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镁离子联合金雀异黄素对自发性高血压大鼠血压的影响*

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摘要 目的:探讨镁离子联合金雀异黄素对自发性高血压大鼠血压的影响。**方法:**选用雌性 6 周自发性高血压大鼠 28 只,饲养 7d 后测量大鼠初始收缩压(SBP)及心率(HR),应用双盲分组原则,将大鼠分成对照组、镁离子组、金雀异黄素组、及联合组,每组各 7 只。饲养 7d 后,取一次性注射器,消毒抽取药物,暴露尾部及血管,进行注射。每 7d 注射一次,连续注射 4 周。比较各组大鼠 SBP、HR、hs-CRP、MCP-1、vWF、血管紧张素(Ang II)。**结果:**给药前四组大鼠 SBP 水平比较无差异($P>0.05$)。给药后对照组 SBP 水平高于其他三组($P<0.05$),镁离子组与金雀异黄素组比较无差异($P>0.05$),联合组大鼠在给药 1 周、2 周、4 周后 SBP 水平显著低于其他三组($P<0.05$)。给药前四组大鼠心率比较无差异($P>0.05$)。给药后对照组、镁离子组、金雀异黄素组与治疗前相比无差异($P>0.05$),联合组低于治疗前 ($P<0.05$)。给药第 2、4 周联合组 HR 水平低于其他三组 ($P<0.05$)。联合大鼠 hs-CRP 水平显著降低 ($P<0.05$), MCP-1、vWF 水平显著升高($P<0.05$)。给药前各组大鼠 Ang II 水平比较无差异($P>0.05$),给药 2 周、4 周联合组 Ang II 水平显著降低 ($P<0.05$)。**结论:**镁离子联合金雀异黄素能提高自发性高血压大鼠血管顺应性,减少炎症反应,预防动脉粥样硬化,降低血压。

关键词:镁离子;金雀异黄素;自发性高血压大鼠;血管

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Effect of Magnesium Ion Combined with Genistein on Blood Pressure in Spontaneously Hypertensive Rats*

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ABSTRACT Objective: To investigate the effect of magnesium ion combined with genistein on blood pressure in spontaneously hypertensive rats (SHR). **Methods:** Twenty-eight female SHR were selected for 6 weeks. 7d after feeding, the initial systolic blood pressure (SBP) and heart rate (HR) of rats were measured. The SHRs were divided into control group, the magnesium ion group, the genistein group and the combined group according to the double-blind, each with 7 cases. After 7d, the rats received drug injection once a week for 4 weeks. Then the SBP, HR, hs-CRP, MCP-1, vWF and angiotensin II (Ang II) in rats were compared. **Results:** The SBP level between the four groups before administration had no significant difference ($P>0.05$); After administration, SBP level in the control group was higher than that in the other three groups ($P<0.05$), no difference was found between magnesium ion group and genistein group ($P>0.05$), moreover the combined group was significantly lower than that in the other three groups at the 1 week, 2 weeks and 4 weeks after administration ($P<0.05$); the HR before administration had no significant difference ($P>0.05$); after administration, no significant changes except combined group occurred ($P>0.05$), the HR in the combined group decreased ($P<0.05$), and was lower than that in the other three groups at 2 weeks and 4 weeks after administration ($P<0.05$); The hs-CRP levels in the combined group were significantly lower than those in the other three groups ($P<0.05$), and the levels of MCP-1 and vWF were higher in the combined group than in the other three groups ($P<0.05$); the levels of Ang II in the four groups showed no significant difference before administration ($P>0.05$), and the levels of Ang II in the combined group were lower than those in the other three groups ($P<0.05$). **Conclusion:** Magnesium ion combined with genistein can improve vascular compliance in SHR, reduce the inflammatory response, prevent atherosclerosis and lower blood pressure.

