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活血化癥方对糖尿病模型大鼠糖脂代谢、血管内皮生长因子和血管紧张素 II1 型受体表达的影响 *

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摘要 目的:探讨活血化癥方对糖尿病模型大鼠糖脂代谢、血管内皮生长因子(VEGF)和血管紧张素 II1 型受体(AT1R)表达的影响。**方法:**选取健康雄性 SD 大鼠 50 只,适应性喂养 7 d 后以随机数字表法分成对照组 10 只、模型组 13 只、中药组 14 只、西药组 13 只。其中模型组与对照组予以纯净水灌胃,中药组予以活血化癥通络中药配方颗粒灌胃,西药组则予以厄贝沙坦灌胃,1 次/d,连续灌胃 16 周。分别比较各组大鼠的糖脂代谢指标水平及 24 h 尿蛋白定量、糖化血红蛋白、血清肌酐水平,并检测肾组织 VEGF 和 AT1R 表达情况。**结果:**模型组、中药组、西药组大鼠空腹血糖(FBG)、总胆固醇(TC)、甘油三酯(TG)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)水平均高于对照组,中药组、西药组大鼠 LDL-C 水平低于模型组,中药组大鼠 FBG 水平低于模型组与西药组($P<0.05$)。模型组、中药组、西药组大鼠 24 h 尿蛋白定量与糖化血红蛋白均高于对照组,中药组、西药组大鼠 24 h 尿蛋白定量低于模型组($P<0.05$)。模型组、中药组、西药组大鼠 VEGF、AT1R 水平均高于对照组,中药组、西药组大鼠 VEGF、AT1R 水平低于模型组,中药组大鼠 AT1R 水平低于西药组($P<0.05$)。**结论:**活血化癥方可有效改善糖尿病大鼠糖脂代谢状态,通过抑制 VEGF 与 AT1R 的表达水平,延缓糖尿病的发生与发展。

关键词:糖尿病;大鼠;活血化癥方;糖脂代谢;血管内皮生长因子;血管紧张素 II1 型受体

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Effects of Huoxue Huayu Recipe on Glycolipid Metabolism, Vascular Endothelial Growth Factor and Angiotensin II1 Type Receptor Expression in Diabetic Rats*

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ABSTRACT Objective: To investigate the effects of Huoxue huayu recipe on glycolipid metabolism, vascular endothelial growth factor (VEGF) and angiotensin II1 type receptor (AT1R) expression in diabetic rats. **Methods:** A total of 50 healthy male SD rats were selected from the experimental animal center of Hebei province, after adaptive feeding 7 d, the rats were randomly divided into control group ($n=10$), model group ($n=13$), Chinese medicine group ($n=14$) and western medicine group ($n=13$). The model group and the control group were irrigated the stomach with pure water, the Chinese medicine group was irrigated the stomach with Huoxue huayu recipe, while the western medicine group was irrigated the stomach with erbesartan, once a day, continuous gavage for 16 weeks. The levels of glycolipid metabolism indexes and 24 h urine protein quantification, glycosylated hemoglobin and serum creatinine were compared among the four groups, and the expression of VEGF and AT1R was examined. **Results:** The levels of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) in the model group, the Chinese medicine group and the western medicine were all higher than those in the control group, the levels of LDL-C in the Chinese medicine group and the western medicine group were lower than that in the model group, the level of FBG in the Chinese medicine group was lower than those in the model group and the western medicine group ($P<0.05$). 24 h urine protein quantification and glycosylated hemoglobin in the model group, the Chinese medicine group and the western medicine were all higher than those in the control group, 24 h urine protein quantification in the Chinese medicine group and the western medicine group was lower than that in the model group ($P<0.05$). The levels of VEGF and AT1R in the model group, the Chinese medicine group and the western medicine were all higher than those in the control group, the levels of VEGF and AT1R in the Chinese medicine group and the western medicine group was lower than that in the model group, and the level of AT1R in the Chinese medicine group was lower than that of the western medicine group ($P<0.05$). **Conclusion:** Huoxue huayu recipe can effectively improve the glycolipid metabolic state of diabetic rats, and it can delay the occurrence and development of diabetes through reducing the expression levels of VEGF and AT1R.

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前言

糖尿病属于临床上最为常见的一种基础疾病,主要是由遗传以及环境因素共同作用引起的^[1,2]。患者长期处于高血糖状态,因此发生心脑血管神经血管等组织结构障碍的风险较高,严重者甚至会发生器官功能衰竭,影响患者的生命健康安全^[3-5]。糖尿病肾病属于糖尿病慢性并发症之一,患者临床特征包括蛋白尿、高血压以及渐进性肾功能降低等,如不给予及时有效的治疗,随着病情的逐渐进展,则会导致肾功能衰竭^[6-8]。目前,临床上治疗糖尿病主要以西医为主,而随着近年来中医药在临床上应用效果得到广泛认可,中医治疗糖尿病成为日益关注的热点。活血化瘀方具有活血行气、祛风止痛以及改善免疫功能的作用^[9]。鉴于此,本研究通过探讨外用活血化瘀方对糖尿病模型大鼠糖脂代谢、血管内皮生长因子(vascular endothelial growth factor, VEGF)和血管紧张素 II 型受体(angiotensin II 1 type receptor, AT1R)表达的影响并予以分析,旨在为临床有效治疗糖尿病提供一种新的手段。现作以下报道。

