

doi: 10.13241/j.cnki.pmb.2020.08.008

天阳复脉汤对糖尿病周围神经病变小鼠临床疗效及其对 JNK 和 p-JNK 蛋白表达的影响 *

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摘要 目的:探索天阳复脉汤对糖尿病周围神经病变小鼠临床疗效及其对 JNK 和 p-JNK 蛋白表达的影响。**方法:**选用 7 周的 db/db 雄性小鼠 120 只,随机分成模型组、硫辛酸组和天阳复脉汤高、中、低剂量组等五组,每组 24 只。选取同窝生 7 周龄 db/m 雄性小鼠 24 只为正常组。模型组和正常组给予等体积蒸馏水,而硫辛酸组灌胃给药,剂量为 78 mg/kg,高剂量组为 6.8 g/kg、中剂量组为 3.4 g/kg、低剂量组为 1.7 g/kg。对比和评估六组小鼠足底热敏反应时间、运动神经传导速度、血清因子及 JNK 及 p-JNK 蛋白表达等指标。**结果:**与正常组和模型组相比,硫辛酸组和天阳复脉汤组小鼠足底热敏反应时间均显著缩短,MNCV 速度均显著提高,血清 TNF- α 和 IL-1 β 水平明显降低,JNK 和 p-JNK 蛋白表达显著下降,差异均具有统计学意义($P<0.05$)。**结论:**天阳复脉汤应用于糖尿病周围神经病变小鼠,可有效增加其运动神经传导速度,缩短其足底热敏反应时间,降低血清 TNF- α 和 IL-1 β 浓度,进而下调 JNK 和 p-JNK 蛋白表达。

关键词:天阳复脉汤;糖尿病周围神经病变;临床疗效;c-jun 氨基末端激酶;磷酸化 c-jun 氨基末端激酶

中图分类号:R-33;R587.2 **文献标识码:**A **文章编号:**1673-6273(2020)08-1436-05

Clinical Effect of Tianyang Fumai Decoction on Diabetic Peripheral Neuropathy in Mice and Its Effect on the Expression of JNK and p-JNK Protein*

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ABSTRACT Objective: To explore the clinical effect of Tianyang Fumai decoction on diabetic peripheral neuropathy in mice and its effect on the expression of JNK and p-JNK protein. **Methods:** 120 cases of mice were selected as the observation subjects, they were divided into the model group, lipoic acid group and Tianyang Fumai decoction high, middle and low dose group according to the random table method, 24 cases were in each group. Besides, 24 7-week-old db/m male mice born in the same litter were selected as normal group. The plantar thermal response time, motor nerve conduction velocity, serum factor and the expression of JNK and p-JNK protein were compared and evaluated in the six groups. **Results:** Compared with the normal group and the model group, the plantar thermosensitive reaction time was significantly shortened, the MNCV speed was significantly increased, the serum TNF- α and IL-1 β levels were significantly decreased, and the expression of JNK and p-JNK protein were significantly decreased in the lipoic acid group and Tianyang Fumai decoction group, the differences were statistically significant ($P<0.05$). **Conclusion:** Tianyang Fumai decoction in the treatment of diabetic peripheral neuropathy mice can effectively increase the motor nerve conduction velocity, shorten the plantar thermosensitive reaction time, reduce the concentration of serum TNF- α and IL-1 β , and then down-regulate the expression of JNK and p-JNK protein.

Key words: Tianyang Fumai decoction; Diabetic peripheral neuropathy; Clinical efficacy; C-jun N-terminal kinase; Phosphorylated c-jun N-terminal kinase

Chinese Library Classification(CLC): R-33; R587.2 **Document code:** A

Article ID: 1673-6273(2020)08-1436-05

前言

糖尿病周围神经病变(Diabetic peripheral neuropathy, DPN)

是指在持续高血糖作用下发生机体代谢障碍、微循环紊乱等症,进而引发神经缺氧缺血的常见糖尿病并发症^[1]。DPN 早期累及感觉神经,症状较为隐匿,仅能通过肌电图诊断出异常。而

* 基金项目:国家自然科学基金项目(81870544)

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(收稿日期:2019-08-23 接受日期:2019-09-18)