Key words: Magnesium ion; Genistein; SHR; Blood vessel

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高血压是临床常见疾病之一,参与多种心脑血管疾病的发生,临床多用降压治疗^[1,2],但单纯降压治疗不能完全保护与逆转靶器官的损害^[3],或可加重心血管疾病。诸多研究证实^[4,5]心率增快是高血压患者死亡的独立危险因素,高心率及高炎症患者

血压水平较高。因此,在选择降压药物的时不仅要考虑常规因素,如患者心脑血管疾病的危险程度^[6,7],还应兼顾心率及炎症反应。

研究表明镁离子能调节血管张力,影响通透性。降低患者

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血镁水平可改善血管平滑肌功能,提高血管顺应性^[8,9]。金雀异黄酮是一种非选择性酪氨酸激酶抑制剂,能起到收缩血管的作用^[10]。目前,临床尚未开展关于镁离子联合金雀异黄酮对高血压作用的研究^[11]。本研究主要探讨了镁离子联合金雀异黄酮对自发性高血压大鼠血管反应性的调节作用,以期为自发性高血压的治疗提供理论支持。

1 资料与方法

1.1 一般资料

选用雌性 6 周自发性高血压大鼠 28 只,体重 100~380g,平均体重(200±50)g。所有大鼠均购于辽宁长生生物技术有限公司,合格号:SCXK2016-0013。试剂及仪器:金雀异黄酮(生产企业: Cayman Chemical Company, 准字号: 10005167)。DMSO、生理盐水、PE、Nitroglycerin 购于美国西格玛公司; MgCl₂、卡巴胆碱、NaHCO₃、KH₂PO₄、CaCl₂、葡萄糖购于美国 Sigma 公司,其他检测试剂购于广州市科之蓝有限公司。

1.2 方法

1.2.1 药剂制备方法 选取金雀异黄酮 1 g 充分溶于 DMSO 中(4 mL),配成母液放于低温冰箱 4℃,单次使用量为 100 μL,需与 DMSO 进行 10 倍稀释,再用生理盐水(0.9%NaCl 溶液)进行 2 倍稀释,注射剂量:0.4 mL/kg。选取 0.71 g 无水镁离子,溶于 100 mL 超纯水,经严格过滤后,注入无菌瓶,配成 MgCl₂ 母液置于低温冰箱 4℃。单次使用 1 mL 母液溶于 DMSO(0.2 mL),注射剂量:1.2 mL/kg。

1.2.2 饲养及标准方法 所有大鼠在恒温(23℃)内饲养,光照 12~13h,以常规昼夜更替进行培育,水源充足,标准大鼠食物合

格。饲养 7d 后测量大鼠初始收缩压(SBP)及心率(HR),随机在大鼠胃部进行编号,应用双盲分组原则,将自发性高血压大鼠分成对照组、镁离子组、金雀异黄酮组及联合组,每组各 7 只。标记原则:大鼠右下肢代表 3 号,左下肢代表 4 号,左上肢代表 5 号,背部代表 6 号,尾根代表 7 号。

1.2.3 注射方法 饲养 7d 后,取一次性注射器,消毒抽取药物,大鼠固定在注射台上,暴露尾部,暴露血管,进行注射。每 7d 注射一次,连续注射 4 周。注射后 2~3h,大鼠情绪稳定后,检测 SBP 及 HR。

1.2.4 指标检测 给药后第 1 周、第 2 周、第 4 周检测大鼠 SBP、HR,应用放免试剂盒检测血清血管紧张素(Ang II)水平。给药后第 4 周,采用酶联免疫吸附双抗体夹心法(ELISA)在检测大鼠血清 hs-CRP、MCP-1、vWF 水平。hs-CRP、MCP-1、vWF 试剂盒购自武汉中美科技有限公司。

1.3 统计学方法

本研究采用 SPSS 29.00 统计学软件处理数据,计量资料采用($\bar{x} \pm s$)表示,多组间比较采用单因素方差分析,两组间比较采用 SNK-q 检验,计数资料用 n(%)描述,组间比较采用 χ^2 检验,以 $P < 0.05$ 表示差异存在统计学意义。

