

论著

冬虫夏草对糖尿病肾病大鼠肾组织HIF-1 α 及VEGF表达的影响

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摘要: 目的: 观察缺氧诱导因子-1 α (hypoxia inducible factor-1 α , HIF-1 α)、血管内皮生长因子(vascular endothelial growth factor, VEGF)在大鼠糖尿病肾病(diabetic nephropathy, DN)肾组织中的表达及冬虫夏草(*Cordyceps sinensis*, CS)干预后对其的影响,探讨冬虫夏草的抗缺氧损伤的肾保护机制。方法: 健康雄性Wistar大鼠通过一次性腹腔注射链脲佐菌素(60 mg/kg)制作成糖尿病模型,4周时测定24 h尿蛋白>30 mg/d为DN模型大鼠($n=30$),随机分为糖尿病肾病组(DN组, $n=15$)和冬虫夏草组(CS组, $n=15$),另取15只正常大鼠作为对照组(NC, $n=15$)。CS组予CS提取原液5.0 g/(kg·d)灌胃,NC和DN组均予以等量饮用水灌胃,分别于灌胃2,4,6周时随机处死三组大鼠各5只,检测24 h尿蛋白定量、尿 β -N-乙酰氨基葡萄糖苷酶(β -N-acetyl glucosaminidase, NAG酶)、血清肌酐水平;HE及MASSON染色观察肾脏组织形态学变化;反转录PCR方法检测HIF-1 α 和VEGF mRNA表达;免疫组织化学方法检测肾组织中HIF-1 α 及VEGF蛋白的表达。结果: 与NC组相比较,DN组肾小管空泡变性明显,肾小球系膜区基质增多,24 h尿蛋白排泄量、尿NAG酶、血肌酐显著升高,肾组织HIF-1 α 和VEGF mRNA及其蛋白表达均显著增加(均 $P<0.05$),两者的表达均随着病程延长而逐渐增强,且两组HIF-1 α 与VEGF表达呈正相关($r=0.850, r=0.887$, 均 $P<0.05$);与DN组相比较,CS组大鼠肾小管病变程度减轻,24 h尿蛋白排泄量、尿NAG酶、血肌酐降低,肾组织HIF-1 α 和VEGF mRNA及其蛋白表达均下调(均 $P<0.05$),但仍明显高于NC组($P<0.05$),但CS治疗第4周、第6周HIF-1 α 的mRNA及蛋白水平差异无统计学意义($P>0.05$)。结论: DN病大鼠肾组织HIF-1 α 及VEGF表达上调,两者呈正相关,提示DN肾组织存在慢性缺氧。CS可通过下调DN肾组织HIF-1 α 及VEGF的表达起到抗慢性缺氧损伤的肾保护作用。

关键词: 糖尿病肾病 缺氧诱导因子-1 α 血管内皮生长因子 冬虫夏草

Effect of *Cordyceps sinensis* on expressions of HIF-1 α and VEGF in the kidney of rats with diabetic nephropathy

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Abstract: Objective: To examine the expressions of hypoxia inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) in the kidney of rats with diabetic nephropathy before and after the treatment of *Cordyceps sinensis*, and to explore the mechanism of *Cordyceps sinensis* against hypoxia. Methods: The diabetes model was produced by intraperitoneal injection of 60 mg/kg streptozotocin, then the rats whose 24 h urine protein level was above 30 mg/d were thought to have suffered diabetic nephropathy. Thirty rats were randomly divided into a diabetic nephropathy group (DN group, $n=15$) and a *Cordyceps sinensis* group (CS group, $n=15$), and another 15 normal rats served as a normal control group (NC group, $n=15$). The CS group were intragastrically administered *Cordyceps sinensis* extract liquid[5.0 g/(kg·d)], the other groups were intragastrically administered drinking water of equal volume. Five rats in each group were killed after 2, 4, and 6 weeks. The 24 h urine protein excretion, urine β -N-acetyl glucosaminidase (NAGase) and serum creatinine were measured; the renal pathological changes were evaluated by HE and Masson staining; the mRNA and protein expressions of HIF-1 α and VEGF were detected by reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry. Results: Compared with the normal control group, the renal tubular vacuolar degeneration was obvious, and the glomerular mesangial matrix increased in the DN group. The 24 h urinary protein excretion, urine NAGase and serum creatinine also increased significantly (all $P<0.05$); the expressions of HIF-1 α and VEGF in the renal tissue gradually increased with time, and the expression of HIF-1 α was correlated with that of VEGF in the 2 groups ($r=0.850, r=0.887$, both $P<0.05$). Compared with the DN group, the pathological changes were relieved, the 24 h urinary protein excretion, urine NAGase and serum creatinine level were decreased, and the expressions of HIF-1 α and VEGF decreased in the CS group (all $P<0.05$), but they were still higher than those in the normal control group ($P<0.05$). There was no significant difference in the mRNA and protein expression of HIF-1 α between the 4th week and the 6th week after the treatment of CS ($P>0.05$).

Conclusion: The expressions of HIF-1 α and VEGF increase in the kidney of rats with diabetic nephropathy, and the positive correlation suggests that there is chronic hypoxia in the renal tissue of diabetic nephropathy. *Cordyceps sinensis* may protect against chronic hypoxia injury in diabetic nephropathy by lowering the expressions of HIF-1 α and VEGF.

Keywords: diabetic nephropathy hypoxia inducible factor-1 α vascular endothelial growth factor

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