doi: 10.13241/j.cnki.pmb.2022.05.004

虫草素对慢性肾脏病大鼠血管内皮损伤的保护作用及其机制 *

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摘要 目的:探讨虫草素对慢性肾脏病(chronic kidney disease,CKD)大鼠血管内皮损伤的保护作用及其机制。**方法:**慢性肾脏病大鼠(n=48)随机平分为四组 - 模型组、虫草素高剂量组、虫草素中剂量组、虫草素低剂量组,虫草素高剂量组、虫草素中剂量组、虫草素低剂量组,分别给予虫草素 160 mg/kg、80 mg/kg、40 mg/kg,模型组灌胃给予等量生理盐水,每天 1 次,连续给药治疗 2 周。**结果:**虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 1 周、治疗 2 周的 24 h 尿量、血清尿素氮(blood urea nitrogen,BUN)与肌酐(serum creatinine,Scr)水平都低于模型组(P<0.05),体重都高于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05)。虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 2 周的结缔组织生长因子(Connective tissue growth factor,CTGF)、血管内皮生长因子(Vascular endothelial growth factor,VEGF)蛋白相对表达水平高于模型组(P<0.05),肾小球硬化指数、肾小管损伤评分都低于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05)。**结论:**虫草素在慢性肾脏病大鼠的应用能发挥血管内皮损伤保护作用,促进改善大鼠的肾功能,提高大鼠的体重,且具有剂量依赖性。

关键词:虫草素;慢性肾脏病;大鼠;血管内皮损伤;血管内皮生长因子;结缔组织生长因子;剂量

中图分类号:R33;R692;R243 **文献标识码:**A **文章编号:**1673-6273(2022)05-818-04

Protective Effect of Cordycepin on Vascular Endothelial Injury in Rats with Chronic Kidney Disease and its Mechanism*

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ABSTRACT Objective: To investigate the protective effect of cordycepin on vascular endothelial injury in rats with chronic kidney disease (CKD) and its mechanism. **Methods:** Chronic kidney disease rats (n=48) were randomly equally divided into four groups-model group, cordycepin high-dose group, cordycepin middle-dose group, cordycepin low-dose group. The cordycepin high-dose group, cordycepin middle-dose group, cordycepin low-dose group were given 160 mg/kg, 80 mg/kg, 40 mg/kg cordycepin, and the model group were given the same amount of normal saline, once a day for 2 weeks. **Results:** The 24 h urine output, blood urea nitrogen (BUN) and serum creatinine (Scr) levels of cordycepin high-dose group, cordycepin middle-dose group and cordycepin low-dose group at 1 week and 2 weeks of treatment were all lower than the model group (P<0.05), and the body weight were higher than the model group (P<0.05). The difference compared among the different dose groups were also statistically significant(P<0.05). The relative expression levels of connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) proteins in the high-dose cordycepin group, the middle-dose cordycepin group, and the low-dose cordycepin group at 2 weeks of treatment were higher than the model group (P<0.05), the glomerular sclerosis index and renal tubular injury score were lower than the model group (P<0.05), and the difference compared among different dose groups were also statistically significant (P<0.05). **Conclusion:** The application of cordycepin in rats with chronic kidney disease can exert protective effect on vascular endothelial damage, promote the improvement of the renal function of rats, and increase the weight of rats, and it is dose-dependent.

Key words: Cordycepin; Chronic kidney disease; Rats; Vascular endothelial injury; Vascular endothelial growth factor; Connective tissue growth factor; Dose

Chinese Library Classification(CLC): R-33; R692; R243 Document code: A

Article ID: 1673-6273(2022)05-818-04

前言

CKD 为临床上常见的肾脏疾病，也已成为世界范围内的公共健康问题,具有一定的死亡率[1]。该病的病理特征为细胞外基质(extracellular matrix,ECM)过度沉积、肾小球内固有细胞数量减少、肾小球硬化和肾小管间质纤维化、肾间质成纤维细胞

* 基金项目:陕西省自然科学基础研究计划项目(2021JQ-905)

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(收稿日期:2021-06-05 接受日期:2021-06-27)

