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苏木对糖尿病大血管病变中 SOD、TNF- α 、MCP-1 的影响 *

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摘要 目的: 探讨苏木对糖尿病大血管病变大鼠血清超氧化物歧化酶 (SOD)、肿瘤坏死因子 α (TNF- α)、单核细胞趋化因子 1 (MCP-1) 水平的影响。**方法:** 将 24 只雄性 SD 大鼠随机分为 4 组, 每组 6 只, 分别为对照组、模型组、 α - 硫辛酸组和苏木组。除去对照组, 余下的 18 只大鼠单次腹腔注射 STZ50 mg/kg 制备糖尿病大鼠模型, 对照组予以注射等体积的柠檬酸 - 柠檬酸钠缓冲液。成功造模后, 苏木组给予 0.15 g/kg/d 的苏木, α - 硫辛酸组给予 20 mg/kg/d 的 α - 硫辛酸, 每日 1 次给药, 连续给药 8 周。8 周末, 检测 and 比较两组大鼠血清中 SOD、TNF- α 、MCP-1 水平的变化。**结果:** 治疗后, 苏木组及 α - 硫辛酸组血清 SOD 含量均高于模型组 ($P < 0.05$), 但苏木组和 α - 硫辛酸组间比较无统计学差异 ($P > 0.05$); 苏木组及 α - 硫辛酸组血清 TNF- α 、MCP-1 含量均显著低于模型组 ($P < 0.05$), 与对照组没有明显差别 ($P > 0.05$)。**结论:** 苏木可提高糖尿病大血管病变大鼠血清 SOD 含量, 降低血清 TNF- α 、MCP-1 含量。**关键词:** 苏木; 糖尿病大血管病变; Superoxide dismutase; Tumor necrosis factor- α ; monocyte chemoattractant protein-1
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Effect of Caesalpinia Sappan on the Serum SOD, TNF- α , MCP-1 Levels in Rats with Diabetic Macroangiopathy*

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ABSTRACT Objective: Investigate the effect of Caesalpinia sappan on the levels of serum superoxide dismutase (SOD), tumor necrosis factor (TNF- α) and monocyte chemokine (MCP-1) in diabetic rats with macrovascular disease. **Method:** 24 male rats were randomly divided into 4 groups, 6 rats in each group, the control group, the model group, the α -lipoic acid group and the Caesalpinia sappan group, respectively. Except the control group, STZ50 mg/kg was injected intraperitoneally in other three groups. The control group was injected with equal volume of citric acid sodium citrate buffer. After successful molding, the Caesalpinia sappan group was given 0.15 g/kg/d of Caesalpinia sappan, α -lipoic acid group was given alipoic acid of 20 mg/kg/d, the drug was given 1 times a day for 8 weeks. After 8 weeks, the changes of SOD, TNF - α , MCP-1 in serum of two groups of rats were detected and compared. **Results:** After treatment, the contents of serum SOD in Caesalpinia sappan group and α -lipoic acid group were higher than those in model group. ($P < 0.05$), there was no statistical difference between two groups yet ($P > 0.05$). The level of serum TNF - α and MCP-1 were significantly lower in the Caesalpinia sappan group and α -lipoic acid group than those in the model group ($P < 0.05$), but there was no obvious difference comparing with the control group ($P > 0.05$). **Conclusion:** Caesalpinia sappan can increase the content of SOD and decrease the content of TNF- α and MCP-1 in the serum of diabetic rats with macrovascular disease.

Key words: Caesalpinia sappan; Diabetic macroangiopathy; SOD; TNF- α ; MCP-1**Chinese Library Classification(CLC):** R-33; R587.2; R285.5 **Document code:** A**Article ID:** 1673-6273(2018)14-2637-04

前言

糖尿病是一种由于胰岛素分泌或胰岛素作用缺陷, 引起机体的糖、脂、蛋白质等代谢异常的疾病, 以胰岛 β 细胞损伤为

主。相关研究^[1-3]表明胰岛 β 细胞损伤与氧化应激有着密切的关系, 氧化应激中产生氧化性物质, 即活性氧自由基(reactive oxygen species, ROS)可以加快胰岛 β 细胞的凋亡, 并且可以引起胰岛 β 细胞的炎症反应。

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糖尿病大血管病是糖尿病的一种严重并发症,主要危害是引起心脑血管病、下肢动脉硬化闭塞症等^[4],具有较高的致残致死率,严重影响患者的生活质量^[5]。大量临床研究表明^[6]糖尿病大血管病变与炎症反应有着密不可分的关系,所以在治疗上应该选用有抗炎及抗氧化作用相关的药物。研究证实^[7]苏木作为一种中药材具有抗氧化、抗炎、抗肿瘤及降糖等作用。因此,本研究主要探讨了研究苏木对糖尿病大血管病变大鼠血清中超氧化物歧化酶 (superoxide dismutase, SOD)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)、单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)水平的影响,以期为糖尿病大血管病的临床治疗提供更多的参考依据。

