

• 实验研究 •

赤芍和硝苯啉对慢性高脂血症兔血浆 TXB₂ 和 6-酮-PGF_{1α} 的影响

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内容提要 本研究对比观察了赤芍和硝苯啉对兔实验性动脉粥样硬化(AS)的影响。结果表明,两种药物均使高脂血症引起的TXA₂/PGI₂比值改变趋向平衡,降低血浆LPO、动脉壁脂质、钙和磷脂及主动脉斑块面积。赤芍明显强于硝苯啉。提示两种药物通过影响钙代谢调节TXA₂/PGI₂平衡是其抗AS主要作用机理之一。赤芍可以作为防治AS的一种新药物用于临床。

关键词 赤芍 硝苯啉 动脉粥样硬化 钙 过氧化脂质 血栓烷-前列环素平衡

前列环素(PGI₂)和血栓烷(TXA₂)的比率在调节血液循环和动脉粥样硬化(AS)的发生发展中起重要作用。磷脂释放内源性花生四烯酸需要Ca⁺⁺,应用干扰Ca⁺⁺活动的药物可以改变花生四烯酸代谢^(1~3)。本研究用中药赤芍和钙通道阻滞剂(CCB)硝苯啉作对比实验研究,观察药物对食饵性慢性高脂血症兔血浆TXB₂和6-酮-PGF_{1α}的影响, TXA₂/PGI₂比值、斑块面积、钙、脂质和过氧化脂质(LPO)之间的相互关系。

材料与方法

一、药物和动物模型

健康雄性新西兰白兔 36 只,体重 1.5~2.0kg, 3~4 月龄(中国科学院上海实验动物中心提供)。随机分为正常、高脂对照组和两个药物治疗组。正常对照组喂普通颗粒饲料;高脂组喂 2%胆固醇颗粒饲料(胆固醇每日 0.5g/kg);治疗组饲料同高脂组,实验开始后即加服硝苯啉每日 15mg/kg(江苏第四制药厂出品,批号 860818),赤芍浸膏片每日 1 片/kg(河南省医学科学研究所实验药厂,每片 0.5g,相当于生药 5g)⁽⁴⁾。

二、观察指标

治疗开始前及开始后每 5 周测定血清脂质、钙和血浆TXB₂及6-酮-PGF_{1α},治疗15周末测定血浆LPO(取血标本前禁食水 12h)。气栓法处死动物,将主动脉至髂动脉段取出,处理后附于玻璃板上,苏丹IV染色,彩色照片,用求积仪测算斑块面积百分值。在锁骨下动脉下取 1~2 mm 长的胸主动脉,切片,苏木

素-伊红染色。分离主动脉内中膜,置110℃恒温10h,用Folch液抽提脂质。

血脂[总胆固醇(TC)、低密度脂蛋白胆固醇(LD-L-Ch)、高密度脂蛋白胆固醇(HDL-Ch)及亚组分(HDL₂-Ch)和组织胆固醇用多联酶法;极低密度脂蛋白胆固醇(VLDL-Ch=TC-(LDL-Ch+HDL-Ch));HDL₂-Ch=HDL-Ch-HDL₃-Ch。LDL分离用SDS法;HDL亚组分分离用聚乙二醇6000法;组织钙用Kramsch法制备,与血清钙均用原子吸收光谱法;组织磷脂用抗坏血酸法;血浆LPO用硫代巴比妥酸荧光法(HITACHI MPF4型);血浆TXB₂和6-酮-PGF_{1α}用放射免疫测定法。

三、统计处理:各组各个指标间作组间比较,t检验,不同指标间作线性相关分析。

结 果

一、治疗组药物对血脂的影响:实验前各组间血脂无明显差别。实验后高脂对照组逐渐升高,10周末赤芍组HDL-Ch和HDL₂-Ch,硝苯啉组HDL-Ch显著高于高脂对照组($P<0.05$);15周末差异更显著($P<0.01$)。15周末赤芍组TC、LDL-Ch、VLDL-Ch和硝苯啉组TC则显著低于高脂对照组($P<0.05\sim0.01$),两种药物均显著降低TC/HDL-Ch、TC/HDL₂-Ch、LDL-Ch/HDL-Ch和LDL-Ch/HDL₂-Ch比值(见表1)。

