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黄芪甲苷对糖尿病 KKAy 小鼠肾组织 TGF- β 1、SMAD2/3 及 α -SMA 表达的影响

王雅宁¹,刘云启¹,高金祥¹,蔺超²,刘乃国³

(滨州医学院附属医院:1.肾内科;2.骨关节外科;3.临床医学实验中心,山东滨州 256603)

[摘要] **目的** 观察黄芪甲苷对糖尿病 KKAy 小鼠肾组织转化生长因子 β 1(TGF- β 1)、SMAD2/3、 α -平滑肌肌动蛋白(α -SMA)表达的影响,探讨其延缓肾脏纤维化的可能机制。**方法** 雄性 C57BL/6J 小鼠 10 只作为对照组,20 只 2 型糖尿病模型 KKAy 小鼠予以高脂饮食至 14 周,随机数字法分为模型组和黄芪甲苷组,每组 10 只,黄芪甲苷组给予黄芪甲苷 $40\text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$,模型组与对照组给予等量生理盐水。实验期间,各组动物自由饮食、饮水。血糖仪测量 16、20、24 周龄时各组小鼠的血糖水平。24 周时处死,观察各组小鼠肾的病理学变化,免疫组织化学法测定 TGF- β 1、SMAD2/3、 α -SMA 的表达。**结果** (1)血糖:与对照组相比,14 周龄的 KKAy 小鼠血糖明显升高,模型组血糖在 16、20、24 周时血糖明显升高($P<0.05$),黄芪甲苷组与其相比,血糖下降($P<0.05$)。(2)肾组织形态学:对照组肾小球及肾小管结构清晰,未出现肾间质纤维化,模型组肾小球系膜基质增宽,系膜细胞增多,肾小管上皮细胞细胞质空泡样变性,肾间质炎性细胞增多,黄芪甲苷组肾小管上皮细胞细胞质较少,未呈现明显的纤维化。(3)肾组织 TGF- β 1、SMAD2/3、 α -SMA 的表达:对照组 TGF- β 1 表达微弱,而模型组 TGF- β 1 显著表达于肾小管上皮细胞细胞质($P<0.01$);与模型组相比,黄芪甲苷组 TGF- β 1、 α -SMA 表达明显下调($P<0.05$);对照组肾小管与肾小球细胞核有少量磷酸化的 SMAD2/3 表达,模型组表达增加($P<0.01$),与模型组相比,黄芪甲苷组表达减少($P<0.05$)。**结论** 黄芪甲苷通过影响 TGF- β /SMADS 信号通路,下调 TGF- β 1、 α -SMA 表达,改善糖尿病小鼠肾脏纤维化。

[关键词] 黄芪甲苷;糖尿病肾病;转化生长因子;肌动蛋白- α ;Smads 信号蛋白

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The effect of astragaloside on TGF- β 1, SMAD2/3, and α -SMA expression in the kidney tissues of diabetic KKAy mice

Wang Yaning¹, Liu Yunqi¹, Gao Jinxiang¹, Lin Chao², Liu Naiguo³

(1. Department of Nephrology; 2. Department of Bone and Joint Surgery; 3. Department of Clinical and Medicine Lab, the Affiliated Hospital of Binzhou Medical University, Binzhou, Shandong 256603, China)

