

中医阴阳的实验性研究(II)

附子、肉桂和六味地黄方对高血压大鼠尿醛固酮等的影响

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内容提要 本文资料证实助阳药附子或附子加肉桂(附桂)明显地增高二肾一夹型高血压大鼠的血压。对该模型PRA、ACE和UKa浓度的影响,助阳药附子或附桂与滋阴药六味地黄方之间无有意义的区别。但助阳药附子却明显地增高UA的排出($P < 0.001$),六味地黄方则不改变它的排出。这和对血压的观察一样,提示二肾一夹型高血压大鼠可能为中医的“阴虚”模型。

对附桂八味丸拆方的研究曾发现^①,助阳药附子和附桂(附子+肉桂)对二肾一夹型肾血管性高血压(一侧肾动脉用0.2mm内径的银夹夹窄,另侧肾脏保持完整)大鼠,有明显升高血压的作用。但滋阴六味地黄方(熟地、山药、萸肉、泽泻、丹皮和茯苓)对此模型的血压没有影响。为观察药物作用下某些体液因素的变化,作了进一步的实验。本文主要研究了附子、肉桂和六味地黄方对二肾一夹型高血压大鼠血浆肾素活性(PRA)、血清血管紧张素I转换酶活性(ACE)、尿激肽释放酶活性(UKa)和尿醛固酮浓度(UA)等的影响。

材料和方法

药物用常法水煎,剂量按体重为成人的十倍。每日给大鼠灌胃一次,每周六次,连续给药四周。

实验用2~3个月月龄的Wistar纯种大鼠。测得正常大鼠血压后,用0.2mm内径银夹制造二肾一夹型肾血管性高血压疾病模型。手术后每周测量血压一次,术后4~5周时血压达到并稳定在高水平,分组给药或水观察。

用代谢笼收集每只大鼠24小时尿液,用以测定醛固酮和激肽释放酶。尿醛固酮用放射免疫法进行测定^②,以每24小时毫微克(ng/24h)为单位。激肽释放酶由分光光度法进行测定^③,用苯甲酰精氨酸乙酯(BAEE)作基质,以每分钟水解基质的微克分子量

($\mu\text{mol}/\text{min}$)为单位。给药或水终了,各组大鼠快速断头采血。用放射免疫法测定血浆肾素活性^④,以每小时每毫升血浆产生的毫微克血管紧张素I(ng/ml/h)为活性单位。血清内血管紧张素I转换酶(即激肽酶II)活性用直接测定法^⑤,甘氨酸-组氨酸-甘氨酸(GHG)作基质,以10分钟10微升血清产生1毫微克分子量(nmol/10 μl /10min)组氨酸-甘氨酸(HG)为酶活性单位。本文测定值统计均以均数±标准误($\bar{M} \pm \text{SE}$)表示。

结 果

一、对血压的作用

80只大鼠分成正常($n=14$)、高血压对照($n=17$)、附子($n=15$)、附桂($n=17$)和六味地黄($n=17$)五组。它们用药或水前的血压分别为 98.0 ± 0.7 、 148.0 ± 2.8 、 144.0 ± 3.3 、 142.0 ± 2.9 和 $148.0 \pm 1.8 \text{ mmHg}$,用药后第四周的血压分别为 100.0 ± 0.8 、 146.0 ± 3.4 、 158.0 ± 2.5 、 157.0 ± 3.0 和 $146.0 \pm 2.1 \text{ mmHg}$ 。附子、附桂两组用药后使二肾一夹型高血压大鼠的血压明显的升高,而六味地黄组的血压没有明显的变化。图1示各组血压变化过程。正常组大鼠血压一直保持在100mmHg上下。高血压对照组术后一周血压即明显升高,第四周后达到并稳定在高水平。附子、附桂二组大鼠,给药后一周血压在原水平上继续升高,二至三周时即达最高水平。六味地黄组基本稳定在给药前

