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人参皂苷 Rg1 对糖尿病肾病大鼠血清氧化应激指标、炎性因子及肾组织 TGF-β1、MCP-1 mRNA 的影响 *

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摘要 目的：研究人参皂苷 Rg1 对糖尿病肾病（DN）大鼠血清氧化应激指标、炎性因子及肾组织生长转化因子 -β1（TGF-β1）、单核细胞趋化因子蛋白 -1（MCP-1）mRNA 的影响。**方法：**选取 60 只 SD 大鼠，将其以随机抽签法分为 Rg1 组、模型组以及对照组，各 20 只。其中 Rg1 组与模型组大鼠均选择腹腔内一次性注射链脲佐菌素（STZ）55 mg/kg 建立 DN 大鼠模型，Rg1 组予以人参皂苷 Rg1 治疗，模型组与对照组则予以等量的生理盐水干预。比较干预 12 周后各组肾功能相关指标、血清氧化应激指标、炎性因子及肾组织 TGF-β1、MCP-1 mRNA 表达情况。**结果：**Rg1 组、模型组大鼠干预 12 周后血肌酐（Scr）、尿素氮（BUN）、胱抑素 C（CysC）水平均高于对照组，而 Rg1 组大鼠干预 12 周后 Scr、BUN、CysC 水平均低于模型组（均 $P<0.05$）。Rg1 组、模型组大鼠干预 12 周后血清超氧化物歧化酶（SOD）、谷胱甘肽（GSH）水平均低于对照组，丙二醛（MDA）水平高于对照组（均 $P<0.05$）；Rg1 组大鼠干预 12 周后血清 SOD、GSH 水平均高于模型组，MDA 水平低于模型组（均 $P<0.05$）。Rg1 组、模型组大鼠干预 12 周后血清白细胞介素 -6（IL-6）、白细胞介素 -1β（IL-1β）、肿瘤坏死因子 -α（TNF-α）水平均高于对照组，而 Rg1 组血清炎性因子水平低于模型组（均 $P<0.05$）。Rg1 组、模型组大鼠干预 12 周后肾组织 TGF-β1、MCP-1 mRNA 表达水平均高于对照组，且 Rg1 组低于模型组（均 $P<0.05$）。**结论：**人参皂苷 Rg1 可显著改善 DN 大鼠血清氧化应激指标，下调血清炎性因子水平以及肾组织 TGF-β1、MCP-1 mRNA 表达。

关键词：糖尿病肾病；人参皂苷 Rg1；氧化应激；炎性因子；单核细胞趋化因子蛋白 -1；生长转化因子 -β1

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Effects of Ginsenoside Rg1 on Serum Oxidative Stress Indicators, Inflammatory Factors and Kidney Tissue TGF-β1 and MCP-1 mRNA in Diabetic Nephropathy Rats*

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ABSTRACT Objective: To study the effects of ginsenoside Rg1 on serum oxidative stress indicators, inflammatory factors, kidney tissue transforming growth factor-β1 (TGF-β1) and monocyte chemoattractant protein-1 (MCP-1) mRNA of diabetic nephropathy (DN) rats. **Methods:** 60 SD rats were selected as, which were divided into Rg1 group, model group and control group according to random lottery method, 20 SD rats in each group. Rats in the Rg1 group and model group were given one-time intraperitoneal injection of streptozotocin (STZ) 55 mg/kg to establish DN rat model. Rg1 group was given Rg1 intervention, model group and control group were given the same amount of normal saline intervention. Renal function related indicators, serum oxidative stress indicators, inflammatory factors and mRNA expressions of kidney tissue TGF-β1 and MCP-1 were compared 12 weeks after intervention. **Results:** 12 weeks after intervention, the serum creatinine(Scr), Blood urea nitrogen(BUN) and Cystatin C(CysC) levels of rats in the Rg1 group and model group were higher than those in the model group, while The levels of Scr, BUN and CysC in Rg1 group were lower than those in model group at 12 weeks after intervention (all $P<0.05$). 12 weeks after intervention, the serum superoxide dismutase (SOD) and glutathione(GSH) levels of rats in Rg1 group and model group were lower than those in control group, while malondialdehyde (MDA) level was higher than those in control group (all $P<0.05$). The serum SOD and GSH levels of rats in the Rg1 group were higher than those in the model group, and MDA level was lower than those in the model group at 12 weeks after intervention (all $P<0.05$). Serum interleukin-6 (IL-6), interleukin-1β(IL-1β), and tumor necrosis factor-α(TNF-α) of rats in the Rg1 group and the model group were all higher than those in the control group at 12 weeks after intervention, while the serum inflammatory factors levels in the Rg1 group were lower than those in the model group (all $P<0.05$). The expression levels of kidney tissue TGF-β1mRNA and MCP-1 mRNA of rats in the Rg1 group and model

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group were higher than those in the control group at 12 weeks after intervention, which in the Rg1 group were lower than those in the model group (all $P<0.05$). **Conclusion:** Ginsenoside Rg1 can significantly improve the serum oxidative stress indicators of DN rats, down-regulate the expression level of inflammatory factors and mRNA expressions of kidney tissue TGF-β1and MCP-1.