二、治疗组药物对血浆TXB₂和6-酮-PGF_{1α}的影响:实验前血浆TXB₂、6-酮-PGF_{1α}和TXB₂/6-酮-PGF_{1α}比值各组间无明显差别。与正常对照组比,高脂组血浆TXB₂和TXB₂/6-酮-PGF_{1α}比值于第5周末

表1 硝苯啉和赤芍浸膏片对高脂膳食兔血脂与血栓烷和前列环素的影响 ($\bar{x} \pm S$)

组 别		LDL-Ch	HDL-Ch	HDL ₂ -Ch	TXB ₂	6-酮-PGF _{1α}
		(mmol/L)				(pg/ml)
基础值	正常对照	0.589±0.146	0.523±0.053	0.281±0.069	264.24±22.43	472.00±38.09
	高脂对照	0.645±0.193	0.541±0.041	0.284±0.031	247.52±14.92	461.10±40.20
	硝苯啉	0.564±0.288	0.564±0.058	0.315±0.075	250.00±18.47	480.67±35.15
	赤芍浸膏	0.599±0.250	0.560±0.070	0.308±0.098	267.42±20.02	453.81±37.92
5周	正常对照	0.644±0.106**	0.519±0.052	0.271±0.050	246.67±10.33**	470.00±59.33**
	高脂对照	15.807±6.189	0.633±0.123	0.374±0.103	427.71±62.90	365.57±35.66
	硝苯啉	12.782±6.576	0.617±0.092	0.371±0.101	290.56±30.32**	421.88±31.84
	赤芍浸膏	14.824±6.670	0.621±0.094	0.363±0.113	267.13±29.50**	450.00±53.05**
10周	正常对照	0.611±0.132**	0.542±0.084	0.297±0.089	269.00±10.00**	478.00±18.46**
	高脂对照	21.609±5.522	0.606±0.127	0.358±0.139	568.57±38.48	280.00±39.16
	硝苯啉	19.879±4.809	0.756±0.079*	0.489±0.052	348.75±23.57**	360.00±55.68**
	赤芍浸膏	15.747±5.288	0.777±0.113*	0.520±0.137*	306.25±11.88**	396.25±17.68**
15周	正常对照	0.567±0.101**	0.533±0.058**	0.268±0.062**	305.00±20.49**	456.67±31.25**
	高脂对照	38.319±6.476	0.760±0.051	0.473±0.069	652.86±49.23	219.29±35.41
	硝苯啉	33.819±6.600	0.915±0.060**	0.619±0.069**	422.50±31.05**	371.88±55.67**
	赤芍浸膏	30.021±5.298*	0.989±0.067**	0.701±0.067**	383.75±18.47**	381.25±57.43**

注: 与高脂对照组比较, * $P < 0.05$, ** $P < 0.01$

即显著升高, 6-酮-PGF_{1α}明显降低, 15周末差异更明显($P < 0.01$); 赤芍组和硝苯啉组在第5周末无明显变化, 至第10周末才出现显著变化, 即变化时间后移, 且其幅度赤芍组明显小于硝苯啉组。见表1。

三、治疗组药物对血清钙的影响: 各组血清钙水平在整个研究过程中差异不显著($P > 0.05$)。

四、治疗组药物对主动脉内中膜生化成分和主动脉斑块面积的影响: 赤芍组和硝苯啉组主动脉内中膜TC、钙和磷脂含量显著低于高脂组, 主动脉斑块面积百分值均较高脂组明显减少(见表2)。肉眼所见: 典型粥样硬化病变主要分布于兔主动脉弓部, 腹主动脉较少; 光镜检查: 高脂组兔主动脉内膜泡沫细胞灶性蓄积, 中层泡沫细胞浸润。两药物治疗组兔主动脉改变与高脂组相似, 但程度较轻。

五、治疗组药物对血浆LPO的影响(见表2): 治

疗第15周末, 高脂组和硝苯啉组血浆LPO水平显著高于正常对照组($P < 0.001$), 赤芍组与正常对照组无明显差别($P > 0.05$); 两种药物治疗组均显著低于高脂组($P < 0.001$)。