2 结果

2.1 各组大鼠 SBP 水平的变化情况

给药前,四组大鼠 SBP 水平比较差异无统计学意义($P > 0.05$)。给药后 1、2、4 周,对照组大鼠 SBP 水平高于其他三组($P < 0.05$),镁离子组与金雀异黄酮组比较无差异($P > 0.05$),联合组 SBP 水平显著低于其他三组($P < 0.05$),见表 1。

表 1 大鼠 SBP 水平变化情况比较($\bar{x} \pm s$, mmHg)
Table 1 Comparison of SBP level in rats ($\bar{x} \pm s$, mmHg)

Groups	n	Pre administration	At 1 weeks after administration	At 2 weeks after administration	At 4 weeks after administration
Control group	7	181.78± 8.74	140.59± 9.12*	153.54± 8.54*	165.59± 8.14*
Magnesiumion group	7	181.59± 8.41	133.52± 7.59**	123.51± 3.21**	118.59± 7.56**
Genistein group	7	180.51± 8.40	133.59± 7.50**	124± 3.31**	118.21± 7.55**
Joint group	7	181.42± 8.42	110.59± 9.12	103.59± 3.36	98.59± 7.52

注:* $P < 0.05$,与联合组比;# $P < 0.05$,与对照组比。

Note: * $P < 0.05$, compared with the Joint group, # $P < 0.05$, compared with the control group.

2.2 各组大鼠 HR 变化情况比较

给药前四组大鼠心率比较无差异($P > 0.05$)。给药后对照组、镁离子组、金雀异黄酮组与治疗前相比无差异($P > 0.05$),联合组低于治疗前($P < 0.05$)。给药第 2、4 周联合组 HR 水平低于其他三组($P < 0.05$),见表 2。

2.3 各组大鼠血清 hs-CRP、MCP-1、vWF 水平的变化情况

给药后 4 周,联合大鼠血清 hs-CRP 水平显著低于其他三组($P < 0.05$),血清 MCP-1、vWF 水平明显高于其他三组($P < 0.05$),详见表 3。

2.4 各组大鼠血清 Ang II 水平的变化情况

给药前,各组大鼠血清 Ang II 水平比较无差异($P > 0.05$),给药 2 周、4 周联合组血清 Ang II 水平显著低于其他三组($P <$

0.05),见表 4。

3 讨论

高血压是一种常见慢性疾病,能引起心脏、脑血管、外周静脉血管、肾脏等靶器官损伤及病变^[12-13],是心肌梗死主要危险因素,是心力衰竭促进因素^[14]。高血压发生与小动脉病变有关,缓进型高血压早期多伴小动脉痉挛^[15-17],可累及全身动脉血栓,加快动脉粥样硬化形成^[18]。小动脉长期痉挛可增加动脉内膜压力负荷,损伤血管,造成缺血、缺氧,导致小动脉玻璃样变,最终导致血管腔狭窄及管壁僵硬,引发高血压^[19]。血管重构是一个动脉生理变化过程,Ang II 参与血管重构过程,低水平 Ang II 能改善血管僵硬形态^[20],协调转化生长因子^[21],改善动脉形态学。黄

表 2 大鼠 HR 变化情况($\bar{x} \pm s$, h/min)Table 2 HR changes in rats ($\bar{x} \pm s$, h/min)

Groups	n	Pre administration	At 1 weeks after administration	At 2 weeks after administration	At 4 weeks after administration
Control group	7	442.57± 31.62	442.54± 31.64	443.57± 31.63*	443.54± 31.64*
Magnesiumion group	7	442.54± 34.64	434.59± 28.44	430.54± 28.40*	424.42± 28.42*
Genistein group	7	442.55± 31.60	433.52± 27.59	425.59± 27.50*	426.59± 29.42*
Joint group	7	442.51± 31.63	413.51± 31.21	366.23± 31.31	348.59± 31.36

注: * $P < 0.05$, 与联合组比。Note: * $P < 0.05$, compared with the Joint group.表 3 各组大鼠血清 hs-CRP、MCP-1、vWF 水平的变化情况($\bar{x} \pm s$)Table 3 Changes of serum hs-CRP, MCP-1 and vWF levels of rats($\bar{x} \pm s$)