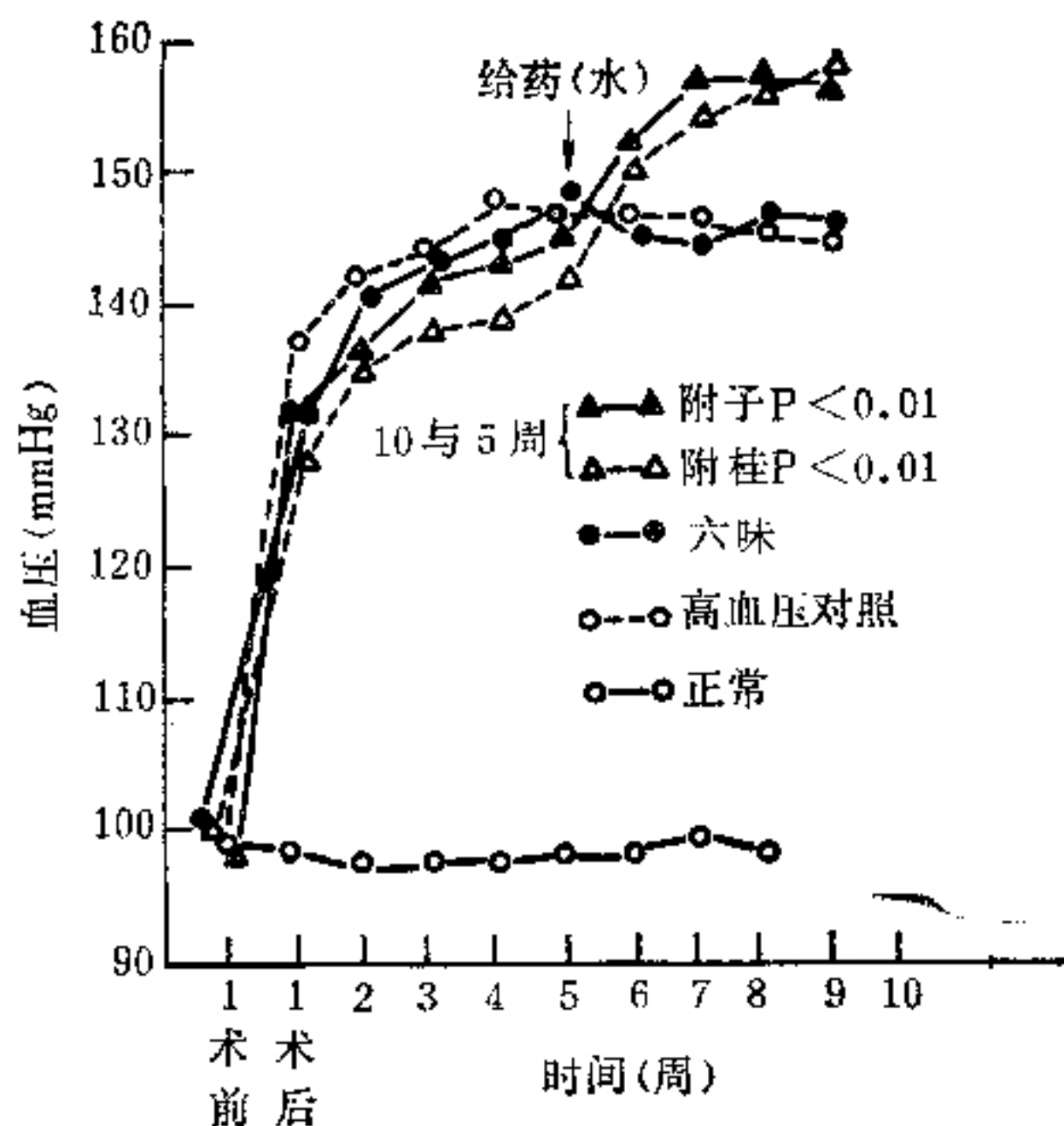


图1 附子等各组大鼠血压的变化

的血压水平。

二、PRA、ACE、UKa和UA的变化

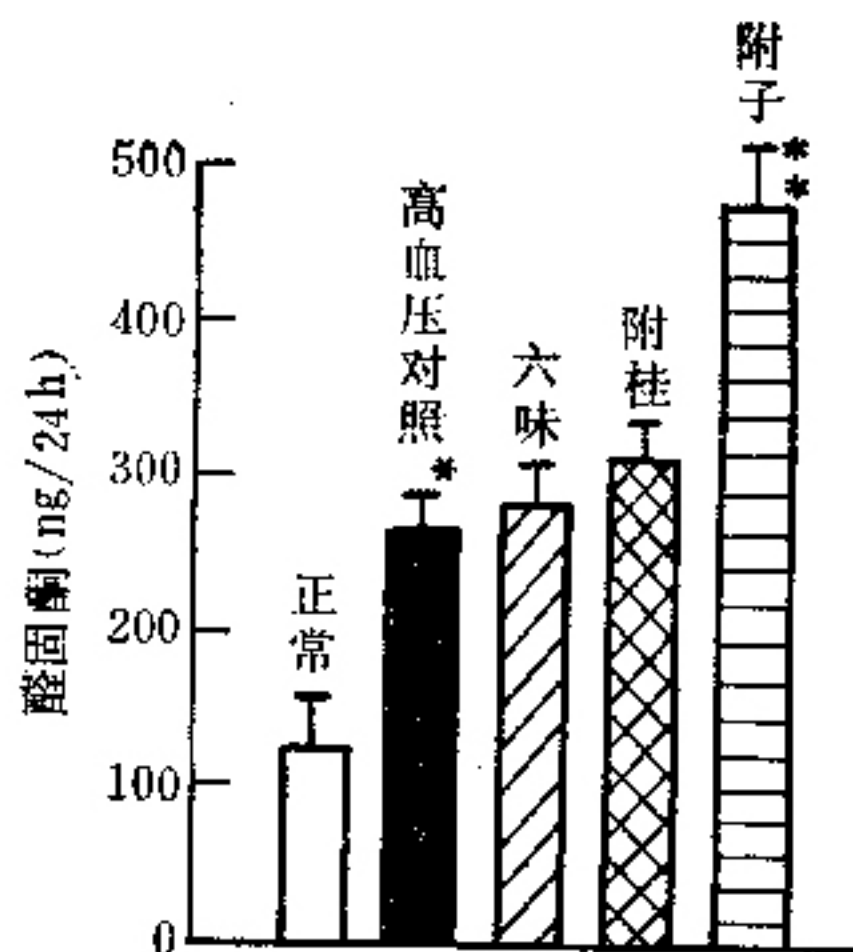
各组大鼠于手术后10周(给药或水4周时)收集尿液和采血。各指标的变化见附表。

二肾一夹型高血压大鼠 PRA 比正常 血压对照组大鼠为高($t=1.8132$)。六味地黄、附子和附桂组的PRA比高血压对照组略有降低,但无明显差异($P>0.05$)。对 PRA 的影响三个给药组之间无明显区别 ($P>0.05$)。

正常和高血压大鼠 ACE 水平无明显差异 ($P>0.05$)。六味地黄、附子和附桂三给药组均明显地低于高血压对照组($P<0.05$),但三组间的影响无明显差异。

正常和高血压大鼠有相似的 UKa 水平。三组给药组中唯附子组较高血压组为高($P<0.05$)、附子与六味地黄组间有一定差异($P<0.05$)。

高血压对照组大鼠手术后10周时,24小时UA排出量比正常组显著为高($P<0.01$)。六味地黄组与高血压组无显著差异($P>0.05$),而附子组显著高于高血压对照组($P<0.001$)。附桂组 UA 略高于高血压大鼠,但无明显差异($P>0.05$)。图2即显示这种变化。



• 正—高 $P<0.01$ • • 高—附子 $P<0.001$

图2 附子等对尿醛固酮的影响

讨 论

本实验进一步证实了附子或附桂确使二肾一夹型高血压大鼠的血压明显地升高。而六味地黄方对高血压大鼠的血压没有明显的作用。

