

丹参对肝纤维重吸收的作用

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内容摘要 在复合病因作用下, 实验性大白鼠肝硬化形成后, 停止病因刺激, 经丹参注射液治疗3周后处死动物。在光镜及电镜下观察到, 给药组动物肝内无纤维增生或仅有轻度纤维增生, 而对照组动物仍呈明显肝硬化或重度纤维增生。肝内胶原蛋白含量, 给药组明显低于对照组; 尿羟脯氨酸排出量, 则高于对照组。实验结果表明, 丹参可促进已形成的胶原纤维降解, 肝纤维重吸收。

肝硬化仍是目前危害人民健康的常见病、多发病。国内外虽有些药物用于防治肝硬化, 如秋水仙碱、D-青霉胺⁽¹⁾, 以及葫芦素B⁽²⁾、齐墩果酸⁽³⁾, 但其作用均属于防止肝硬化的发生。当肝硬化形成后, 如何促进肝内已形成的胶原纤维降解, 使硬化的肝脏再次恢复正常, 则是尚未解决的课题。

丹参是我国常用的传统中草药, 用于活血化瘀治疗多种疾病。我们以往研究证明丹参可防止肝硬化的发生⁽⁴⁾, 并可促进肝脏再生⁽⁵⁾。现对丹参是否可以促进已形成的纤维重吸收, 进行了如下实验。

材料与方法

实验动物: 大白鼠, 体重170~210g, 雌雄兼用。

实验药物: 丹参注射液, 上海制药厂出品, 每日剂量为0.5g/100g体重, 皮下注射。

实验方法: 取大白鼠23只, 分成三组, 即肝硬化对照组、给药组及正常对照组。实验第1天, 前两组动物皮下注射CCl₄0.5ml/100g体重, 以后每隔3天皮下注射油剂CCl₄(40%植物油溶液)0.3ml/100g体重。单纯玉米面(前两周加入20%猪油)加入0.5g%胆固醇为饲料, 30%酒精为唯一饮料。实验第九周, 撤除上述全部病因刺激, 恢复正常膳食及饮水, 给药组开始给药, 肝硬化对照组给生理盐水。于给药后1、2、3周末收集各组动物16小时尿, 测定尿羟脯氨酸含量。于实验第11周末断头处死全部动物。取肝左叶固定于10%福尔马林液, 石蜡包埋, 切片, 作HE染色及VG染色, 进行组织学观察。取小块肝组织, 二甲肿酸钠缓冲, 2.5%戊二醛及1%锇酸双固定, 环氧树脂618包埋, 超薄切片(500Å), 醋酸铅和枸橼酸铅双染色, JEM100CX型电镜观察。其余肝组织留作尿羟脯氨酸测定, 以计算肝胶原蛋白含量⁽⁶⁾。

结 果

一、丹参对肝胶原蛋白含量的影响

如表1所示, 肝硬化形成后, 经丹参治疗3周, 动物肝脏胶原蛋白含量明显减少, 与肝硬化对照组相比差异显著。

表1 丹参对肝胶原蛋白含量的影响

组 别	动物数	肝胶原蛋白含量 (mg/g干肝重, $\bar{M} \pm SE$)
肝硬化对照	9	29.43 ± 1.55
丹 参	8	*24.76 ± 1.14
正常对照	6	16.39 ± 0.93

* 与肝硬化对照组比 $P < 0.05$

二、丹参对尿羟脯氨酸排泄的影响

表2 丹参对尿羟脯氨酸排泄的影响

组 别	动物数	尿羟脯氨酸含量(μ mol/ml, $\bar{M} \pm SE$)		
		给药1周	给药2周	给药3周
肝硬化对照	8	8.59 ± 0.73	6.38 ± 0.6	10.43 ± 1.33
丹 参	8	7.28 ± 0.84	8.8 ± 1.18	*16.25 ± 2.07
正常对照	6	5.92 ± 0.97	2.88 ± 0.6	7.79 ± 1.14

* 与肝硬化对照组比 $P < 0.05$

表2结果表明, 肝硬化形成后经丹参治疗的动物, 第1、2周尿羟脯氨酸排泄量与对照组无明显差异, 第3周尿羟脯氨酸排出量明显多于对照组, 经统计学处理, 差异显著。

三、丹参对肝硬化动物组织学的影响

如表3所示, 实验第8周末, 动物在复合病因刺激下发展为较严重的肝硬化, 停止病因刺激后3周, 对照组动物肝内纤维虽有不同程度吸收, 但中度及重度肝纤维化的动物仍占8只中的6只。镜下显示肝正

常结构破坏,代之以假小叶,并有较明显的纤维隔形成(图1)。而经丹参治疗的动物中,轻度或无纤维增生者占8只中的6只,肝纤维化程度明显轻于对照组,镜下观察,肝组织结构基本恢复正常(图2)。

表3 丹参对纤维重吸收的影响

组别	动物数	肝纤维化程度*				平均
		-	+	++	+++	
肝硬化对照	8	0	2	2	4	2.2*
丹参	8	3	3	2	0	0.87*
正常对照	6	6	0	0	0	0.0*

