key Laboratory of the Special Environmental Medicine of Xinjiang, General Hospital of Xinjiang Military Command, Urumqi, Xinjiang, 830000, China; 3 The No.69240 Army Hospital of PLA, Urumqi, Xinjiang, 830000, China)

ABSTRACT Objective: To investigate the protective effects of curcumin pretreatment on myocardial injury, apoptosis and Caspase-3 activity of different stage heatstroke rats in dry-heat environment of desert. **Methods:** 80 Sprague-Dawley rats were randomly divided into 2 groups (n=40): Saline control group and Curcumin pretreatment group. Each group was divided into four subgroups (n=10): 0min group (normal temperature group), 50 min group (mild heatstroke group), 100 min group (moderate heatstroke group), 150 min group (severe heatstroke). Rats of the saline group were given 0.9% normal saline, the curcumin group was administered with curcumin, the dose was 100 mg/kg bw, and the rats were administered continuously for 7 days. The rats of 0 min group were put at room temperature, the other groups were transferred to the climate cabin (The Simulated Climate Cabin for Special Environment of Northwest of China) with the conditions of (41.5± 0.5)℃ temperature, (10± 1) % relative humidity to make the rat heatstroke model of dry heat environment of desert. The rats were anesthetized at the corresponding time points and blood and heart tissues were collected. The serum myocardium zymogram: creatine kinase (CK), isoenzyme of creatine kinase (CK-MB) and lactate dehydrogenase (LDH) were detected, cellular apoptosis was analyzed by TUNEL assay, Caspase-3 activity were detected by Caspase-3 colorimetric kit. **Results:** The serum myocardium zymogram (CK, CK-MB, LDH), myocardial apoptosis rate and Caspase-3 activity were all increased with the exposed time in the dry heat environment and the progression of the heat stroke. The serum CK, CK-MB and LDH, myocardial apoptosis rate and Caspase-3 activity were significantly lower in curcumin pretreatment group than control group at the 50 min, 100 min and 150 min time point(P<0.01). **Conclusions:** Curcumin pretreatment may through inhibiting the myocardial apoptosis and increasing the Caspase-3 activity to exert protective

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作者简介:张立(1971-),男,副主任医师,主要研究方向:儿童心肺疾病的临床与基础研究,E-mail: 2486652948@qq.com

Δ 通讯作者:刘江伟(1970-),男,博士后,教授,主任医师,博士生导师,主要研究方向:特殊环境战创伤及普外临床与基础研究,E-mail: ljw273273@163.com;

康燕(1971-),女,副主任医师,主要研究方向:军事医学研究,E-mail: ky330164406@163.com

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effects on myocardial injury during heatstroke in dry heat environment of desert.

Key words: Curcumin; Dry heat environment; Myocardial injury; Apoptosis; Caspase-3

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前言

戈壁沙漠地区具有夏季气候高、昼夜温差大、干燥、太阳辐射强等特点^[1]。中暑是热应激的最严重形式,是指人体在高温环境下,由于水和电解质丢失过多、散热功能衰竭引起的以中枢神经和心血管功能障碍为主要表现的热损伤疾病,尽管采取积极干预,死亡率仍可达 15-33%^[2]。近年来,戈壁沙漠地区夏季中暑的发生率呈逐年上升的趋势^[1]。研究表明心肌细胞凋亡参与了沙漠干热环境中暑所致的心肌损伤^[3]。

姜黄素是从植物姜黄的根须中提取的多酚类化合物,近年来研究表明其对多脏器损伤具有保护作用,姜黄素预处理可明显延长干热环境中暑大鼠的生存时间^[4,5]。凋亡效应因子半胱天冬氨酸蛋白酶 3(Caspase-3)是凋亡的最终执行因子,检测 Caspase-3 活性可在一定程度上反映细胞的凋亡情况^[6]。目前,姜黄素对沙漠干热环境大鼠心肌损伤的保护作用尚未见文献报道。本研究通过建立沙漠干热环境大鼠中暑模型^[7],探讨姜黄素预处理对沙漠干热环境不同阶段中暑大鼠心肌酶及细胞凋亡的影响及其可能机制。