六、血、组织成分和主动脉斑块面积间的相关关系: 血浆TXB₂和TXB₂/6-酮-PGF_{1α}比值与血清TC/HDL-Ch、TC/HDL₂-Ch、LDL-Ch/HDL-Ch、LDL-Ch/HDL₂-Ch比值, 主动脉内中膜TC、钙、磷脂含量, 血浆LPO水平和主动脉斑块面积呈显著性正相关($r = 0.4242 \sim 0.8907$, $P < 0.05 \sim 0.001$); 6-酮-PGF_{1α}与之呈显著负相关($r = -0.4721 \sim -0.7887$, $P < 0.01 \sim 0.001$); 主动脉斑块面积与血浆LPO水平和主动脉内中膜TC、钙及磷脂含量亦呈显著正相关($r = 0.6256 \sim 0.9322$, $P < 0.001$)。

表2 血浆LPO和主动脉内中膜生化成分及主动脉斑块面积的改变 ($\bar{x} \pm S\bar{x}$)

组别	血浆LPO	主动脉内中膜(mmol/g干组织)			主动脉斑块面积(%)
	TBA值(μmol/L)	TC	Ca++	磷脂	
正常对照	2.2345±0.3774*	0.0127±0.0010*	0.0414±0.0049*	0.0067±0.0016*	—
高脂对照	6.5915±1.4956	0.2046±0.0101	0.0898±0.0082	0.0220±0.0059	78.74±7.00
硝苯啉	3.7321±0.7214*	0.1305±0.0258*	0.0516±0.0058*	0.0102±0.0047*	30.91±6.77*
赤芍浸膏	2.4243±0.5170*	0.0568±0.0127*	0.0452±0.0039*	0.0089±0.0026*	20.28±4.39*

注: 与高脂对照组比较, * $P < 0.001$

讨 论

最近的研究结果表明, CCB不能明显改变血脂蛋白组分水平, 但可以有效地防治不同方式诱致的各种动物AS模型的发生与发展, 促进斑块消退, 其机理尚不十分清楚⁽⁸⁾。AS形成与TXA₂-PGI₂失衡有关, 体外研究发现TXA₂-PGI₂的改变与脂质和钙代谢密切相关, 急慢性高脂血症均使血浆TXA₂和血浆及动脉壁LPO增加, PGI₂水平显著降低, 本结果与之一致^(1,5)。最近, Skrinska等⁽⁵⁾报道TXA₂合成酶抑制剂明显抑制高脂血症诱致的兔AS形成, 机理是通过抑制TXA₂合成酶影响花生四烯酸代谢, 使TXA₂合成代谢转向PGE₂。

磷脂释放内源性花生四烯酸需要Ca⁺⁺, TXA₂和PGI₂均影响Ca⁺⁺的跨膜运动, TXA₂增加细胞内Ca⁺⁺释放, PGI₂则抑制之, 影响Ca⁺⁺代谢的药物可以改变花生四烯酸代谢和TXA₂-PGI₂的生物活性。实验和临床研究表明, 硝苯啶、尼莫的平和硫氮革酮等抑制血小板聚集和TXA₂释放, 调节血浆和组织内的TXA₂-PGI₂平衡。新近Akopov等⁽⁶⁾的研究结果表明, 异搏定和硫氮革酮体内外通过消除TXA₂-PGI₂失衡的不利结果改变花生四烯酸对AS形成的影响, 增强PGI₂的抗AS形成和降低TXA₂的致AS作用。然而赤芍和CCB对慢性高脂血症兔血浆TXA₂-PGI₂代谢的影响尚未见系统报道。本研究结果显示高脂血症使家兔血浆TXB₂和TXB₂/6-酮-PGF_{1α}比值显著升高, 6-酮-PGF_{1α}明显降低, 与文献结果一致⁽⁵⁾。赤芍和硝苯啶使高脂血症引起的TXA₂升高和PGI₂下降幅度明显减小, 变化的出现时间后移, TXB₂/6-酮-PGF_{1α}比值趋向平衡, 减轻AS斑块的严重程度。CCB调节TXA₂-PGI₂平衡的机理可能是: (1)抑制生物膜肌醇磷脂代谢, 减少磷脂源性花生四烯酸释放。(2)拮抗内源性ADP和(或)抑制ADP释放和摄取。(3)抑制Ca⁺⁺内流减少LPO产生^(2,5)。本结果表明, 赤芍和硝苯啶不改变血清Ca⁺⁺浓度, 却显著降低动脉壁钙含量, 说明组织细胞钙代谢在TXA₂-PGI₂代谢中起重要作用, 调节TXA₂-PGI₂平衡是赤芍和硝苯啶防治AS形成的主要作用机