随着病情进展,DPN多表现为四肢麻木、感觉器官损伤、肌肉萎缩、心动过速及心肌梗死等症状,若不及时诊断和治疗,将会严重影响患者日常生活质量,甚至威胁患者生命安全^[2,3]。DPN发病机制较为复杂,可能与糖脂代谢异常、氧化应激、炎症反应、细胞凋亡、微血管病变及血旺细胞损伤等有关^[4,5]。既往研究表明^[6,7],c-jun氨基末端激酶(JNK)是一类蛋白激酶,其磷酸化(p-JNK)后可激活小胶质细胞的增殖和分化信号,促使机体分泌炎症因子。目前临床有硫辛酸、甲钴胺、前列腺素E1及依帕司他等西药从不同角度作用于DPN,且均可产生一定的临床疗效,但长期使用会对机体造成不可避免的并发症和毒副作用,临床治疗依从性较低^[8,9]。而中药方剂因其安全、疗效好而被广泛应用^[10]。天阳复脉汤是我们根据自身多年治疗DPN的临床经验自拟的中药方剂,具有温肾扶阳,活血通络之功效,目前拟推广至DPN临床治疗。本文探讨其对DPN小鼠临床疗效及其对JNK和p-JNK蛋白表达的影响,旨在探讨DPN发病机制的同时观察天阳复脉汤的临床疗效,为临床治疗研究提供依据。

1 材料和方法

1.1 材料

1.1.1 实验动物 购买年龄为7周的db/db小鼠120只,体重为30~45g,均为雄性,级别是SPF。同时购买24只db/m同窝雄性小鼠(上海斯莱克实验动物有限责任公司,许可证号:生产许可SCXK(沪)2017-0005),小鼠饲养条件:专用饲料、定量摄入已灭菌饮用水、室温20~25℃,湿度为45~65%,光照12h昼夜循环。

1.1.2 仪器 DP-YLS-6B智能亚欧热板仪,北京亚欧德鹏科技有限公司;MHY-22579酶联免疫分析仪,北京美华仪科技有限公司;TG-16S微量高速离心机,上海锦玫仪器设备有限公司;WD-9413B凝胶成像系统,北京海天友诚科技有限公司;MD3000/8生物信号采集处理系统,上海艾研生物科技有限公司。

1.1.3 药物 天阳复脉汤配方:附片10g,肉桂5g,补骨脂10g,肉苁蓉5g,鹿角霜10g,菟丝子15g,熟地12g,山茱萸15g,山药10g,枸杞15g,当归12g,黄连10g,茯苓10g,人参10g,丹参12g,鸡血藤15g,怀牛膝8g,泽泻5g及甘草15g等19味生药材,以蒸馏水煎煮上述药材,浓缩成高剂量0.68g/mL、中剂量0.34g/mL和低剂量0.17g/mL的药液;硫辛酸胶囊,蓬莱诺康药业有限公司,批准文号:国药准字H20133253,规格:0.3g/粒。

1.1.4 试剂 肿瘤坏死因子- α (TNF- α)、白细胞介素-1 β (IL-1 β)酶联免疫试剂盒,上海士锋生物科技有限公司;JNK和p-JNK单克隆抗体,均为兔来源型,美国Abcam公司。

1.2 试验方法

在实验室条件下适应性饲养1周后,观察无异常或死亡事件后,将存活,且空腹血糖值 ≥ 11.1 mmol/L的120只糖尿病小鼠随机分成模型组、硫辛酸组(78mg/kg)、天阳复脉汤高(6.8g/kg)、中(3.4g/kg)、低剂量组(1.7g/kg),给药剂量以人与小鼠体表面积进行换算,每组24只。同时选取24只存活db/m小鼠为正常组。正常组和模型组给予10mL/kg蒸馏水,而给药组给予10mL/kg相应药物,每日灌胃1次,连续给药8周。

1.3 观察指标

1.3.1 足底热敏反应时间 于最后一次灌胃给药结束后,预热智能亚欧仪,设置温度为55℃。当温度达到设定值后,将小鼠放置于热敏板即时开启计时器,以小鼠出现舔后足动作作为小鼠足底热敏反应事件,每只小鼠重复测定3次,需间隔20min,计算平均值。