1 材料和方法

1.1 实验动物及材料

80 只 SPF 级雄性 SD 大鼠,体重 190~220 g,购自新疆医科大学实验动物中心,生产许可证号 SCXK(新)2011-0001。在新疆军区总医院动物实验中心 SPF 级环境饲养 1 周,环境温度(25±2)℃,相对湿度(35±5)%,各 12 h 白天与黑夜循环的房子中,饲料与水随意供应。全自动生化仪 BS180(深圳迈瑞生物医疗电子股份有限公司),(BI2000 图像分析系统(成都泰盟科技有限公司)。姜黄素购自日本化成株式会社(CI-75300),羧甲基纤维素钠钩子购自源叶生物,TUNEL 试剂盒系 Abcam 公司产品,Caspase-3 比色测定试剂盒购自 Biovision 公司。实验经新疆军区总医院实验动物伦理及福利委员会审批通过。

1.2 实验方法

1.2.1 模型建立及取材 大鼠在 SPF 室适应性饲养 7 天,饲养温度(25±2)℃,相对湿度(35±5)%,饲料与水随意供应。将其随机分为 2 组(n=40):盐水对照组和姜黄素预处理组,每组下分为 4 个亚组(n=10):0 min 组(即常温对照组),干热 50 min 组(轻度中暑组),干热 100 min 组(中度中暑组),干热 150 min 组(重度中暑组)。盐水组大鼠给予 0.9%生理盐水灌胃,姜黄素组大鼠给予 100 mg/kg 姜黄素 +5%羧甲基纤维素钠溶液配置成混悬液灌胃^[1];各组大鼠均连续灌胃 7 天。0 min 组置于常温环境中[温度(25±2)℃,相对湿度(35±5)%],其余组在西北特殊环境人工实验舱(新疆军区总医院研制)设置的干热环境[(41±0.5)℃,湿度(10±1)%]中复制不同程度的大鼠中暑模型^[7]。在相应时间麻醉并处死大鼠,下腔静脉采血,取一部分心肌组织于 10%甲醛溶液,另一部分于液氮中冻存。

1.2.2 心肌酶 CK、CK-MB 及 LDH 水平检测 在相应时间点,采用 3%戊巴比妥麻醉大鼠,通过下腔静脉收集血液,3000 r/min 离心 10 分钟收集血清,全自动生化分析仪(mindray BS-180)检测进行 CK、CK-MB 及 LDH 含量。

1.2.3 用 TUNEL 法检测心肌细胞凋亡 TUNEL 法检测心肌组织细胞凋亡(按说明书方法进行),并在光学显微镜下观察,计算凋亡率;阳性细胞即为凋亡细胞核,表现为棕色;显色蓝色细胞核的细胞为正常细胞 400 倍视野下拍照,每张切片随机选取 5 个视野统计凋亡细胞数及总细胞数,取其平均值。计算心肌细胞凋亡指数(apoptotic index, AI)= 凋亡细胞数(TUNEL 阳性)/总细胞数(DAPI 阳性)×100%,染色及计数均采用双盲法。

1.2.4 Caspase-3 活性检测 取心肌液氮冷冻组织,应用 Caspase-3 比色测定试剂盒测定(参照说明书操作),用酶标免疫测定仪(Bio-Rad, USA)测定波长 405 nm 下的吸光度值反映 Caspase-3 活性,实验重复 3 次。

1.3 统计学分析

统计学软件采用 SPSS 23.0,计量资料均以均数±标准差表示,同一时间点两组间比较采取独立样本的 t 检验,两组不同时间点之间比较采用单因素方差分析,以 P<0.05 为差异有统计学意义。

2 结果

2.1 姜黄素预处理对处于干热环境不同时间的大鼠血清 CK、CK-MB、LDH 水平的影响

姜黄素预处理组在干热环境放置 50 min、100 min 和 150 min 时的血清 CK、CK-MB、LDH 水平均明显低于对照组(P<0.01),见图 1。

2.2 姜黄素预处理对处于干热环境不同时间的大鼠心肌凋亡的影响

显微镜下观察:凋亡细胞核染呈棕色,见图 2。姜黄素预处理组在干热环境放置 50 min、100 min 和 150 min 时心肌细胞凋亡率明显低于对照组[50 min 时, (14.27±1.70)% vs. (19.65±2.56)%; 100 min 时, (17.10±2.25)% vs. (24.82±2.45)%; 150 min 时, (25.89±2.49)% vs. (38.80±2.11)%; P<0.01],见图 3。

2.3 心肌组织 Caspase-3 活性检测

姜黄素预处理组在干热环境放置 50 min、100 min 和 150 min 时心肌细胞 Caspase-3 活性明显低于对照组 [50 min 时, (0.0206±0.0027) vs. (0.0259±0.0040); 100 min 时, (0.0322±0.0041) vs. (0.0409±0.0045); 150 min 时, (0.0425±0.0036) vs. (0.0552±0.0072); P<0.01],见图 4。