[Abstract] **Objective** To study the effect of astragaloside on TGF- β 1, SMAD2/3, and α -SMA expression in the kidney tissue of diabetic KKAy mice, and evaluate its potential role in renal interstitial fibrosis. **Methods** 20 type 2 diabetic KKAy mice were randomly divided into model group and astragaloside group, while 10 male C57BL/6J mice were selected as the control. Astragaloside at $40\text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ was given when the KKAy mice fed with high-fat diet to 14 weeks old. The mice in the control and model group received normal saline at $40\text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. Blood glucose meter was used to detect the blood glucose value of each mice at 16th, 20th and 24th week. The mice were killed at 24 weeks old and the kidney tissue samples were collected. Pathology morphological changes were observed. **Results** (1) blood glucose value; compared with the control group, the blood glucose value of KKAy mice at 14 week increased significantly, and that of model group also increased significantly at 16th, 20th and 24th week ($P<0.05$); the blood glucose value of astragaloside group decreased compared with control group ($P<0.05$). (2) Morphology of kidney; in the control group, the glomerular and tubular had clear structure, there was no renal interstitial fibrosis; in the model group, the renal glomerular mesangial matrix had broaden, mesangial cell had increased, renal tubular epithelial cell cytoplasm showed vacuole degeneration, renal interstitial inflammatory cell had increased. In astragaloside group, there were few renal tubular epithelial cell cytoplasm, and there was no obvious fibrosis. (3) TGF- β 1, SMAD2/3, and α -SMA expression levels of the kidney issue; compared with control group, mice in model group up-regulated TGF- β 1, SMAD2/3 and α -SMA expression ($P<0.05$). TGF- β 1, SMAD2/3, and α -SMA expression levels in astragaloside group were significantly lower than those in the model group ($P<0.05$). There was few phosphorylated SMAD2/3 expression in renal tubular and glomerular nuclei, while that of model group increased ($P<0.01$), and compared with model group, that of the astragaloside group decreased ($P<0.05$). **Conclusion** Astragaloside can delay the renal fibrosis process in diabetic mice by influencing the TGF- β /SMADS signaling pathway and down-regulating TGF- β 1 and α -SMA expression, thus to relieve renal fibrosis in diabetic mice.

[Key words] astragaloside; diabetic nephropathy; TGF- β 1; α -SMA; SMAD

糖尿病肾病是糖尿病微血管病变中的重要并发症之一,是导致终末期肾病和糖尿病患者死亡的主要原因。肾小管及肾

小球的炎症、纤维化是糖尿病肾病进展为终末期肾病的主要病理基础,并且肾小管的损伤先于肾小球损伤^[1-2]。因此,阻断肾小管纤维化在延缓肾功能恶化过程中起着重要的作用。包括转化生长因子 $\beta 1$ (TGF- $\beta 1$)在内的许多细胞因子参与了肾脏纤维化的过程。TGF- $\beta 1$ 可诱导肾小管上皮细胞向纤维母细胞转化,且在糖尿病肾病的发展过程中,TGF- $\beta 1$ 表达增加^[3-4]。作为 TGF- β 家族的下游信号转导蛋白,Smads 信号蛋白(SMAD)蛋白同肾脏纤维化密切相关。有研究发现,TGF- β 刺激肾小管上皮细胞时,SMAD2 发生磷酸化并且转入核内,促使肾小管上皮细胞表达胶原蛋白及 α -平滑肌肌动蛋白(α -SMA)增加^[5-6]。黄芪甲苷是从豆科植物黄芪中提取出来的具有抗氧化、抗炎的物质,可通过多种途径保护肾脏。本研究通过观察黄芪甲苷对糖尿病 KKAY 小鼠肾组织 TGF- $\beta 1$ 、SMAD2/3 及 α -SMA 表达的影响,探讨其对肾间质纤维化的保护作用,为临床应用黄芪甲苷保护肾脏提供实验依据。

1 材料与方法

1.1 材料

1.1.1 实验动物 雄性 C57BL/6J 小鼠 10 只及 KKAY 小鼠 20 只,体质量 22~24 g,购自中国医学科学院动物中心,饲养于无特定病原体(SPF)级动物实验室;

1.1.2 主要试剂 黄芪甲苷(美国 Sigma 公司);DAB 试剂盒、TGF- $\beta 1$ 和 α -SMA 多克隆抗体(北京中山生物科技有限公司);磷酸化 SMAD2/3 多克隆抗体(武汉博士德公司)。

1.2 方法

1.2.1 动物分组及给药 高脂饮食饲养至 14 周龄的 KKAY 小鼠当随机血糖大于 13.9 mmol/L 时提示造模成功^[7],随机数字法分成模型组和黄芪甲苷组(每日灌胃,剂量为 40 mg · kg⁻¹ · d⁻¹),同龄雄性 C57BL/6J 小鼠作为对照组,实验期间,各组动物自由饮食、饮水。