1.3.2 运动神经传到速度(MNCV) 于最后一次灌胃给药结束后,应用MD3000/8生物信号采集处理系统。首先将清醒小鼠行仰卧体位固定,记录电极有两个,分别放在小鼠踝关节坐骨神经部位和足底第二趾;刺激电极放在小鼠右侧坐骨神经传出位置。记录复合动作电位潜伏期,重复测定3次,间隔5min, $MNCV = \text{两记录电极间距(cm)} / \text{复合电位潜伏期(s)}$ 。

1.3.3 血清TNF- α 和IL-1 β 于最后一次灌胃给药结束后,腹部主动脉取血2mL置于抗凝管中,TG-16S型离心机3000rpm,5min,取上清液,应用酶联免疫法测定小鼠血清TNF- α 和IL-1 β 浓度,严格按照标准操作规程测量。

1.3.4 JNK和p-JNK蛋白表达 于最后一次灌胃给药结束后,脱颈处死,截取小鼠背根神经节,提取总蛋白,应用SDS-PAGE凝胶电泳法,电泳完毕后,转移至PVDF滤膜中。应用Western blot法测定JNK和p-JNK蛋白表达情况,凝胶成像系统扫描条带,记录并比较各组购买蛋白(JNK和p-JNK)和内参照灰度值的比值。

1.4 统计学分析

采用SPSS23.0,计量资料以($\bar{x} \pm s$)表示,多组比较行单因素方差分析法,两两比较行LSD-t检验法,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组小鼠足底热敏反应时间比较

与正常组相比,模型组小鼠热敏反应时间明显延长($P < 0.05$);与模型组相比,硫辛酸组和天阳复脉汤组小鼠足底热敏反应时间均显著缩短($P < 0.05$),详细数值及统计值见表1。

2.2 各组小鼠MNCV比较

与正常组相比,模型组小鼠MNCV速度明显缩短($P < 0.05$);与模型组相比,硫辛酸组和天阳复脉汤组小鼠MNCV速度均显著提高($P < 0.05$),详细数值及统计值见表2。

2.3 各组小鼠血清TNF- α 和IL-1 β 比较

与正常组相比,模型组小鼠血清TNF- α 和IL-1 β 水平均显著上升($P < 0.05$);与模型组相比,硫辛酸组和天阳复脉汤组小鼠血清TNF- α 和IL-1 β 明显下降($P < 0.05$),详细数值及统计值见表3。

2.4 各组小鼠JNK和p-JNK蛋白表达比较

与正常组相比,模型组小鼠JNK和p-JNK蛋白表达明显上升($P < 0.05$);与模型组相比,硫辛酸组和天阳复脉汤组小鼠JNK和p-JNK蛋白表达显著下降($P < 0.05$),详细数值及统计值见表4,Western blot比较见图1。

3 讨论

DPN是糖尿病患者常见的并发症,主要累及感觉神经、运动神经及自主神经,临床多表现为冷暖不知、心动过速或过缓、肌无力及面瘫等症状,若不及时诊断并控制病情,将会干扰患

表 1 六组小鼠足底热敏反应时间比较(n=24, $\bar{x} \pm s$)Table 1 Comparison of plantar thermal response time in six groups of mice (n=24, $\bar{x} \pm s$)

Groups	Plantar thermosensitive reaction time(s)
Normal group (10 mL/kg distilled water)	11.45± 2.09
Model group (10 mL/kg distilled water)	21.89± 3.53*
Lipoic acid group (78 mg/kg)	17.87± 2.91**
High dose group of Tianyang Fumai decoction (6.8 g/kg)	14.91± 3.21**
Tianyang Fumai decoction medium dose group (3.4 g/kg)	15.23± 3.23**
Tianyang Fumai decoction low dose group (1.7 g/kg)	17.39± 2.19**
F	34.762
P	<0.001

Note: Compared with the normal group, * $P<0.05$; Compared with the model group, ** $P<0.05$.