1 材料与方法

1.1 材料

1.1.1 实验动物 清洁级健康雄性 SD 大鼠 24 只, 体重 210-230g, 购自黑龙江中医药大学实验动物中心 (许可证号 SYXK(黑)2013-012)。

1.1.2 主要药物及试剂 苏木水提取物 (预制成的颗粒冲剂, 购自三九医药公司); α - 硫辛酸注射液 (重庆药友制药有限公司);链脲佐菌素 STZ(美国 Sigma 公司);柠檬酸、柠檬酸钠(山东省中创柠檬生化有限公司);SOD、TNF- α 、MCP-1 ELisa 试剂盒(北京博奥森生物技术有限公司)。

1.1.3 仪器 全自动血糖仪 (德国拜耳医药保健有限公司);I Mark 酶标仪(沈阳进出口贸易有限公司);台式高速冷冻离心机(湖北星科科学仪器有限公司);318W 型洗板机 (上海三科仪器有限公司);电热恒温水槽(上海精宏实验设备有限公司);精密电子天平(赛多利斯科学仪器有限公司)。

1.2 实验方法

1.2.1 动物模型制备与实验分组 24 只 SD 大鼠随机选取 6 只作为对照组, 余下的 18 只大鼠禁食 12 h 后单次腹腔注射 STZ 50 mg/kg, 注射前在闭光条件下将 STZ 粉与柠檬酸 - 柠檬酸钠缓冲液按 1 g 比 10 mL 的比例配置。72 h 后给予大鼠尾静脉采血, 检测血糖数值, 将血糖 ≥ 16.7 mmol/L 的 18 只大鼠定

为造模成功的大鼠, 随机将其分成模型组、 α - 硫辛酸组和苏木组。 α - 硫辛酸组给予 α - 硫辛酸 20 mg/kg/d 腹腔注射 8 周, 苏木组给予苏木 0.15 g/kg/d 灌服 8 周; 对照组、模型组予等体积的生理盐水灌服 8 周。

1.2.2 观察指标 大鼠饲养 8 周后, 分别向四组大鼠的腹腔注射 10% 水合氯醛进行麻醉, 腹主动脉取血, 3000 r/min, 温度 4℃, 离心 20 分钟, 收集上层血清。采用黄嘌呤氧化酶法测定血清中 SOD 的含量, 采用 Elisa 法检测血清中 TNF- α 、MCP-1 的含量。

1.3 统计学处理

应用 SPSS22.0 软件进行统计学分析, 所有数据均用($\bar{x} \pm s$)表示, 组间均数采用 t 检验, 以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组治疗前后血清 SOD 的比较

与对照组比较, 模型组大鼠血清 SOD 含量明显降低, 差异具有统计学意义($P < 0.05$); 与模型组比较, α - 硫辛酸组、苏木组中大鼠血清 SOD 含量明显升高, 差异具有统计学意义($P < 0.05$)。而 α - 硫辛酸组和苏木组的血清 SOD 含量比较差异无统计学意义($P > 0.05$), 见表 1。

2.2 两组治疗前后血清中 TNF- α 含量的比较

与对照组比较, 模型组大鼠血清 TNF- α 含量升高, 差异具有统计学意义($P < 0.05$); 与模型组比较, α - 硫辛酸组、苏木组中大鼠血清 TNF- α 含量明显降低, 差异具有统计学意义($P < 0.01$), 但 α - 硫辛酸组和苏木组的大鼠血清 TNF- α 含量比较差异无统计学意义($P > 0.05$), 见表 1。

2.3 两组治疗前后血清中 MCP-1 含量的比较

与对照组比较, 模型组血清 MCP-1 含量升高, 差异具有统计学意义($P < 0.05$); 与模型组比较, α - 硫辛酸组、苏木组中大鼠血清 MCP-1 含量降低, 差异具有统计学意义($P < 0.05$), 但 α - 硫辛酸组和苏木组的大鼠血清 TNF- α 含量比较差异无统计学意义($P > 0.05$), 见表 1。

表 1 两组大鼠治疗前后血清中 SOD、TNF- α 、MCP-1 含量的比较(ng/L, $\bar{x} \pm s$)

Table 1 Comparison of the serum SOD, TNF- α and MCP-1 levels before and after treatment between two groups(ng/L, $\bar{x} \pm s$)

Groups	Amount(n)	SOD	TNF- α	MCP-1
Control group	6	77.95 $\pm$ 8.49 [▲]	127.76 $\pm$ 15.20 ^{▲▲}	178.47 $\pm$ 48.47 ^{▲▲}
Model group	6	63.15 $\pm$ 7.79 [*]	180.45 $\pm$ 20.42 ^{**}	294.53 $\pm$ 41.20 ^{**}
α -lipoic acid group	6	75.41 $\pm$ 10.80 [▲]	135.52 $\pm$ 23.22 ^{▲▲}	195.31 $\pm$ 80.08 [▲]
Caesalpinia sappan group	6	73.17 $\pm$ 10.49 [▲]	132.10 $\pm$ 13.35 ^{▲▲}	196.70 $\pm$ 72.06 [▲]

Note: compared with the blank control group, ^{*} $P < 0.05$, ^{**} $P < 0.01$; compared with the model control group, [▲] $P < 0.05$, ^{▲▲} $P < 0.01$.