增生等[2,3]。随着病情的进展,约有 1/3 的患者可进展到肾衰竭。现代研究表明慢性肾脏病进展的本质是肾组织遭受损伤后发生瘢痕化重塑与纤维化，在这个过程中涉及到炎症细胞浸润、成纤维细胞激活、微血管减少等[4]。目前对慢性肾脏病仍缺乏理想的治疗方法,西医多采用透析来维持晚期慢性肾脏病患者的生命,但是存在一定的缺陷,对于患者的依从性比较高,且存在各种并发症[5]。冬虫夏草是一种珍贵的民间滋补中药,主要分布于我国西藏那曲、四川甘孜、甘肃玉树等地区的高寒地带和雪山草原[6,7]。冬虫夏草是子座和菌核(蛹的尸体部分)组成的复合体,属核菌纲、球壳目、麦角菌科[8]。冬虫夏草具有抗肿瘤、补肾壮阳、止血化痰、调节人体免疫功能等多种功效[9],其主要活性成分包括甾醇、多糖、核苷类物质、虫草素、脂肪酸醇等[10,11]。其中虫草素是冬虫夏草的主要活性成分，具有减轻炎症细胞浸润、抗氧化、促进肾小管上皮细胞增殖、提高免疫力抑制肾小球系膜细胞增生等多种作用[12,13]。本文具体探讨了虫草素对慢性肾脏病大鼠血管内皮损伤的保护作用及其机制,以明确虫草素的作用价值。现总结报道如下。

1 资料与方法

1.1 研究材料

6 周龄雄性 SD(Sprague Dawley)大鼠 50 只购自北京维通利华实验动物有限公司 (SPF 级，体重 200-220 g，批号 204881411)。所有动物相关实验均征得了实验用动物伦理委员会的同意,均得到了动物伦理待遇,并严格遵循实验用动物相关规定和原则。饲养条件:屏障环境,4 只 1 笼,标准饲料喂养,恒湿 55%± 5%,恒温 22℃± 2℃,人工光照明暗各 12 h/ 天,24 h 自由取食和饮水,适应性喂养 1 周进行实验。

虫草素购自中美华东制药公司,戊二醛、福尔马林、水合氯醛、异丙醇、无水乙醇、氯仿等购自国家集团化学试剂有限公司抗 CTGF 抗体、抗 VEGF 抗体购自美国 sigma 公司,酶联免疫检测试剂盒购自大连宝生物工程有限公司。

1.2 慢性肾脏病大鼠模型的建立

采用腺嘌呤灌胃诱导大鼠慢性肾脏病模型,即于每日上午 10:00 对大鼠进行 2.5%腺嘌呤混悬液灌胃,剂量 200 mg/kg,连续 4 周后,第 5~7 周改为隔日灌胃,剂量及浓度不变,连续 3 周,造模共需 7 周,然后在造模后第 8 周进行血液生化指标检测以确定建模成功与否。

1.3 大鼠分组与处理

将建模成功的大鼠(n=48)随机分为四组 - 模型组、虫草素高剂量组、虫草素中剂量组、虫草素低剂量组,每组 12 只。虫草素高剂量组、虫草素中剂量组、虫草素低剂量组,分别给予虫草素 160 mg/kg、80 mg/kg、40 mg/kg,模型组灌胃给予等量生理盐水,每天 1 次,连续给药治疗 2 周。

1.4 观察指标

(1)在治疗 1 周、治疗 2 周称取大鼠体重,观察大鼠生存状态。(2)在上述同一时间点,测定大鼠的 24 h 尿量。同时进行尾静脉取血,分离血清后,测定大鼠血清 BUN、Scr 含量。(3)在治疗 2 周后处死大鼠,摘取大鼠的残肾,然用 10%中性甲醛溶液固定,常规石蜡包埋,制成 4 μm 石蜡切片,病理切片后行肾小球硬化指数、肾小管损伤评分,都分为 1-4 分评分,分数越高,肾脏病变严重。(4)研磨残肾,定量蛋白含量后,采用 Western blot 法检测 CTGF、VEGF 表达水平,以 B-actin 作为内对照。

1.5 统计方法

本研究所有数据均以均数± 标准差表示，计量数据以均数± 标准差表示,对比为 t 检验;计数数据以百分比表示,对比为卡方分析,检验水准为α=0.05。

2 结果

2.1 大鼠体重变化对比

所有大鼠都存活,模型组:大鼠精神萎靡、活动减少,皮毛颜色加深多尿,毛粗,耳缘、尾部苍白。

经虫草素治疗后,虫草素高剂量组、虫草素中剂量组、虫草素低剂量组大鼠的生存状态较模型组都明显好转。

虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 1 周、治疗 2 周的体重都高于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05)。见表 1。