表 2 六组小鼠 MNCV 数值比较(n=24, $\bar{x} \pm s$)Table 2 Comparison of MNCV values in six groups of mice (n=24, $\bar{x} \pm s$)

Groups	MNCV(m/s)
Normal group (10 mL/kg distilled water)	28.65± 5.09
Model group (10 mL/kg distilled water)	16.31± 3.76*
Lipoic acid group (78 mg/kg)	23.76± 4.87**
High dose group of Tianyang Fumai decoction (6.8 g/kg)	29.89± 8.01**
Tianyang Fumai decoction medium dose group (3.4 g/kg)	24.02± 6.34**
Tianyang Fumai decoction low dose group (1.7 g/kg)	22.47± 5.02**
F	17.527
P	<0.001

Note: Compared with the normal group, * $P<0.05$; Compared with the model group, ** $P<0.05$.

表 3 六组小鼠血清 TNF- α 和 IL-1 β 比较(n=24, $\bar{x} \pm s$)Table 3 Comparison of serum TNF- α and IL-1 β values in six groups of mice (n=24, $\bar{x} \pm s$)

Groups	TNF- α (ng/L)	IL-1 β (ng/L)
Normal group (10 mL/kg distilled water)	351.09± 35.21	51.87± 13.21
Model group (10 mL/kg distilled water)	491.65± 53.82*	69.79± 14.09*
Lipoic acid group (78 mg/kg)	379.43± 44.63**	53.69± 13.65**
High dose group of Tianyang Fumai decoction (6.8 g/kg)	429.11± 58.32**	60.67± 12.01**
Tianyang Fumai decoction medium dose group (3.4 g/kg)	431.78± 66.19**	60.81± 13.87**
Tianyang Fumai decoction low dose group (1.7 g/kg)	443.51± 45.32**	61.32± 10.09**
F	22.181	5.889
P	<0.001	<0.001

Note: Compared with the normal group, * $P<0.05$; Compared with the model group, ** $P<0.05$.

者日常生活,威胁患者生命安全^[11]。中医研究表明^[12,13],DPN 主因为气虚、阴虚、淤血及脉络阻塞。气虚则会血液运输不畅、皮肾阳虚、津液失衡及痰液聚集;阴虚则会血液循环迟缓、口舌干燥、痰多尿少;淤血则致脉络阻塞、不通则痛,因而 DPN 患者常见四肢麻木、疼痛及肌无力等症状。而天阳复脉汤具有补肾壮阳、活络气血、疏通脉络之功效,可直接改善 DPN 临床表征,从根源治疗 DPN,且毒副作用小。临床常用 db/db 小鼠作为糖尿病动作模型,且 7 周龄左右小鼠开始出现 DPN 症状,病理改变

主要为髓神经缺失、运动传导速度骤缓及足底疼痛感受器失效等^[14]。天阳复脉汤是笔者自拟的中药验方,方剂中附片、肉桂、补骨脂、肉苁蓉及鹿角霜等具有温补肾阳之功效^[15],菟丝子、熟地、山茱萸、山药、枸杞及当归等具有补肾填精的作用^[16],黄连具有坚阴清虚热的功效,茯苓、人参等具有益气健脾的作用^[17],丹参、鸡血藤、怀牛膝等发挥活血通络的作用^[18],泽泻可渗利水湿^[19],而甘草能调药和中^[20],方剂中诸药物君臣佐使,共同发挥活血化瘀、补肾壮阳及疏通脉络的疗效。目前临床上尚无天阳

表 4 六组小鼠 JNK 和 p-JNK 蛋白比较 (n=24, $\bar{x} \pm s$)Table 4 Comparison of expression of JNK and p-JNK protein in six groups of mice (n=24, $\bar{x} \pm s$)

Groups	JNK	p-JNK
Normal group (10 mL/kg distilled water)	0.46 $\pm$ 0.12	0.69 $\pm$ 0.11
Model group (10mL/kg distilled water)	2.10 $\pm$ 0.43*	2.34 $\pm$ 0.33*
Lipoic acid group (78 mg/kg)	0.79 $\pm$ 0.19*#	1.14 $\pm$ 0.29*#
High dose group of Tianyang Fumai decoction (6.8 g/kg)	1.23 $\pm$ 0.34*#	1.05 $\pm$ 0.23*#
Tianyang Fumai decoction medium dose group (3.4 g/kg)	1.18 $\pm$ 0.31*#	1.56 $\pm$ 0.32*#
Tianyang Fumai decoction low dose group (1.7 g/kg)	1.45 $\pm$ 0.32*#	1.63 $\pm$ 0.45*#
F	83.307	84.741
P	<0.001	<0.001

Note: Compared with the normal group, * P <0.05; Compared with the model group, # P <0.05.