1.2.2 标本采集 分别于 16、20、24 周时尾静脉取血测量血糖水平;24 周龄时处死各组小鼠,以 4%多聚甲醛固定肾组织。

1.2.3 指标检测 小鼠禁食 6 h 后罗氏血糖仪监测血糖。

1.2.4 肾组织病理形态学观察 石蜡包埋肾组织后切片,进行常规苏木精-伊红(HE)染色及 Masson 染色,在光镜下观察;免疫组织化学:据 SABC 试剂盒说明书测定 TGF- $\beta 1$ 、SMAD2/3 及 α -SMA 表达情况,随机数字法选取 10 个以上肾小球测定上述蛋白表达。

1.3 统计学处理 所有数据应用 SPSS 19.0 进行统计分析,所有数据均以 $\bar{x} \pm s$ 表示,组间差异采用 *t* 检验或单因素方差分析及 LSD 检验,以 *P* < 0.05 差异有统计学意义。

2 结 果

2.1 一般状态比较 对照组老鼠对外界反应灵敏,毛色顺滑。模型组小鼠精神状态差,步履缓慢,烦渴多尿,反应差,毛发枯燥。随着周龄的增加,上述症状更加明显。黄芪甲苷组小鼠的精神状态及反应能力介于两组之间。

2.2 黄芪甲苷对 KKAY 糖尿病小鼠血糖的影响 与对照组相比,14 周龄的 KKAY 小鼠血糖明显升高,模型组血糖在 16、20、24 周时血糖明显升高(*P* < 0.05),黄芪甲苷组与其相比,血糖下降(*P* < 0.05)。见表 1。

2.3 黄芪甲苷对 KKAY 糖尿病小鼠组织形态学的影响 对照组小鼠肾小球及肾小管结构清晰,没有肾间质纤维化。模型组肾小球系膜基质增宽,系膜细胞增多,肾小管上皮细胞细胞空泡样变性,肾间质炎性细胞增多。黄芪甲苷组肾小管上皮细胞细胞质较少,未呈现明显的纤维化。见图 1。

表 1 各组小鼠末梢血糖水平($\bar{x} \pm s$,mmol/L)					
组别	<i>n</i>	14 周	16 周	20 周	24 周
对照组	10	5.91±0.68	5.15±0.72	5.31±0.69	5.38±0.76
模型组	10	15.82±1.65 ^a	21.62±2.2 ^a	26.15±3.04 ^a	26.81±2.85 ^a
黄芪甲苷组	10	16.15±1.56 ^a	13.51±1.34 ^{ab}	18.37±1.98 ^{ab}	17.23±1.56 ^{ab}