1 材料与方法

1.1 实验动物与分组

选取购自河北省实验动物中心的健康雄性 SD 大鼠 50 只,体重为 90-120 g,平均体重为(106.42±10.32)g。适应性喂养 7 d 后以随机数字表法分成对照组 10 只、模型组 13 只、中药组 14 只、西药组 13 只。对于本次研究我院实验动物伦理委员会已批准。

1.2 模型制备与干预方法

(1)大鼠造模:模型组、中药组、西药组大鼠以普通饲料适应性喂养 7 d 后,一次性腹腔注射链脲佐菌素(购自 ENZO 公司)55 mg/kg,对照组大鼠则腹腔注射等体积不含有链脲佐菌素的 0.1 M 枸橼酸缓冲液。72 h 后测量血糖水平,随机连续三

次静脉血糖水平高于 16.7 mmol/L 的大鼠即为造模成功的糖尿病模型大鼠。(2)给药方式:模型组与对照组予以等剂量的纯净水灌胃,中药组予以活血化瘀通络中药配方颗粒进行灌胃,每次剂量为 3.92 g/kg;活血化瘀通络中药配方主要包括丹参、川芎、水蛭、地龙、全蝎,由广东一方制药有限公司生产。西药组则予以厄贝沙坦(扬子江药业集团北京海燕药业有限公司,国药准字:H20100164,规格:75 mg)灌胃,每次剂量为 24 mg/kg。1 次/d,连续灌胃 16 周。给药期间不予以胰岛素以及其他相关措施干预。

1.3 观察指标

采用日立 7060 全自动生化分析仪检测空腹血糖(fasting plasma glucose, FBG)、总胆固醇(total cholesterol, TC)、甘油三酯(triglycerides, TG)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)、糖化血红蛋白和血清肌酐的水平。收集各组 24 h 的尿液,应用双缩脲法检测 24 h 尿蛋白定量。采用 Western-blot 法检测肾组织中的 VEGF 表达情况,采用免疫组织化学法检测肾组织中 AT1R 表达情况,其结果由我院两位经验丰富的病理医师通过双盲法进行阅片评估。

1.4 统计学方法

采用 SPSS20.0 软件进行统计分析,糖脂代谢指标水平、VEGF、AT1R 水平等计量资料以($\bar{x} \pm s$)表示,实施 t 检验,计数资料以[n(%)]表示,实施 χ^2 检验,检验水准设置为 $\alpha=0.05$ 。

2 结果

2.1 各组大鼠糖脂代谢水平对比

模型组、中药组、西药组大鼠 FBG、TC、TG、HDL-C、LDL-C 水平均高于对照组,中药组、西药组大鼠 LDL-C 水平低于模型组,中药组大鼠 FBG 水平低于模型组与西药组($P<0.05$)。见表 1。

表 1 各组大鼠糖脂代谢水平对比($\bar{x} \pm s$)

Table 1 Comparison of glycolipid metabolism levels of rats in each group($\bar{x} \pm s$)

Groups	n	FBG(mmol/L)	TC(mmol/L)	TG(mmol/L)	HDL-C(mmol/L)	LDL-C(mmol/L)
Control group	10	4.79±0.38	1.79±0.23	0.94±0.33	0.77±0.10	0.28±0.05
Model group	13	24.15±3.25 [#]	4.48±1.38 [#]	3.20±0.70 [#]	0.96±0.10 [#]	2.04±1.12 [#]
Chinese medicine group	14	21.38±3.01 ^{#*}	4.33±1.01 [#]	3.22±0.79 [#]	0.91±0.07 [#]	1.50±0.52 ^{#*}
Western medicine group	13	25.01±3.05 [#]	4.46±1.22 [#]	3.60±1.38 [#]	0.98±0.15 [#]	1.43±0.55 ^{#*}

Note: compared with control group, [#] $P<0.05$; compared with model group, ^{*} $P<0.05$; compared with western medicine group, [¥] $P<0.05$.

2.2 各组大鼠 24 h 尿蛋白定量、糖化血红蛋白、血清肌酐水平对比

模型组、中药组、西药组大鼠 24 h 尿蛋白定量与糖化血红蛋白均高于对照组,中药组、西药组大鼠 24 h 尿蛋白定量低于模型组($P<0.05$);四组大鼠血清肌酐水平对比均无统计学差异($P>0.05$)。见表 2。

2.3 各组大鼠 VEGF、AT1R 水平对比

模型组、中药组、西药组大鼠 VEGF、AT1R 水平均高于对照组,中药组、西药组大鼠 VEGF、AT1R 水平低于模型组,中药组大鼠 AT1R 水平低于西药组($P<0.05$)。见表 3。