*见参考文献(7)

四、电镜观察

肝硬化对照组动物肝脏,部分肝细胞发生坏死,电镜下可见到细胞崩解的碎片,未坏死的肝细胞胞浆内糖原消失,内质网扩张呈大囊泡。部分胞浆内可见脂滴,核周空泡加大,核蛋白体有脱落现象,肝细胞窦面微绒毛变平坦,数目减少,狄氏腔明显扩张,其中可见增生多量胶原纤维,内皮细胞肿胀(图3)。在有坏死肝细胞区域,可见多数炎细胞与成纤维细胞,其

细胞周围有较多的胶原纤维,有的成纤维细胞胞浆内可见大脂滴,似为贮脂细胞,但已向成纤维细胞过渡。在成纤维细胞聚集区中并见有一个细胞,界线明显,无核,胞浆内细胞器消失,但可见深浅不一的球形滴,浅者似为脂滴,略深者可见到贝壳样结构,似为脂褐素,推测这些物质为退变的细胞,降解的脂质向脂褐素过渡。

给药组动物肝细胞结构已基本恢复正常,内质网呈平行密集的扁平囊,无核蛋白体脱落现象,线粒体未见扩张,未见坏死的肝细胞,偶见有形成脂褐素样物质,但较对照组明显减少,肝细胞周围狄氏腔未见扩张,微绒毛已基本恢复原状,全片未见到明显胶原纤维增生区域,仅在肝间质小胆管周围见到少量胶原纤维,并见到各种炎症细胞,在肝细胞间偶尔也见到纤维细胞,但其周围与肝细胞密切相接,未见到胶原纤维(图4)。

讨 论

在肝硬化形成过程中,由于肝细胞变性、坏死而导致炎症反应,肝细胞再生及纤维组织增生,严重者



图1 实验第11周末,肝硬化对照组肝脏,肝正常结构破坏,纤维增生形成假小叶,假小叶内肝细胞仍有变性,假小叶外有较宽的纤维组织隔形成 HE×100 图2 肝硬化形成后,经丹参治疗3周的动物肝脏,增生的纤维几乎全被重吸收,肝细胞除有轻度变性外,其余接近正常, HE×100。 图3 肝硬化对照组动物肝脏,电镜下观察狄氏腔扩张,肝窦面微绒毛变平,内皮细胞两侧可见增生的胶原纤维,×6700 图4 经丹参治疗三周的动物肝脏,电镜下观察,细胞器基本恢复正常,图中可见一纤维细胞与肝细胞密切相接,未见胶原细胞,×18000

纤维增生分割肝小叶而形成大小不等的结节即假小叶。当肝硬化形成后有两种情况,一种为可逆性,即停止病因刺激后,胶原纤维可被重吸收⁽⁸⁾,肝脏结构恢复正常。一种则为不可逆性,即停止病因刺激,肝硬化仍沿着变性坏死→炎症→纤维化恶性循环继续发展。后者一般而言,纤维隔较宽,已有玻璃样变,纤维隔含血管少,炎细胞少,因而纤维不易被重吸收。由于实验第8周末仍属可逆性肝硬化,故停止病因刺激后,肝硬化对照组部分肝脏纤维组织出现轻度重吸收现象,但经丹参治疗的动物,肝纤维化较对照组明显减轻,且肝脏胶原蛋白含量亦明显低于对照组,说明药物有促进肝纤维重吸收的作用。

羟脯氨酸是胶原降解的产物,经尿排出,因此测定尿羟脯氨酸量可反应肝内胶原降解的速度⁽⁹⁾。实验结果表明,经药物治疗3周后,动物尿羟脯氨酸排泄量明显高于对照组,间接证明药物可促进胶原纤维的降解。

体内胶原分解主要是通过胶原酶的作用,在中性环境中,经胶原酶作用,可将胶原蛋白裂解为两部分,一部分为大的3/4,一部分为小的1/4,裂解后的碎片,再经非特异性蛋白酶作用逐渐分解⁽¹⁰⁾。因此,胶原降解的关键与胶原酶的作用密切相关。丹参促进胶原降解可能是通过增加胶原酶的产生或增强胶原酶的活性而实现的。

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乌头汤加味治疗产后痛痹

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1983年1月~1986年12月,笔者以乌头汤加味治疗产后痛痹5例,效果满意,现举例于下。

张××,26岁,女工,1984年12月19日晚分娩后自觉右侧髌部关节及右膝关节轻度冷痛,一周后因感受风寒导致病情加重,右髌膝两关节疼痛加剧,屈伸困难,伴高热汗出。化验检查:抗链“O” >500 u。血沉60 mm/h。血常规:血红蛋白12.1g,红细胞405万,白细胞5000,中性71%,淋巴29%。右髌膝关节正侧位X线片,骨质均未见明显改变,心电图及胸透心肺均正常。诊断为急性风湿性关节炎,在某医院用消炎镇痛等治疗近两个月病情有增无减,于1985年2月20日邀笔者诊治,证见右髌膝关节冷痛恶寒,外观无异常改变,压之疼痛加重,髌关节重于膝关节。患者咳嗽、深呼吸或稍高声说话即增加患部疼痛。面色少华,舌淡苔白,脉沉细弱,纳差,喜暖恶寒,喜食热饮,遇冷即全身发颤等一派阴寒里虚之证象,此因患者产后气血亏损,