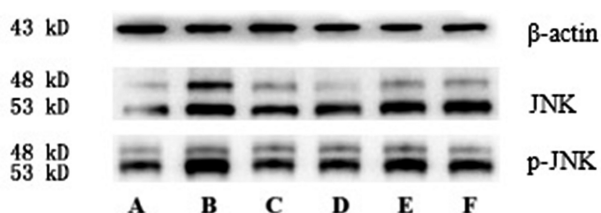


图 1 六组小鼠背根神经节中 JNK 及 p-JNK 蛋白表达结果

Fig.1 Expression of JNK and p-JNK protein in dorsal root ganglia of six groups of mice

Note: A: normal group (10 mL/kg distilled water);

B: model group (10 mL/kg distilled water); C: lipoic acid group (78 mg/kg); D: Tianyang Fumai decoction high dose group (6.8 g/kg);

E: Tianyang Fumai decoction medium dose group (3.4 g/kg);

F: Tianyang Fumai decoction low dose group (1.7 g/kg)

复脉汤应用于 DPN 治疗的实例,本文探讨天阳复脉汤对 DPN 小鼠临床疗效及其对 JNK 和 p-JNK 蛋白表达的影响,旨在为临床治疗研究提供依据。

本文研究表明,硫辛酸组和天阳复脉汤组小鼠足底热敏反应时间均显著缩短,硫辛酸组和天阳复脉汤组小鼠 MNCV 速度均显著提高,硫辛酸组和天阳复脉汤组小鼠血清 TNF- α 和 IL-1 β 明显下降 (P <0.05),提示天阳复脉汤可有效缓解小鼠 DPN 临床病变症状,降低小鼠炎症反应。分析认为,氧化应激反应参与调节 DPN 发生、发展过程^[21],而硫辛酸是天然抗氧化剂,可有效清除机体内过剩自由基,同时还可以通过提高机体内谷胱甘肽浓度,抑制机体脂代谢异常而改善 DPN 症状^[22]。本文研究结果中天阳复脉汤可与硫辛酸取得相近的临床疗效,且高剂量组疗效优于硫辛酸组,进一步证实天阳复脉汤的临床有效性。研究表明^[23,24],天阳复脉汤中山东茺莢、人参等中草药可下调血清炎症因子而抑制机体炎症反应。

DPN 的发病机制较为复杂,可能与胰岛素抵抗、炎症反应及氧化应激反应有关^[25]。JNK 磷酸化后激活信号通路,在机体细胞增殖、分化及凋亡、氧化应激等过程中发挥重要作用^[26,27],且药理研究表明^[28],JNK 基因在高脂饮食的介导下可降低机体免疫功能,而诱发炎症反应。本文研究表明,与正常组相比,模型组小鼠 JNK 和 p-JNK 蛋白表达明显上升(P <0.05);与模型组相比,硫辛酸组和天阳复脉汤组小鼠 JNK 和 p-JNK 蛋白表达

显著下降(P <0.05)。提示天阳复脉汤可有效降低 JNK 和 p-JNK 蛋白表达。相关性研究表明^[29],JNK 蛋白表达与机体炎症反应呈正相关,中药方剂可通过多种组分发挥抗炎作用,进而抑制 JNK 基因转录过程,下调 JNK 和 p-JNK 蛋白表达水平,并可间接证明天阳复脉汤通过降低 JNK 基因转录水平而发挥改善 DPN 临床疗效的作用^[30,31]。

综上所述,天阳复脉汤对糖尿病周围神经病变小鼠可有效增加其运动神经传导速度,缩短其足底热敏反应时间,降低其血清 TNF- α 和 IL-1 β 浓度,进而下调其 JNK 和 p-JNK 蛋白表达。

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