^a:*P* < 0.05,与对照组比较;^b:*P* < 0.05,与模型组比较。

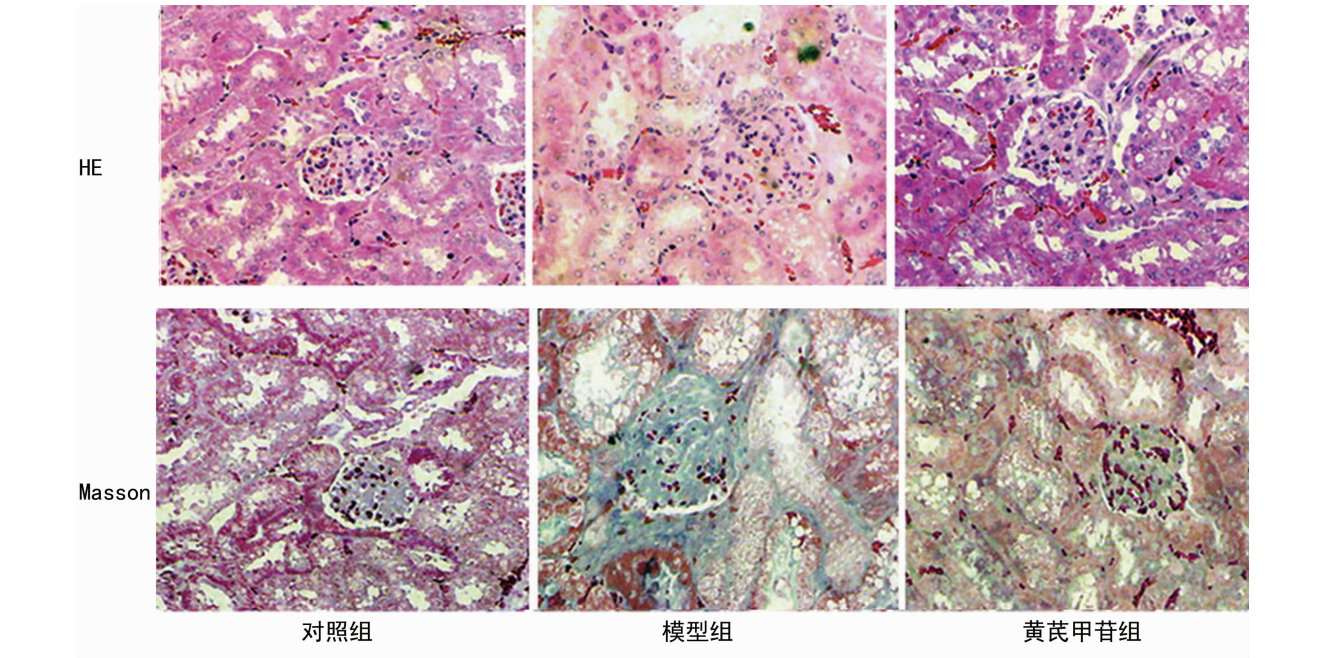


图 1 黄芪甲苷对 KKAY 糖尿病小鼠组织形态学的影响(×200)