3 讨论

Ye J 等^[8]研究认为中暑可引起多器官和系统损伤及并发症,其中心肌酶 CK 的升高和血小板(PLT)的降低在评估疾病进展过程中具有重要的诊断意义。我们前期研究结果表明在沙漠干

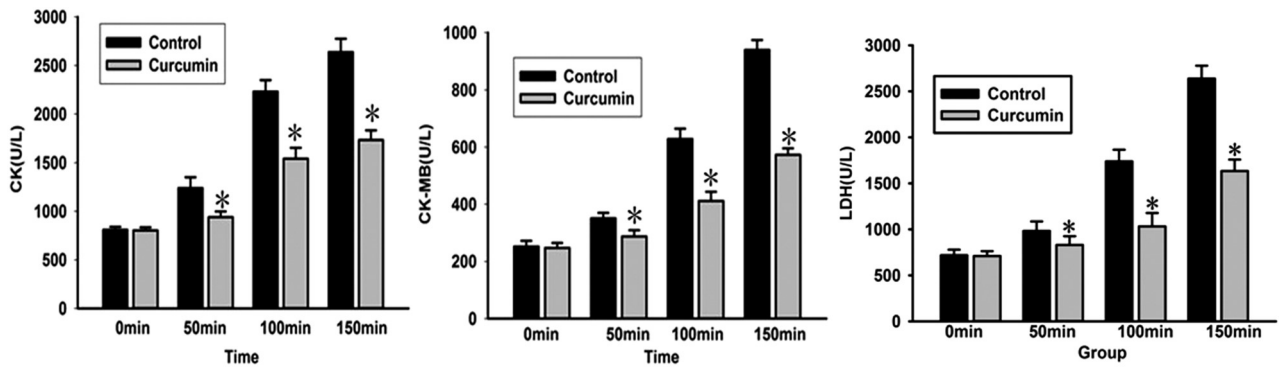


图1 姜黄素预处理对处于干热环境不同时间的大鼠血清 CK、CK-MB、LDH 水平的影响

Fig.1 The effects of curcumin pretreatment on the serum CK,CK-MB and LDH levles of rats in dry-heat environment of desert

Note:*P<0.01 vs. control group.

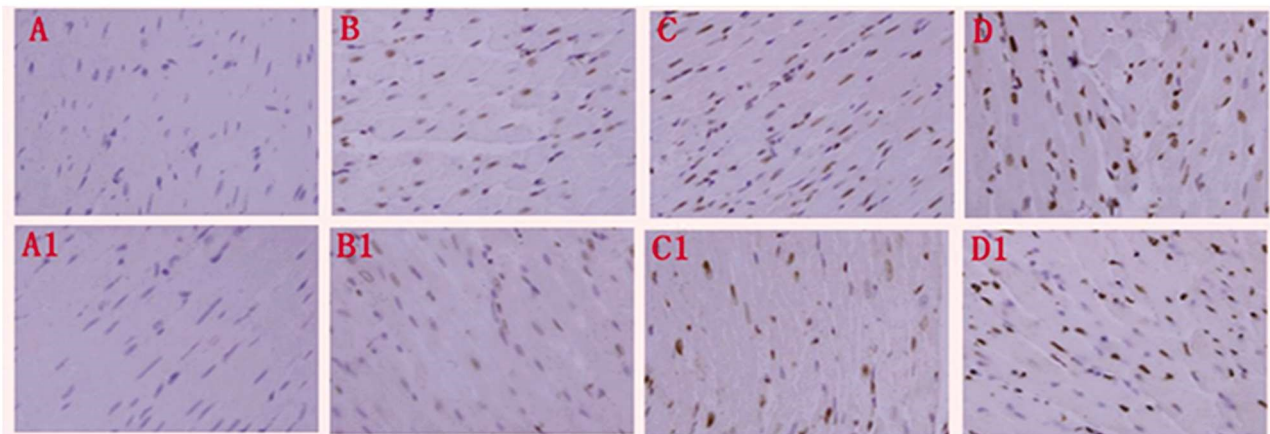


图2 姜黄素预处理对处于干热环境不同时间的大鼠心肌凋亡的影响(Tunel 染色× 200)

Fig.2 The effects of curcumin pretreatment on the apoptosis of myocardial cells (Tunel× 200)

Note: A. 0 min control group; A1. 0 min curcumin group; B. 50 min control group; B1. 50 min curcumin group; C. 100 min control group; C1. 100 min curcumin group; D. 100 min control group; D1. 150 min curcumin group.