3 讨论

近年来,随着我国人口老龄化问题的日益加重,糖尿病发病率逐年上升^[10]。其中糖尿病肾病是属于糖尿病常见并发症之一,具有较大的危害性^[11,12]。该病的发病机制较为复杂,可能与糖代谢紊乱、氧化应激以及血流动力学变化等多种因素相关,迄今为止尚未彻底明确^[13-15]。因此,糖尿病的发病机制及糖尿病

肾病发生和发展的机理已成为目前临床研究的重要课题。中医认为,糖尿病发病机制为气阴两虚,而糖尿病日久不愈引起的瘀血内阻是导致肾损害的重要机制,属于"络病"范畴,临床治疗应当以活血化瘀、软坚散结为主^[16,17]。

表 2 各组大鼠 24 h 尿蛋白定量、糖化血红蛋白、血清肌酐水平对比($\bar{x} \pm s$)

Table 2 Comparison of 24 h urine protein quantification, glycosylated hemoglobin and serum creatinine levels of rats in each group($\bar{x} \pm s$)

Groups	n	24h urinary protein quantification(mg/24h)	Glycosylated hemoglobin (%)	Serum creatinine(μ mmol/L)
Control group	10	10.79 $\pm$ 1.20	3.19 $\pm$ 0.37	35.83 $\pm$ 8.01
Model group	13	28.08 $\pm$ 2.27 [#]	6.32 $\pm$ 0.63 [#]	28.57 $\pm$ 8.81
Chinese medicine group	14	20.01 $\pm$ 1.70 ^{#*}	6.12 $\pm$ 0.57 [#]	30.81 $\pm$ 5.63
Western medicine group	13	19.87 $\pm$ 1.91 ^{#*}	6.09 $\pm$ 0.60 [#]	30.79 $\pm$ 5.67

Note: compared with control group, [#]P<0.05; compared with model group, *P<0.05.

表 3 各组大鼠 VEGF、AT1R 水平对比($\bar{x} \pm s$)

Table 3 Comparison of VEGF and AT1R levels of rats in each group($\bar{x} \pm s$)

Groups	n	VEGF(pg/mL)	AT1R(%)
Control group	10	0.34 $\pm$ 0.02	1.16 $\pm$ 0.88
Model group	13	0.72 $\pm$ 0.04 [#]	9.27 $\pm$ 1.57 [#]
Chinese medicine group	14	0.44 $\pm$ 0.01 ^{#*}	5.69 $\pm$ 1.42 ^{#**}
Western medicine group	13	0.48 $\pm$ 0.02 ^{#*}	6.91 $\pm$ 1.60 ^{#*}

Note: compared with control group, [#]P<0.05; compared with model group, *P<0.05; compared with western medicine group, [¥]P<0.05.

本研究结果发现,中药组大鼠 LDL-C 水平低于模型组,FBG 水平低于模型组与西药组,提示了活血化瘀方可有效改善糖尿病模型大鼠的糖脂代谢状态。主要原因在于活血化瘀方中的丹参具有改善微循环、降压以及抗炎等功效;而川芎具有活血行气、祛风止痛的功效;地龙则有镇痛抗炎以及提高免疫力的功效;全蝎具有抗血栓以及调节免疫功能的功效^[18]。此外,中药组大鼠 24h 尿蛋白定量低于模型组,这提示了外用活血化瘀方对糖尿病模型大鼠的肾功能具有一定的保护作用。究其原因,笔者认为丹参可通过对一氧化氮的产生以及转化生长因子- β 的表达产生抑制作用,从而达到改善肾功能的目的^[19-21]。同时,川芎中所含有的川芎嗪可有效增加肾血管流量,从而减轻肾组织细胞的脂质过氧化损伤^[22,23]。此外,地龙对肾脏Ⅳ型胶原蛋白的表达具有一定的抑制作用,从而有效改善细胞外基质聚集,继而减轻肾小球硬化和肾小管损伤,最终达到降低 24 h 尿蛋白定量的目的^[24,25]。最后,通过检测肾组织 VEGF 和 AT1R 表达水平可知,中药组、西药组大鼠 VEGF、AT1R 水平低于模型组,中药组大鼠 AT1R 水平低于西药组,这提示了西药与活血化瘀方均可能是通过降低 VEGF、AT1R 的表达水平,进一步发挥治疗的作用。VEGF 是目前作用最强的血管通透因子,其和肾小球滤过屏障的各个部分均有一定的联系^[26-27]。有研究报道显示,肾脏 AT1R 的表达可间接反映肾脏局部肾素-血管紧张素系统(renin angiotensin system, RAS)的活性,而 RAS 失常在糖尿病肾病的发生、发展过程中发挥着重要作用^[28-30],本研究也证实了活血化瘀方可能是通过阻断肾脏局部 RAS 系统实现保护肾脏的作用。

综上所述,活血化瘀方可有效改善糖尿病大鼠糖脂代谢状

态,对肾功能起到一定的保护作用,其中 VEGF、AT1R 的表达水平在治疗糖尿病中发挥的作用,还需今后进行深入的研究。

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