Key words: Diabetic nephropathy; Ginsenoside Rg1; Oxidative stress; Inflammatory factors; Monocyte chemokine protein-1; Issue transforming growth factor-β1

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前言

糖尿病肾病(Diabetic nephropathy,DN)属于临床上较为常见的糖尿病严重并发症之一,且已有成为终末期肾病首位原因的趋势,患者以高血糖、炎症、氧化应激以及进行性肾功能减退为主要特征,是糖尿病患者死亡、残疾的重要原因[1-3]。有研究报道显示,生长转化因子-β1(Transforming growth factor-β1,TGF-β1)属于多功能肽之一,可经多种途径对细胞外基质的代谢以及细胞增殖造成影响,属于DN发病机制的重要通路[4]。另有研究报道提出,单核细胞趋化因子蛋白-1(Monocyte chemoattractant protein-1,MCP-1)属于单核/巨噬细胞特异性趋化因子,对DN具有极强的趋化激活作用,在DN的发生、发展过程中发挥着至关重要的作用[5]。人参皂苷Rg1是提取自云南文山三七中的人参皂苷单体,具有多种生物学功能,其治疗DN的具体作用机制尚需要进一步研究[6-8]。鉴于此,本文通过研究人参皂苷Rg1对DN大鼠血清氧化应激指标、炎性因子及肾组织TGF-β1、MCP-1 mRNA的影响,旨在明确人参皂苷Rg1治疗DN的作用机制,继而为临床中寻找DN的治疗靶点提供参考,现作以下报道。

1 材料与方法

1.1 实验动物与分组

选取60只SD大鼠,所有大鼠均为雄性,体重为(200±20)g,购自重庆市疾病预防控制中心,动物许可证号:SYXK(渝)2017-0021。将大鼠按随机抽签法分为Rg1组、模型组以及对照组,每组各20只。

1.2 相关试剂及仪器

人参皂苷Rg1购自上海斯莱克景达有限公司,生产批号为20167165。链脲佐菌素(Streptozotocin,STZ)购自Sigma公司,生产批号为S0130。TGF-β1、MCP-1原位杂交试剂盒均购自天津灏洋生物工程有限公司。酶联免疫吸附法相关试剂盒均购自上海酶联生物科技有限公司。试验仪器包括美国强生Surestep血糖仪以及日本岛津7200型全自动分析仪。

1.3 研究方法

(1)建立DN大鼠模型:Rg1组与模型组大鼠均选择腹腔内一次性注射STZ 55 mg/kg建立DN大鼠模型,对照组则注射等量的枸缘酸钠溶液。注射72h后进行血糖以及尿糖的监测,血糖≥16.7 mmol/L,尿糖4个"+"以上则提示DN造模成功。(2)干预方式:三组大鼠均饲养于同一动物房内,予以标准饮食。其中Rg1组予以人参皂苷Rg1灌胃治疗,使用剂量为21 mg/kg。模型组与对照组则予以等量的生理盐水灌胃,3组大鼠均干预12周。(3)相关指标检测:干预12周后,将大鼠麻醉后处死,收集血液和肾脏组织,血液经3000 r/min离心15min,离心半径8cm,分离血清保存于-30℃低温冰箱中待测。① 肾功能相关指标水平检测:采用日本岛津7200型全自动分析仪检测血肌酐(Serum creatinine,Scr)、尿素氮(Blood urea nitrogen,BUN)以及胱抑素C(Cystatin C,CysC)水平。② 血清氧化应激指标水平检测:包括超氧化物歧化酶(Superoxide dismutase,SOD)、谷胱甘肽(Glutathione,GSH)、丙二醛(Malondialdehyde,MDA),检测方式为酶联免疫吸附法,具体操作按试剂盒说明书进行。③ 血清炎性因子水平检测:包括白细胞介素-6(Interleukin-6,IL-6)、白细胞介素-1β(Interleukin-1β,IL-1β)、肿瘤坏死因子-α(Tumor necrosis factor-α,TNF-α),检测方式为酶联免疫吸附法,具体操作务必以试剂盒说明书进行。④ 肾组织TGF-β1、MCP-1 mRNA表达检测采用原位杂交法,根据相关试剂盒说明书完成相关操作,采用0.01M的PBS代替探针作为阴性对照。采用ICMIAS系列多功能图像分析系统进行原位杂交实验结果的图像分析,随机抽取5个视野,测定平均积分光密度值。