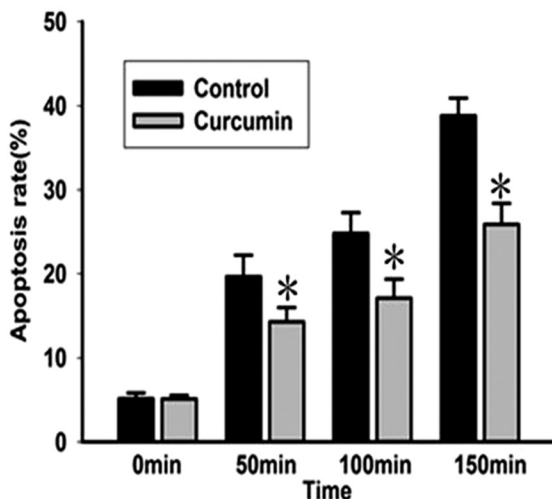


图3 姜黄素预处理对处于干热环境不同时间的大鼠心肌凋亡率的影响

Fig.3 The effects of curcumin pretreatment on the apoptotic rate of myocardial cells

Note:*P<0.01 vs. control group.

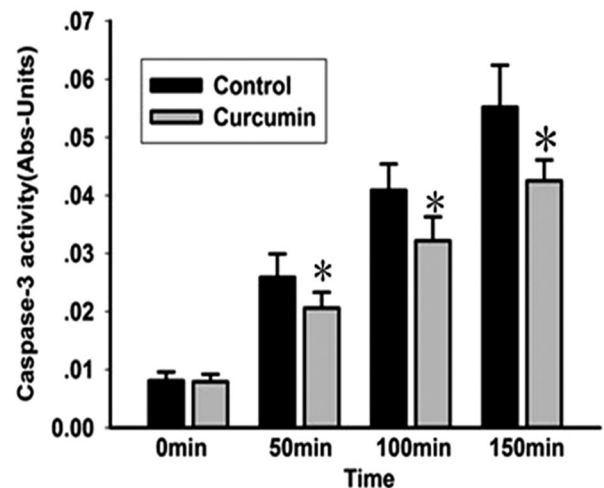


图4 姜黄素预处理对处于干热环境不同时间的大鼠心肌 Caspase-3 活性的影响

Fig.4 The effects of curcumin pretreatment on Caspase-3 activity of myocardial cells

Note:*P<0.01 vs. control group.

热环境下,心肌细胞凋亡参与心肌损伤过程^[3]。Wang X 等^[9]研究认为湿热应激可通过血管紧张素 II(Ang II)信号通路提高氧化应激水平和心肌细胞凋亡,是湿热环境应激引起心血管功能

障碍和严重的心肌细胞损害的重要原因。Liu D 等^[10]研究发现原花青素能够减少缺血再灌注心肌细胞凋亡,其机制部分通过减少活性氧(ROS)、p53、Caspase-9、Caspase-3 和 Bax 的表达,并

通过增加 Bcl-2 和 Bcl-2/Bax 比值来发挥作用。He W 等^[11]发现大鼠冠状动脉栓塞(CME)后核因子 E2 相关因子 2(Nrf2)、血红素氧化酶-1(HO-1)和 Bcl-2 的表达下降,而心肌细胞凋亡、Bax 表达和 Caspase-3 裂解增加,应用尼可地尔预处理可有效抑制 CME 所致的心肌细胞凋亡并提高心脏功能,其保护作用主要与调控心肌细胞 Nrf2/HO-1 通路有关。Liu P 等^[12]研究发现心肌梗死后的缺血再灌注因过量的 ROS 聚集,造成线粒体介导的心肌细胞凋亡,从而加重心肌细胞损害,鼠尾草酸能够通过上调 Bcl-2 和下调 Bax 和 caspase-3 水平抑制 H9c2 心肌细胞的缺氧/复氧(hypoxia/reoxygenation, H/R)所致的细胞凋亡而发挥心肌保护作用。因此,抑制心肌细胞凋亡是目前保护心肌细胞和促进心脏功能恢复的重要方向。