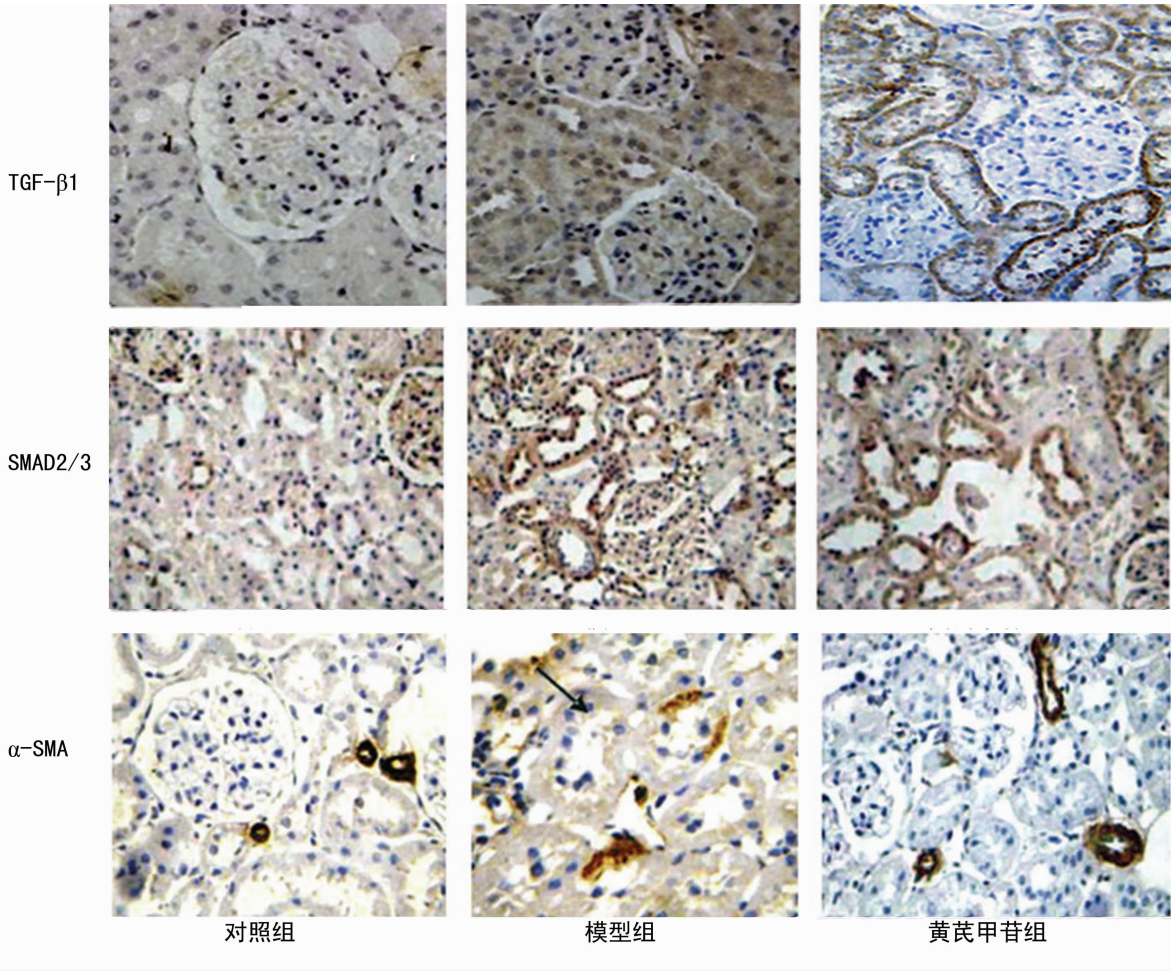


图 2 黄芪甲苷对 KKAy 糖尿病小鼠肾组织 TGF-β1、SMAD2/3 及 α-SMA 表达的影响(免疫组织化学×200)

2.4 黄芪甲苷对 KKAy 糖尿病小鼠肾组织 TGF-β1、SMAD2/3 及 α-SMA 表达的影响 对照组 TGF-β1 表达微弱,而模型组 TGF-β1 显著表达于肾小管上皮细胞细胞质($P<0.01$);与模型组相比,黄芪甲苷组 TGF-β1、α-SMA 表达明显下调($P<0.05$);对照组肾小管与肾小球细胞核有少量磷酸化的 SMAD2/3 表达,模型组表达增加($P<0.01$),同模型组相比,黄芪甲苷组表达减少($P<0.05$)。见表 2、图 2。

表 2 各组小鼠肾组织 TGF-β、SMAD2/3、α-SMA 平均吸光度值($\bar{x}\pm s$)

组别	TGF-β1	SMAD2/3	α-SMA
对照组	47.52±5.61	5.26±0.48	106.95±10.53
模型组	106.58±9.83 ^a	14.53±1.39 ^a	144.24±14.74 ^a
黄芪甲苷组	66.25±6.87 ^b	9.07±0.88 ^b	107.36±11.21 ^b

^a: $P<0.01$,与对照组比较;^b: $P<0.05$,与模型组比较。

3 讨 论

黄芪甲苷是豆科植物膜荚黄芪的干燥根,是从黄芪总苷中分离的一类单体化合物,是豆科植物黄芪的主要成分,具有抗应激、降低血糖、调节免疫、利尿消肿、保护肾脏等多种药理学作用^[8]。膜荚黄芪具有延缓糖尿病肾病发展及延缓肾小球系膜基质增生的作用。然而,有关黄芪甲苷的肾脏保护机制尚未完全阐明。有研究表明,在高糖或链脲霉素诱导的 1 型糖尿病大鼠模型中,黄芪甲苷通过增加足细胞 α3β1 整合素的表达,下

调整整合素的表达,发挥对足细胞的保护作用^[9]。此外,黄芪甲苷通过 Caspase-3 调节 Bax/Bcl-2 以抑制足细胞凋亡^[10]。有研究者发现,在急性肾损伤时,黄芪甲苷通过抑制核因子-κB (NF-κB)表达及阻断 p38MAPK 通路来减少炎症因子的释放,修复损伤的肾小管^[11-12]。有研究证实,黄芪甲苷可通过下调 TGF-β1 及阻断 p38MAPK 通路,抑制高糖诱导的人肾小管上皮细胞发生凋亡^[13-14]。最近研究证实,黄芪甲苷通过抑制肾小管上皮细胞产生活性氧从而减轻氧化应激,阻断上皮细胞转分化的发生^[15-16]。因此,假设黄芪甲苷通过 TGF-β1 介导的细胞通路影响炎症及纤维化,此项研究旨在观察黄芪甲苷对糖尿病 KKAy 小鼠 TGF-β1、SMAD2/3 及 α-SMA 表达的影响,探讨其对肾间质纤维化的作用。