Groups	n	hs-CRP(ng/mL)	MCP-1(pg/mL)	vWF(ng/mL)
Control group	7	2300.78± 368.74*	45.59± 6.54*	2780.45± 369.12*
Magnesium ion group	7	1875.91± 368.41*	46.59± 6.21*	3987.58± 324.54*
Genistein group	7	1875.90± 368.43*	46.58± 6.22*	3989.51± 324.59*
Joint group	7	1869.42± 368.43	51.87± 6.28	5557.59± 1352.62

注: * $P < 0.05$, 与联合组比。Note: * $P < 0.05$, compared with the joint group.表 4 各组大鼠血清 Ang II 水平的变化情况($\bar{x} \pm s$, pg/ml)Table 4 Changes of serum Ang II level s of rats in each group ($\bar{x} \pm s$, pg/ml)

Groups	n	Pre administration	At 1 weeks after administration	At 2 weeks after administration	At 4 weeks after administration
Control group	7	721.78± 84.74	722.74± 84.51	726.78± 84.55*	728.78± 84.51*
Magnesium ion group	7	721.59± 84.41	655.52± 77.59	625.51± 85.21*	618.59± 87.56*
Genistein group	7	721.51± 83.30	633.59± 77.50	623.23± 83.3* ¹	618.21± 87.55*
Joint group	7	721.42± 84.42	572.57± 72.12	562.57± 83.36	532.57± 87.52

注: * $P < 0.05$, 与联合组比。Note: * $P < 0.05$, compared with the joint group.

丹娥等^[22]研究发现血管重构参与高血压的发生,动脉重构尤其是颈动脉重构能加快动脉硬化进程,下调血管顺应性,损伤血管缓冲能力,导致高血压进展并诱导并发症发生。有研究^[23]表明大动脉重构典型表现为动脉中层增厚,血管变窄,管壁增厚。Ang II 低表达能缓解动脉紧张,松弛管壁,能有效抑制血管收缩,改善血液流变学。hs-CRP 是炎症标志物,参与血管细胞增生和动脉粥样硬化形成^[24]。MCP-1 是炎症始动因子及标志物,参与并扩大炎症反应。vWF 是血管内皮细胞损伤的重要参考指标,能反映血管内皮损伤的炎症程度^[25]。

本研究结果表明镁离子联合金雀异黄素能提高血管顺应性,起降低血压的作用。这与之前的研究结果一致,镁离子+金雀异黄素组对抗高血压的效果在第 25 天和第 30 天明显优于金雀异黄素组,从第 15 天开始效果优于镁离子组。从第 2 周开始,联合组效果显著优于其他组,说明金雀异黄素与镁离子联合使用对自发性高血压大鼠血压控制具有协同作用。金雀异黄素是一种大豆异黄酮类植物雌激素,可调节离子通道,增强心房肌细胞氯离子通道电流的敏感性,加快细胞膜电位复极,舒

张血管平滑肌^[26],其具体机制可能与制电压门控钙离子通道或促进钾离子通道的开放使血管平滑肌细胞超极化从而舒张血管有关。镁离子可调解血管内皮功能,保护内皮细胞,舒张血管^[27]。此外,本研究中联合组大鼠心率在给药后 2、4 周显著低于其他三组,且血清 hs-CRP 水平显著降低,MCP-1、vWF 水平显著升高,提示镁离子与金雀异黄素联合作用自发性高血压大鼠能起到调节心率,减少炎症反应,改善血管内皮损伤^[28]。且研究显示联合组大鼠 Ang II 水平较低,说明镁离子与金雀异黄素联合能有效改善自发性高血压大鼠血管重构,可能起到预防动脉粥样硬化的作用^[29]。

综上所述,镁离子联合金雀异黄素能改善自发性高血压大鼠血管反应性,提高血管顺应性,改善心率,降低血压,保护血管内皮功能,减少炎症反应,预防动脉粥样硬化。

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