体内存在着多个血压调节系统,确保机体血压水平适应复杂多变的体内外环境。其中肾素—血管紧张素—醛固酮系统和激肽释放酶—激肽—前列腺素系统就是两个相对应的血压调节系统。一般认为,二肾一夹型肾血管性高血压为肾素依赖性高血压,即认为肾素的增高参与发病⁽⁶⁾,而高血压的维持机理尚有其它因素的参与,如醛固酮的增高等。本实验高血压对照组和正常组的PRA分别为 16.12 ± 4.28 和 $5.28\pm0.70\text{ng/ml/h}$,虽因正常例数过少和测定值离散性较大而统计仅接近于显著,但前者高于后者的趋势仍是明显的。附子组、附桂组的PRA略低于高血压组,并未观察到对高血压大鼠进一步增高PRA的作用。

体内存在着大量的血管紧张素Ⅰ转换酶,使用这个酶的抑制剂,如Captopril,有可能获得满意的降压效果⁽⁷⁾。附子、附桂和六味地黄方虽一定程度降低ACE(分别为 $P<0.05$ 、 $P<0.05$ 和 $P<0.01$),但对高血压大鼠的作用它们之间并无差异⁽⁸⁾。

目前认为激肽系统与高血压有一定联系⁽⁹⁾,其中尿激肽释放酶(肾脏Ka)至少对肾内局部血管扩张和

钠利尿作用,似乎有利于降压。有报告一肾一夹型高血压大鼠Ka低于正常大鼠,而二肾一夹型高血压大鼠Ka排出与假手术组无明显差异⁽¹⁰⁾。关于肾性高血压UKa的排出报告尚不一致。本实验二肾一夹型高血压大鼠的UKa排出与正常血压大鼠无明显差异。没有看到UKa在高血压和几种药物作用下的明显意义。

尿醛固酮的测定表明,高血压大鼠比正常血压大鼠明显为高($P < 0.01$)。虽然滋阴六味地黄方对高血压大鼠的UA排出未见明显作用,但助阳药附子却使它

的排出显著升高($P < 0.001$)。这提示单味附子使高血压大鼠的血压明显升高可能与醛固酮的增高有一定联系。助阳药附子对二肾一夹型高血压大鼠没有治疗作用,而使血压进一步升高,又使与高血压的维持机制密切相关的醛固酮也明显升高。从药物验证的观点看,这进一步增加了此型高血压为中医阴虚模型的可能性,有必要作进一步探索。