理之一。

临床和实验研究表明, 赤芍能够显著降低肺动脉压、缓解心绞痛和改善脑循环^(4,7)。机理可能与抑制TXB₂和花生四烯酸代谢及血小板聚集有关。本结果显示赤芍作为抗氧化剂明显抑制高脂血症引起的LPO产生, 其调节TXA₂-PGI₂平衡和减轻AS斑块严重程度的作用明显强于硝苯啶。提示赤芍抗AS的机理可能是: (1)抑制血小板聚集。(2)抑制LPO产生。(3)改善脂蛋白组分比值。(4)减少Ca⁺⁺沉积于动脉壁, 调节TXA₂-PGI₂平衡。(5)激活腺苷酸环化酶增加动脉壁cAMP浓度。

本结果支持脂质改变引起TXA₂-PGI₂失衡与LPO有关的学说, 亦强烈提示与细胞内钙超负荷有关, 为Ca⁺⁺代谢异常导致TXA₂-PGI₂失衡提供了有力的证据。

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《中国医药学报》征订启事

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The Clinical and CT Analysis of 35 Cases of Lumbar Disc Herniation before and after Non-Operative Treatment

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35 cases of lumbar disc herniation were examined by clinical diagnosis and CT scanning. The results showed that there were 36 disc herniation (1 case of dual disc herniation). The radius vector of disc was 6.3 mm and the transverse diameter was 18.6 mm. There were 30 cases with sac of dura mater of spinal cord or nerve roots pressed and adhesive, yellow ligaments pachismus, lateral recessus filling and narrow bony lumbar vertebral canal. All patients were treated by means of manipulation. The clinical results showed that 29 cases (82.8%) had superior effects and 33 cases were effective. The clinical effective rate was 94.2%. CT rescanning showed that disc reposition completely returned was 6 cases, and partially returned was 24 cases. The successful rate of the reposition by manipulation was 83.3%. The clinical analysis and CT showed that herniation of lumbar disc could be repositioned by means of manipulation. The reposition of herniation of disc was a key factor in clinical results but was by no means the only one. With regard to long duration of illness, repeated invasion, combined narrow bony lumbar vertebral canal, and non-improved central type herniation after a long period of treatment, the herniation of disc should be treated by operation.

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Effects of Nifedipine and *Paeonia lactiflora* on Plasma TXB₂ and 6-Keto-PGF₁α in Cholesterol-fed Rabbits

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The authors examined the influences of nifedipine and *Paeonia lactiflora* (PL) on plasma LPO, TXB₂ and 6-keto-PGF₁α in cholesterol-fed rabbits. In this study, oral administration of nifedipine (15 mg/kg per day) and PL (0.5 g/kg per day) with 2% cholesterol diet for 15 weeks caused 60.75% and 74.24% reduction in the lesion area of aorta respectively. The levels of plasma LPO, TXB₂, cholesterol, phospholipid and calcium of the intimalmedia of the aorta in the treated groups were significantly lower than those in the control group, but the level of 6-keto-PGF₁α in the treated groups was significantly higher. The durations of TXB₂ elevation and 6-keto-PGF₁α reduction were delayed. The ratio of TXB₂/6-keto-PGF₁α tended to balance. The ratio of TXB₂/6-keto-PGF₁α was significantly positive correlation with the percentage of lesion area of the aorta. It is demonstrated that calcium metabolism plays an important role in thromboxane, prostaglandin, and LPO synthesis. In conclusion, the inhibition of LPO production and the regulation of TXA₂-PGI₂ balance may be one of the mechanisms of anti-atherogenesis of calcium antagonists and PL.

(Original article on page 669)

The Changes of Cyclic Nucleotides and Its Enzymes in the Spleen and Plasma of Similar Spleen Deficiency Rats Induced by Rhubarb and the Readjusting Function of Yiqi Jianpi Decoction (益气健脾汤)

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In order to investigate the nature of Spleen deficiency and the mechanism of immunodepression due to Spleen deficiency and explore the pharmacological action of Chinese drugs of Yiqi Jianpi decoction(YQJP), the authors had established the rats model by abministration Rhubarb. The preliminary results demonstrated that the symptoms manifested in rats were similar to those of Spleen deficiency syndrome. The changes of cyclic nucleotides in the spleen and plasma were