3 讨论

糖尿病常见的并发症有周围神经病变、糖尿病肾病、糖尿病视网膜病变及糖尿病大血管病变等, 糖尿病大血管病变作为其主要的并发症之一越来越受到人们的关注。现代医学通常采用抗凝、降脂和抗氧化的药物对其进行治疗, 能够有效的改善高氧化应激状态, 疗效较为显著。糖尿病大血管病变的病理基

础是动脉粥样硬化, 由于长期的高血糖状态使血管壁过多沉积胆固醇、脂质等物质, 导致血脂代谢异常, 引发糖尿病大血管病变^[8-10]。Brownlee 等人^[11-13]提出 " 糖尿病并发症的共同机制 " 学说, 认为氧化应激是糖尿病大血管和微血管并发症共同的发病机制。正常人体中的氧化性物质与抗氧化物质一直处于动态平衡, 当机体遇到有害刺激时两者的平衡状态被打乱, 进而产生过多的 ROS^[14,15]。ROS 的含量与氧化应激反应程度呈正相关,

即 ROS 含量升高说明氧化应激反应发生增多,反之则减少。高血糖状态时,机体会产生过多的 ROS^[6],引起血管炎症反应,这不仅会对血管内皮细胞造成损伤^[7],而且会造成血管内皮功能紊乱,导致动脉粥样硬化加剧,血管内会形成动脉硬化斑块,从而引发糖尿病大血管病变。

SOD 作为一种抗氧化物,是一种从牛血红蛋白中分离出的物质,又称为肝蛋白^[8]。SOD 可以清除机体内因有害刺激产生的过量 ROS,来帮助维持机体代谢的平衡,并减轻氧自由基对细胞造成的损害,同时修复受损细胞、恢复血管内皮功能,从而起到抗氧化的作用^[9]。当血清中 SOD 降低,抗氧化能力减弱,自由基会在体内大量堆积,进而增加糖尿病大血管病及其他并发症的发生几率^[20]。动脉粥样硬化是动脉壁受损引发的一种慢性炎症性疾病,作为糖尿病大血管病变的病理基础,其发生与发展一直伴随着炎症反应的参与。虽然动脉粥样硬化发病机制尚不明确^[21],但 TNF- α 、MCP-1 两种因子参与炎症反应已被证实^[22]。有关研究表明^[23-25]糖尿病大血管病患者的血清中 TNF- α 的含量会呈现升高状态,在高血糖或胰岛素抵抗发生时 TNF- α 过度表达,这会对血管内皮细胞造成损害,增加血管的通透性,促使血管内斑块的形成。同时,也有研究表明^[26]当糖尿病患者受到高血糖、炎症等刺激时,MCP-1 的表达会明显升高,MCP-1 可使单核细胞移至受损的血管内皮细胞发生趋化、聚集、粘附等一系列反应,使血管平滑肌细胞异常增生,从而促进动脉粥样硬化的形成。

苏木属于豆科中药,具有活血化瘀、舒筋通络和消肿止痛等功效,主要成分有巴西苏木素、查尔酮及原苏木素等。其中,巴西苏木素具有抗炎、抗氧化^[27,28]等作用。原苏木素具有抗炎作用,能抑制 TNF- α 的表达。前期对苏木的研究主要集中在治疗糖尿病肾病方面,多从血糖、肌酐、尿素氮、蛋白尿等指标入手,证实苏木可以降低糖尿病肾病大鼠的血糖并改善肾功能,这些都属于苏木对糖尿病小血管病的研究^[29,30]。还有研究表明^[31]苏木在治疗糖尿病大血管病变中起到了一定的治疗作用,它在维持糖尿病大鼠血管完整性,加强血管内皮功能方面有较好的功效。本实验探索了苏木对糖尿病大血管病中 SOD、TNF- α 、MCP-1 含量的影响,结果显示苏木可以提升血清 SOD 的含量,降低血清 TNF- α 、MCP-1 的含量,其治疗作用与 α -硫辛酸相当,对治疗糖尿病大血管病有一定的促进作用,为治疗糖尿病大血管病提供了新的线索。

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