(本文由茅守玉、张照英、韦炳寅同志协作部分技术工作,特此致谢)

附表 附子等各组 PRA、ACE、UKa和 UA 的变化($M \pm SE$)

项目 组别	PRA ng/ml/h	ACE nmol/10 μ l/10min	UKa μ mol/min	UA ng/24h
正 常	5.28 $\pm$ 0.70(9)	80.42 $\pm$ 6.00 (9)	22.41 $\pm$ 2.73 (14)	119.33 $\pm$ 30.24 (15)
高血压对照	16.12 $\pm$ 4.28(17)	86.26 $\pm$ 4.11 (17)	23.80 $\pm$ 2.85 (17)	264.12 $\pm$ 23.13** (17)
附 子	10.84 $\pm$ 3.43(12)	68.19 $\pm$ 4.92* (14)	32.42 $\pm$ 3.30 (14)	472.14 $\pm$ 38.03*** (14)
附 桂	9.99 $\pm$ 2.53(13)	65.64 $\pm$ 5.67* (14)	25.30 $\pm$ 2.69 (16)	305.00 $\pm$ 20.02 (16)
六味地黄	10.79 $\pm$ 2.87(13)	62.82 $\pm$ 4.25** (13)	21.43 $\pm$ 2.63 (14)	279.29 $\pm$ 25.72 (14)

注:正—高 } * $P < 0.05$ ()动物数量
 高一给药组 } * * $P < 0.01$
 * * * $P < 0.001$

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A Study on the Influences of Natural Cordyceps Sinensis and Its Cultured Mycelia on Murine Immuno-Organs and Functions of Mononuclear Phagocyte System

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By means of immunological methods, we found that the natural Cordyceps sinensis and its cultured mycelia have significant effect on the immuno-organs of mice, such as splenomegaly, liver enlargement and the shrinkage of thymus. Under the light microscope we also observed that the Kupffer's cells and the phagocytes increased in the spleen. All these findings suggest that the functions of mononuclear phagocyte system are activated by these drugs. But there is no significant difference between natural Cordyceps sinensis and its cultured mycelia in their action ($P < 0.05$). The pharmacological functions of both are similar. The experimental results may throw some light on their clinical application.

(Original article on page 42)

Activation of Murine Peritoneal Macrophage by the Natural Cordyceps sinensis and Its Cultured Mycelia

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Natural Cordyceps sinensis and cultured mycelia were given to experimental mice intramuscularly in dose of 5g/kg per day for 4 days. Results showed that phagocytic index and percentage of phagocytosis of the murine peritoneal macrophages (PM) increased markedly as compared with controls ($P < 0.001$). But there were no significant differences between natural Cordyceps sinensis and its cultured mycelia. The activity of the acid phosphatase in activated PM was also elevated ($P < 0.01$). All these results suggest that the natural Cordyceps sinensis and its cultured mycelia have similar effects.

(Original article on page 45)

Experimental Research of Yin-Yang Theory in TCM (II) Effect of Mankshood, Bark of Chinese Cassia Tree and Liu Wei Di Huang Fang on Urinary Aldosterone etc. in Renovascular Hypertensive Rats

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This paper confirms that mankshood used singly or in combination with bark of Chinese cassia tree as Yang-tonifying drugs could obviously increase the blood pressure in two-kidney one-clip Goldblatt hypertensive rats, but Liu Wei Di Huang Fang (rehmannia compound Radix Rehmanniae, Fructus Corni, Rhizoma Dioscoreae, Rhizoma Alismatis, Cortex Moutan Radicis and Poria) of Yin-nourishing drug did not alter the blood pressure in them. On the other hand, the plasma renin activity (PRA), angiotensin I converting enzyme (ACE), urinary kallikrein (UKa) and urinary aldosterone (UA) were determined. Ten weeks after operation (four weeks after giving the drug) the effect of mankshood and Liu Wei Di Huang Fang on PRA was nearly the same, and their effect on ACE and UKa showed no significant change either. However, the level of aldosterone excretion in these rats was higher than that of normotensive rats ($P < 0.01$). mankshood further increased UA excretion in the hypertensive rats ($P < 0.001$), but Liu Wei Di Huang Fang made no change in UA excretion.

Just as the action of mankshood as a Yang-tonifying drug on the blood pressure, the action of mankshood on aldosterone might suggest that two-kidney one-clip Goldblatt hypertensive rats might be a Yin-Xu (Yin-deficiency) model of TCM.

(Original article on page 48)