1.4 统计学方法

数据分析主要依靠SPSS20.0软件完成,以[n(%)]表示计数资料,实施χ^2检验。以($\bar{x}\pm s$)表示计量资料,两组比较实施t检验,多组比较实施单因素方差分析。以$P<0.05$说明差异有统计学意义。

2 结果

2.1 各组大鼠干预12周后Scr、BUN、CysC水平对比

Rg1组、模型组大鼠干预12周后Scr、BUN、CysC水平均高于对照组,而Rg1组大鼠干预12周后Scr、BUN、CysC水平均低于模型组(均$P<0.05$),见表1。

2.2 各组大鼠干预12周后血清氧化应激指标水平对比

Rg1组、模型组大鼠干预12周后血清SOD、GSH水平均低于对照组,MDA水平高于对照组,且Rg1组大鼠干预12周后血清SOD、GSH水平均高于模型组,MDA水平低于模型组(均$P<0.05$)。见表2。

2.3 各组大鼠干预12周后血清炎性因子水平对比

Rg1组、模型组大鼠干预12周后血清IL-6、IL-1β、TNF-α均高于对照组,而Rg1组上述各项指标水平低于模型组(均$P<0.05$)。见表3。

2.4 各组大鼠干预12周后肾组织TGF-β1、MCP-1 mRNA表达对比

Rg1组、模型组大鼠干预12周后肾组织TGF-β1、MCP-1 mRNA表达水平均高于对照组,且Rg1组上述指标表达水平低于模型组(均$P<0.05$)。见表4。

表 1 各组大鼠干预 12 周后 Scr、BUN、CysC 水平对比($\bar{x}\pm s$)

Table 1 Comparison of Scr, BUN and CysC levels of rats in each group at 12 weeks after intervention($\bar{x}\pm s$)

Groups	n	Scr(μmol/L)	BUN(mmol/L)	CysC(mg/L)
Rg1 group	20	65.23± 7.32#*	3.80± 0.47#*	1.30± 0.17#*
Model group	20	150.32± 35.29#	9.12± 1.04#	3.58± 0.39#
Control group	20	40.61± 6.33	2.13± 0.40	1.09± 0.18
F	-	6.871	4.394	4.560
P	-	0.001	0.023	0.017

Note: Compared with the control group, #$P<0.05$; Compared with the model group, *$P<0.05$.

表 2 各组大鼠干预 12 周后血清氧化应激指标水平对比($\bar{x}\pm s$)

Table 2 Comparison of serum oxidative stress indicators at 12 weeks after intervention in each group of rats($\bar{x}\pm s$)

Groups	n	SOD(U/L)	GSH(mmol/L)	MDA(μmol/L)
Rg1 group	20	71.22± 8.01#*	7.49± 0.91#*	6.13± 0.72#*
Model group	20	32.35± 4.48#	3.12± 0.31#	9.92± 1.04#
Control group	20	85.17± 8.44	9.35± 1.04	4.77± 0.63
F	-	8.341	5.879	6.334
P	-	0.000	0.001	0.000

Note: Compared with the control group, #$P<0.05$; Compared with the model group, *$P<0.05$.

表 3 各组大鼠干预 12 周后血清炎性因子水平对比($\bar{x}\pm s$)

Table 3 Comparison of serum inflammatory cytokines in rats at 12 weeks after intervention($\bar{x}\pm s$)

Groups	n	IL-6(ng/L)	IL-1β(ng/L)	TNF-α(ng/L)
Rg1 group	20	824.39± 80.84#*	302.74± 37.55#*	1345.27± 160.28#*
Model group	20	1523.72± 203.74#	693.24± 70.49#	2645.38± 311.48#
Control group	20	705.35± 73.84	205.28± 20.90	1202.48± 189.83
F	-	13.697	11.584	23.230
P	-	0.000	0.000	0.000

Note: Compared with the control group, #$P<0.05$; Compared with the model group, *$P<0.05$.

表 4 各组大鼠干预 12 周后肾组织 TGF-β1、MCP-1 mRNA 表达对比($\bar{x}\pm s$)

Table 4 Comparison of expression of kidney tissue TGF-β1 and MCP-1 of rats at 12 weeks after intervention($\bar{x}\pm s$)

Groups	n	TGF-β1 mRNA	MCP-1 mRNA
Rg1 group	20	0.19± 0.02#*	0.24± 0.04#*
Model group	20	0.40± 0.03#	0.37± 0.05#
Control group	20	0.13± 0.02	0.18± 0.04
F	-	8.256	4.394
P	-	0.000	0.020

Note: Compared with the control group, #$P<0.05$; Compared with the model group, *$P<0.05$.