越来越多的研究表明姜黄素通过多个细胞凋亡通路在心肌损伤保护中发挥作用。Li J 等^[13]研究发现纳米姜黄素能够通过抑制还原型烟酰胺腺嘌呤二核苷酸磷酸(NADPH)介导的氧化应激来减轻棕榈酸盐(PA)诱导的心肌细胞凋亡,此保护作用可能通过内质网应激(ERS)相关通路实现。Yu W 等^[14]研究认为姜黄素能够通过抑制 NADPH-介导的氧化应激来减轻高糖诱导的心肌细胞凋亡,此保护效应可能主要通过 PI3K/Akt 介导的相关信号通路实现。Li W 等^[15]将姜黄素类似物 14 p 预处理 pH9c2 心肌细胞可以激活 Nrf2 信号通路,减少 H₂O₂ 诱导的丙二醛(MDA)和超氧化物歧化酶(SOD)水平,继而抑制叔丁基过氧化氢(TBHP)诱导的细胞死亡和 Bax/Bcl-2-Caspase-3 通路的激活,因而认为姜黄素类似物 14 p 在减少氧化应激和通过激活 Nrf2 减少心肌缺血再灌注损伤中具有广阔的应用前景。Lv FH 等研究发现^[16]姜黄素能够拮抗心肌梗死后的心肌细胞凋亡并抑制炎症细胞浸润,其抑制作用可能与其抑制心肌细胞核因子 κ B (NF- κ B) 的表达、激活过氧化物酶体增殖物激活受体- γ (PPAR- γ)和 Bcl-2 的表达有关。Duan W 等^[17]在大鼠心肌缺血灌注损伤后给予姜黄素可以减少心肌细胞凋亡数,上调抗凋亡蛋白 Bcl-2,下调促凋亡蛋白 Caspase-3,认为其机制可能是通过激活 JAK2/STAT3 信号通路为心肌细胞传递生存信号,从而抑制细胞凋亡来减少心肌损伤。Sukardi R 等^[18]在法乐氏三联症手术患者术前给予口服姜黄素(45 mg/天)两周,发现姜黄素可在心脏缺血期间发挥明显的心脏保护作用,主要是通过抑制心肌细胞 c-Jun N-末端激酶和 Caspase-3 活性来实现。Yeh CH 等^[19]研究认为姜黄素是一种 NF- κ B 抑制剂,可以减缓心肺转流术中促炎因子大量产生,并减少缺血再灌注损伤中心肌细胞凋亡来发挥心脏保护作用。Huang Z 等^[20]研究发现姜黄素主要通过诱导心肌细胞的 Bcl 2 的表达和抑制 Bax, beclin 1、BNIP3 (Bcl 2/腺病毒 E1B 19kDa 结合蛋白 3)和 SIRT1(沉默信息调节因子 2 相关酶 1) 的表达水平来抑制细胞凋亡和自我吞噬,从而在 H9c2 心肌细胞的缺氧/复氧(H/R)损伤中发挥心肌保护作用。有研究认为姜黄素预处理能够通过上调 miR-7a/b 和下调特殊蛋白 1(SP1)来抑制缺氧诱导的心肌细胞凋亡来发挥心肌保护作用^[21]。本研究中,随着大鼠在沙漠干热环境暴露时间的延长,其血清肌酸激酶(CK)、肌酸激酶同工酶(CK-MB)及乳酸脱氢酶(LDH)水平呈逐渐上升趋势,表明沙漠干热环境中暑可引起心肌损伤^[7]。而姜黄素预处理组心肌酶水平、细胞凋亡率、Caspase-3 活性均明显低于对照组,表明姜黄素可能通过减少心肌

细胞的凋亡来发挥心肌细胞的保护作用。其确切机制尚未阐明。其可能机制:1. 姜黄素预处理能够通过抑制细胞色素 c/Caspase-3 活性,减少活性氧簇(ROS)形成、保持线粒体膜电位,减少线粒体肿胀和线粒体外膜破裂来发挥心肌保护作用^[22,23]。2.通过激活 Nrf2 信号通路,减少中暑诱导的氧化应激水平,进而抑制中暑引起的细胞死亡和 Bax/Bcl-2-caspase-3 通路的活性增高来实现^[15]。3.通过抑制心肌细胞核因子 κ B(NF- κ B)的表达、激活过氧化物酶体增殖物激活受体- γ (PPAR- γ)和 Bcl-2 的表达,提高 Caspase-3 活性,从而拮抗中暑引起的心肌细胞凋亡并抑制炎症细胞浸润^[16]。总之,沙漠干热环境中暑可造成心肌细胞损伤,姜黄素预处理可以通过减少心肌细胞凋亡、增加 Caspase-3 活性,在沙漠干热环境中暑大鼠心肌损伤保护中发挥重要作用。

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