肾间质纤维化及肾小管损伤在肾脏疾病发展过程中起了重要的作用,且与肾功能下降密切相关。肾小管上皮细胞转分化是糖尿病肾病进程中的关键一环,且在此进程中肾功能恶化的重要机制之一就是肾小管间质纤维化。在肾小管间质纤维化发展过程中,承担细胞外基质合成的细胞主要为肌成纤维母细胞,而近曲小管上皮细胞可转分化为肌成纤维母细胞。因此,延缓慢性肾脏病发展的关键就是抑制肾小管间质纤维化^[17-18]。肾小管上皮细胞在受到刺激后转分化为成纤维母细胞,进而分泌某些细胞因子,细胞极性消失,大量细胞外基质积聚,最终导致肾间质纤维化。在肾小管上皮细胞转分化过程中,TGF-β1 扮演了重要角色,而作为 TGF-β 家族的下游信号转导蛋白,SMAD 蛋白同肾脏纤维化密切相关。在本研究中,

探讨了黄芪甲苷对糖尿病 KKAy 小鼠血糖及肾脏病理形态学的影响。实验结果显示,与对照组相比,模型组肾组织纤维化及血糖明显升高;同模型组相比,黄芪甲苷组肾间质纤维化减轻,血糖水平下降,细胞增生减少,这提示黄芪甲苷可减少糖尿病 KKAy 小鼠血糖水平,延缓肾脏纤维化的发展。此外,与对照组相比,模型组 TGF- β 1、SMAD2/3 及 α -SMA 表达明显增加,与模型组相比,黄芪甲苷组上述指标表达下降。 α -SMA 是肾小管上皮细胞转分化的标志,其水平高低可反映肾脏纤维化的程度。先前的体外研究发现,SMAD2/3 表达于人系膜细胞,且在 TGF- β 1 导致胶原 I 分泌增加的过程中也有 SMAD 信号通路的参与^[19-20]。肾小管上皮细胞转分化分为 4 个过程:肾小管上皮细胞间紧密连接的破坏; α -SMA 的表达及肌动蛋白细胞骨架的重排;肾小管基底膜的破坏;肾小管上皮细胞发生迁移,侵袭能力增加。TGF- β 1 作为关键的细胞因子通过调节细胞增殖和分化参与了上述过程,该因子可抑制基质降解酶的表达,促进肾小管上皮细胞转分化,抑制肾小管细胞增殖,最终导致肾脏炎症及纤维化^[20-21]。体外实验证实,在肾小球系膜细胞及肾小管上皮细胞,高糖刺激可激活 SMAD 信号通路,引起 TGF- β 1 过表达。本实验证实 TGF- β 1、SMAD2/3 及 α -SMA 在糖尿病小鼠肾组织中高表达,同上述研究一致。此外,TGF- β /SMADS 信号通路的激活可使 α -SMA 表达增加^[22-24]。本研究发现,黄芪甲苷可使糖尿病 KKAy 小鼠 TGF- β 1、SMAD2/3 及 α -SMA 表达减弱,说明黄芪甲苷可通过下调 TGF- β 1、SMAD2/3 及 α -SMA 的表达,抑制 TGF- β /SMADS 信号通路,最终减轻肾脏纤维化。

膜荚黄芪以往被认为有利水消肿的功效。本研究发现,黄芪甲苷可通过调节 TGF- β /SMADS 信号通路并且下调 TGF- β 1、SMAD2/3 及 α -SMA 的表达,改善糖尿病小鼠肾脏纤维化,从而通过抑制肾小管间质纤维化及肾小管上皮细胞转分化,发挥肾脏保护作用。

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49%;与此同时细胞的侵袭能力得以降低。

综上所述,本研究成功制备了可以携带目的基因的靶向超声微泡,并在体外可特异性地与靶细胞结合,在超声辐射下靶向释放目的基因,从而提高了转染效率,为肿瘤靶向治疗提供了新思路。

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