3 讨论

DN 的发生、发展与糖尿病的久治不愈密切相关，且随着社会经济的飞速发展以及人们生活水平的逐渐提高，饮食结构已然出现显著的变化，DN 的发病率呈逐年升高趋势[9-11]。该病以肾损伤为早期表现，随着 Scr、BUN 以及 CysC 水平的不断增加，肾小球滤过功能损伤逐渐明显，后期可发展成为肾小球硬化以及肾功能衰竭等，甚至导致终末期肾衰竭的发生[12-14]。因此，对 DN 患者予以早期积极有效的治疗显得尤为重要，亦是目前临床研究的重点。现阶段，已有不少研究证实[15-17]，氧化应激以及炎症反应均在 DN 的发生、发展过程中起着至关重要的作用，可能成为治疗 DN 的有效靶点。TGF-β1 属于 TGF-β 的异构体之一，广泛存在于肾脏中，不仅可刺激系膜细胞合成、分泌胶原Ⅳ以及纤维粘连蛋白[18,19]，同时可减少部分细胞外基质降解相关酶的分泌，从而引起细胞外基质的堆积，加剧肾损害[20-22]。MCP-1 则可促进肾小球系膜细胞的增生以及增值细胞

核抗原表达的增加，同时会促进细胞基质的沉积，进一步促进了肾小球硬化，对 DN 的进展起促进作用[23-25]。

本文结果显示，Rg1 组大鼠干预 12 周后的各项肾功能指标水平均低于模型组，表明了 Rg1 在改善 DN 大鼠肾功能方面具有显著的临床效果。分析原因，我们认为在中医理论下，DN 肾脏变化和血瘀证密切相关，因此活血化瘀药物对该病具有显著的功效，人参皂苷 Rg1 是提取自三七的人参皂苷单体，具有补血不留瘀，化瘀不伤血的功效，这与中医的驱邪扶正治疗原则相符[26]，可显著改善阿霉素肾病大鼠的肾功能，降低 Scr 以及 BUN 水平，且有效改善脂质代谢紊乱状况，缓解肾脏病理损害。本研究中 Rg1 组大鼠干预 12 周后血清氧化应激指标水平以及炎性因子水平相较模型组得以明显改善，究其原因，人参皂苷 Rg1 作为三七总皂苷的重要活性单体，主要成分和人参相似，具有抗肿瘤、扩张血管、抑制血小板聚集、抗炎、抗氧化以及诱导细胞凋亡等药理作用，而大量研究显示[27,28]，肾脏细胞损伤在 DN 的发生、发展过程中起着至关重要的作用，且肾脏氧化应激是导致细胞凋亡的重要因素。DN 状态下，高血糖以及代谢紊乱所产生的糖基化终末产物可促使机体处于氧化应激状态，引起局部炎症反应，因此，我们推测，人参皂苷 Rg1 治疗 DN 大鼠的重要机制可能与其有效减轻肾脏氧化应激反应以及局部炎症反应有关。另外，TGF-β1 可通过抑制组织细胞蛋白水解酶 mRNA 的表达，从而引起细胞外基质降解的减少，同时可促进部分蛋白水解酶抑制剂的产生，进一步导致蛋白水解酶活性的下降，最终导致细胞外基质成分的明显升高，对肾脏造成损害。MCP-1 不但可对单核 / 巨噬细胞发挥特异性趋化作用，提高巨噬细胞的粘附性，直接参与单核 / 巨噬细胞的浸润，同时可通过活化单核 / 巨噬细胞，导致溶酶体酶的大量释放以及超氧化物阴离子和胶原的产生，从而刺激 TGF-β、IL-1 以及 TNF-β 等细胞因子的产生，继而参与肾脏的损伤过程[29,30]。而本研究结果发现 Rg1 组、模型组大鼠干预 12 周后肾组织 TGF-β1、MCP-1 mRNA 表达水平均高于对照组，且 Rg1 组上述指标表达水平低于模型组，这提示了人参皂苷 Rg1 治疗 DN 的主要机制可能与调节肾组织 TGF-β1、MCP-1 mRNA 表达水平有关，对其作用的具体靶点进行更加深入的研究，可能有利于临床 DN 的防治。

综上所述，人参皂苷 Rg1 可显著改善 DN 大鼠肾功能，其中主要作用机制可能与调节血清氧化应激指标，下调炎性因子表达水平以及肾组织 TGF-β1、MCP-1 mRNA 表达有关。

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