表 1 四组治疗不同时间点的大鼠体重变化对比(g)

Table 1 Comparison of Weight Changes in Rats at Different Time Points (g)

Groups	n	Treatment for 1 week	Treatment for 2 weeks
Model Group	12	333.24± 16.39	332.98± 19.37
Low-dose group	12	357.92± 21.73*	379.20± 20.42*
Medium-dose group	12	387.77± 31.47*#	398.76± 21.76*#
High-dose group	12	411.09± 18.32*#△	426.22± 31.42*#△
F		19.732	23.333
P		0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the low-dose group, #P<0.05; compared with the middle-dose group, △ P<0.05.

2.2 肾功能对比

虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 1 周、治疗 2 周的 24 h 尿量、血清 BUN 与 Scr 水平都低于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05)。见表 2。

2.3 肾脏病变评分变化对比

虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 2 周的肾小球硬化指数、肾小管损伤评分都低于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05)。见表 3。

表 2 四组治疗不同时间点的大鼠肾功能变化对比

Table 2 Comparison of renal function changes in rats treated at different time points

Groups	n	24 h urine volume(mL)		BUN(mmol/L)		Scr(μmol/L)	
		Treatment for 1 week	Treatment for 2 weeks	Treatment for 1 week	Treatment for 2 weeks	Treatment for 1 week	Treatment for 2 weeks
Model Group	12	20.42± 1.34	20.34± 2.44	31.65± 2.42	31.77± 3.11	189.25± 12.48	190.11± 13.52
Low-dose group	12	17.33± 2.14*	15.87± 4.18*	19.78± 2.14*	14.76± 2.17*	122.77± 11.74*	100.87± 10.42*
Medium-dose group	12	15.28± 1.57*#	13.87± 2.11*#	12.17± 1.44*#	10.76± 1.44*#	89.87± 6.32*#	76.19± 8.11*#
High-dose group	12	13.22± 1.44*#△	11.09± 1.32*#△	7.11± 0.32*#△	5.85± 1.11*#△	51.57± 4.14*#△	47.76± 3.27*#△
F		24.351	26.014	34.111	36.726	27.933	29.114
P		0.000	0.000	0.000	0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the low-dose group, #P<0.05; compared with the middle-dose group, △ P<0.05.

表 3 四组治疗 2 周的大鼠肾脏病变评分变化对比(分)

Table 3 Comparison of renal lesion scores in rats for 2 weeks (scores)

Groups	n	Glomerulosclerosis index	Renal Tube Injury Score
Model Group	12	3.15± 0.33	3.33± 0.22
Low-dose group	12	2.10± 0.31*	2.17± 0.27*
Medium-dose group	12	1.56± 0.21*#	1.44± 0.18*#
High-dose group	12	0.89± 0.12*#△	1.11± 0.21*#△
F		25.725	21.083
P		0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the low-dose group, #P<0.05; compared with the middle-dose group, △ P<0.05.

2.4 CTGF 和 VEGF 蛋白相对表达水平变化对比

虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 2 周的 CTGF、VEGF 蛋白相对表达水平高于模型组(P<0.05)，不同剂量组别之间对比差异也有统计学意义(P<0.05)。见表 4。

表 4 四组治疗 2 周的大鼠肾脏 CTGF 和 VEGF 蛋白相对表达水平变化对比

Table 4 Comparison of relative expression levels of CTGF and VEGF protein in rats for 2 weeks

Groups	n	CTGF	VEGF
Model Group	12	0.67± 0.11	1.09± 0.16
Low-dose group	12	1.22± 0.32*	1.87± 0.22*
Medium-dose group	12	2.76± 0.21*#	3.09± 0.18*#
High-dose group	12	4.56± 0.13*#△	5.29± 0.22*#△
F		38.713	43.771
P		0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the low-dose group, #P<0.05; compared with the middle-dose group, △ P<0.05.