寒湿之邪乘虚侵袭,深入筋骨,痹阻气血而发病,治宜大辛大热,温化寒湿,益气养血,活血通痹。方用乌头汤加味:大乌头10g 白蜜25g(兑服) 黄芪15g 麻黄10g 炙甘草10g 白芍12g 川芎12g 当归12g 白术10g 云苓12g,水煎服,每日一剂,连服六剂。服药后微汗出,右髌膝关节疼痛明显减轻,伸屈自如,并能下床走动。原方加牛膝15g、龙眼肉30g,续服26剂后上述关节均已不痛,生活可自理,饮食增加,血沉8 mm/小时,抗链“O” <500 u。血红蛋白12.5g,红细胞420万,白细胞6500,中性60%,淋巴36%,一切不适均消,至今未见复发。

本例药用乌头大辛大热,温散筋骨寒湿,麻黄发散陈寒,助乌头驱寒邪,以甘草、白芍甘缓酸敛,佐以白蜜之甘缓和解,黄芪固卫,以防麻黄发散太过,牛膝引药下行,云苓利湿健脾,川芎、当归活血补血,疏风通络,白术、龙眼肉补脾益气而收功效。

G-6-pase and so on recovered markedly, the membrane system (ER, Mit, etc.) recovered to approximately normal condition. It suggested that BDD has an obvious repairing action on CCl₄ induced liver injury in rats. (Original article on page 158)

Studies on Collagen Fibers of Liver Reabsorptive Action of *Salvia miltiorrhiza* on Experimental Cirrhosis

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The liver of rats was developed cirrhosis induced by injection of CCl₄ and dietetic injury after 8 weeks. Then *Salvia miltiorrhiza* (SM) was given to a group, 5 gm/kg body weight was injected subcutaneously once a day for 3 weeks. On the 43rd day all animals were sacrificed. The results indicated that the collagen content of the liver was lower in SM group (24.76 mg/g dry liver weight) than in the cirrhosis control (29.43 mg/g dry liver weight). The urinary hydroxyproline content in SM treated rats were significantly higher (16.25r/ml) than those of the cirrhosis control (10.43r/ml). Light and electron-microscopic study revealed that the fibrosis of liver were less severe in SM group than in the control. There were no collagen fiber or only a little in the liver in 6 out of 8 rats in SM group, whereas 6 out of 8 were severe fibrosis and cirrhosis in the control. These results showed that SM could promote the collagen reabsorption, the collagen fiber of liver were decreased and urinary hydroxyproline excretion increased in SM group. (Original article on page 161)

Experimental Research of Yin-Yang Theory in TCM(VI)

—Analysis to Mutual Effect between *Aconitum carmichaeli* and *Cinnamomum cassia*

Goldblatt and Skelton Hypertensive Rats

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Recently using experimental hypertensive rats and the famous Eight Drugs Pill with *Aconitum carmichaeli* (AC) and *Cinnamomum cassia* (CC), we have confirmed that Goldblatt two-kidney one-clip type (Goldblatt model) and Skelton adrenal regeneration type (Skelton model) are Yin deficiency model and Yang deficiency model respectively. The Yin nourishing drug and Yang invigorating drug usually have opposite effect. In this paper we have observed a mutual control and restriction effect between two Yang invigorating drugs: AC and CC. (1) Blood pressure: Both AC alone or AC with CC, exerted obviously an increase of blood pressure effect on Goldblatt model. But CC alone or CC with AC were able to decrease the blood pressure of Skelton model, the former exerted a stronger effect. It was possible that AC exerted a modulating action on the strong decrease of the blood pressure induced by CC. (2) Aldosterone: There was an increase of urinary aldosterone excretion in either Goldblatt model or Skelton model. CC could relieve the sharp raising aldosterone induced by AC in Goldblatt model. Both AC and CC were able to decrease the level of urinary aldosterone excretion in Skelton model. There was tendency that the two drugs worked in synergism on that model. (3) Enkephaline: The level of brain enkephaline in the hypertensive rats was lower than that in the normotensive rats. In Goldblatt model CC alleviated the decreasing effect on AC induced enkephaline level, while AC could alleviate the raising effect on enkephaline level induced by CC in Skelton model. (4) Hydroxyproline: The level of hydroxyproline in the cardiac muscle of Goldblatt model was high, the Six Drugs Pill with *Rehmannia glutinosa* obviously decreased its concentration, but AC increased it markedly. CC alleviated this action of AC.

In TCM it is known that there is a mutual control and restriction between Yin and Yang to maintain the balance between them. But, we have observed that between two Yang invigorating drugs AC and CC, there is also a mutual control and restriction, so that the effect of the drugs do not overact on the target. There are few references in the medical literature about this phenomenon. We believe that it is possibly very important theoretically and clinically, and we have tried to give an explanation on its mechanism. (Original article on page 164)