3 讨论

慢性肾脏病是各种肾脏疾病晚期的共同归宿，也是肾脏排泄功能、内分泌功能、内环境紊乱为特征的临床综合群[14]。系膜细胞、血管平滑肌细胞、足细胞、小管上皮细胞、成纤维细胞、周细胞、内皮细胞等都参与了慢性肾脏病的发病过程，炎症也是慢性肾脏病的基本病理改变，炎症反应贯穿肾脏疾病发展的始终[15]。持续不退的炎症是肾脏纤维化发生的重要因素，随着组织损伤的进展，浸润的炎症细胞逐渐被活化，可导致组织损伤，其中肾小管间质炎症程度与肾功能恶化的速度存在相关性[16]。

冬虫夏草有 " 黄金草 " 之称，主要其在天然中的资源量比较少，市场价格一直居高不下。历代医家称冬虫夏草为 " 诸虚百损至为上品 "，具有强肾、益精气、补肺等多种功效[17]。现代研究表明冬虫夏草具有抗疲劳、耐缺氧、延缓衰老、调节免疫系统等多种[18]。冬虫夏草含有核苷类、糖醇、多糖类、甾醇类、氨基酸等多种活性成分，其中虫草素具有重要的药用价值。本研究显示虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 1 周、治疗 2 周的体重都高于模型组(P<0.05)，不同剂量组别之间

对比差异也有统计学意义(P<0.05),表明虫草素能增加慢性肾脏病大鼠的体重。当前也有研究[19]表明冬虫夏草菌粉治疗肾衰竭大鼠后,大鼠体重增长较快,精神明显好转,伴随有食欲增加与皮毛色泽光亮,与本研究中相关结果一致。

传统中医认为冬虫夏草有提神、强心壮血、补肾、镇静、平喘祛痰等功效,现代研究证实了冬虫夏草含有虫草素、甘露醇、核苷、麦角固醇、微量元素等多种有效成分,具有调节内分泌、增强免疫力、抗肿瘤、降血压等作用[20,21]。本研究结果显示:虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 1 周、治疗 2 周的 24 h 尿量、血清 BUN 与 Scr 水平、肾小球硬化指数、肾小管损伤评分都低于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05),表明虫草素能促进改善慢性肾脏病大鼠的肾功能,且存在一定剂量效应,结合 Upadhyay M[22] Ye XQ[23]研究结果分析可知:24 h 尿量可以通过损伤肾小球系膜细胞引起肾小球硬化,也可损伤肾小管上皮细胞,参与慢性肾脏病的发生发展,而虫草素对机体的免疫系统具有双向调节功能,对 T 淋巴细胞、B 淋巴细胞、单核巨噬细胞具有刺激活作用,从而可提高肾病综合征缓解率[24]。另外,Yue K 等[24]研究结果显示:冬虫夏草可能通过改善肾小球滤过膜通透性,减轻大鼠蛋白尿水平,进而延缓与逆转肾脏纤维化进程,与本研究相关结果一致。同时虫草素能够改善慢性肾脏病的氧化应激状态,从而抑制肾组织细胞增殖、肥大,从而有利于保护肾小管上皮细胞[25-27]。

血管内皮损伤肾小管损伤是慢性肾脏病的典型病理表现,伴随有间质细胞及细胞间质增多,从而导致肾小球硬化和小管间质的纤维化[28,29]。虫草素能减轻毒物及缺血导致的急性肾小管损伤,促进肾小管上皮细胞再生[30,31]。本研究显示虫草素高剂量组、虫草素中剂量组、虫草素低剂量组治疗 2 周的 CTGF、VEGF 蛋白相对表达水平高于模型组(P<0.05),不同剂量组别之间对比差异也有统计学意义(P<0.05),表明虫草素的应用能通过调节慢性肾脏病大鼠 CTGF、VEGF 蛋白相对表达水平,从而改善其血管内皮损伤状况。Stenvinkel P[32]等研究表明:虫草素减轻了慢性肾脏病大鼠剧烈的炎症反应, 能促进 CTGF、VEGF 的释放,从而具有保护血管内皮细胞的功能,与本研究结论一致。不过慢性肾脏疾病的发生及进展过程是一个复杂的病理过程,虫草素的具体作用机制有待于更加系统深入的研究。

总之,虫草素在慢性肾脏病大鼠的应用能发挥血管内皮损伤保护作用,促进改善大鼠的肾功能,提高大鼠的体重,且具有剂量依赖性。本研究对虫草素在慢性肾脏病的治疗机制进行深入分析,从而为该疾病的治疗提供思路和实验基础。

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