Effect of Nv Shi Solid Drink on Endocrine Regulation in Mice with Kidney-Yin Deficiency Induced by Levothyroxine Sodium

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Abstract

Purpose: To observe the effects of Nv Shi solid drink on thyroid hormone, sex hormones and cyclic nucleotide of kidney-yin deficiency hyperthyroid mice induced by levothyroxine sodium. **Methods:** ICR mice were randomly grouped into normal control group, model group, Nv Shi solid drink high dose group, the middle dose group and low dose group, male and female in half. The kidney-yin deficiency mice models were established by intragastric administration of levothyroxine sodium before intragastric administration of corresponding drugs once a day for 10 consecutive days. One day after the last administration, the effects were observed by measuring weight. And tetraiodothyronine (T4), triiodothyronine (T3), thyrotropin (TSH), testosterone (T), estradiol (E2), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) were tested by ELISA method. **Results:** Compared with the model group, the body weight increased significantly ($p < 0.05$), T3 level decreased significantly in high and medium dose group ($p < 0.01$, $p < 0.05$), and serum T4 and cAMP decreased significantly ($p < 0.01$, $p < 0.05$), TSH increased significantly ($p < 0.01$, $p < 0.05$) in all dose groups, and cAMP/cGMP decreased in the low dose group ($p < 0.05$). The expression of E2 in female decreased significantly in all dose groups, the same as the ratio of E2/T in high dose group ($p < 0.05$). There was no significant change in the expression of sex hormones in male in all dose groups ($p > 0.05$). **Conclusion:** Nv Shi solid drink may improve the kidney-yin deficiency syndrome by adjusting T3, T4, TSH, cAMP and E2 level in the endocrine system of the body and exert the function of nourishing yin and tonifying kidney.

Keywords: Nv Shi solid drink, Kidney-yin deficiency, Sex hormone, Thyroid hormone, Cyclic nucleotide

Introduction

肾阴虚证是指由于肾阴亏损，失于滋养，虚热内生所表现的证候 (Wang & Tian, 2008)。目前有多种肾阴虚证动物模型用于功效评价 (Lin *et al.*, 2013)，其中甲状腺机能亢进肾阴虚证模型较为常用 (Wang, 2013)。这种方法是给实验动物使用甲状腺素，形成外源性甲状腺素水平升高，造成实验动物甲状腺机能亢进，促进体内物质代谢，增加耗氧量，使产热增加，能够模拟甲状腺功能亢进时的消瘦、怕热、多汗、神经过敏、急躁、震颤、心率加快、心输出量增加等症状，表现基

本符合临床肾阴虚的辨证诊治 (Zhang *et al.*, 2015; Fu *et al.*, 2017)。

女仕牌固体饮料由黑木耳、茯苓、枸杞子、桑椹、龙眼肉、玉竹、薏苡仁、莲子、大枣等药食同源的中药组成，具有滋肾阴、补阴血的功效。本实验采用甲状腺激素法建立肾阴虚证动物模型，探讨女仕牌固体饮料对肾阴虚动物模型的影响并阐释作用机制，为阐明药食同源中药复方品种滋阴补肾功效的作用机制提供实验依据。

Methods

1. Instruments and materials

1) Test instrument

全自动多功能酶标仪 (MULTISKAN MK3; 美国Thermo公司, 美国); 电热恒温培养箱 (DH4000A; 天津泰斯特公司, 中国); 低温离心机 (5810R; 德国Eppendorf公司, 德国); MINI shaker (MH-1; Kylin-Bell Lab Instruments QILINBEIER公司, 中国)。

2) Material

女仕牌固体饮料 (批号18E31EAC01; 无限极(中国)有限公司, 中国); 左甲状腺素钠 (批号248922, Merk Serono GmbH, 德国); Mouse E2 elisa kit (CSB-E05109m, 武汉华美生物工程有限公司, 中国); Mouse T elisa kit (CSB-E05101m, 武汉华美生物工程有限公司, 中国); Mouse T3 elisa kit (CSB-E05109m, 武汉华美生物工程有限公司, 中国); Mouse T4 elisa kit (CSB-E05083m; 武汉华美生物工程有限公司, 中国); Mouse TSH elisa kit (CSB-E05116m; 武汉华美生物工程有限公司, 中国); Mouse cAMP elisa kit (20181024; 南京建成生物工程研究所, 中国); Mouse cGMP elisa kit (20181024; 南京建成生物工程研究所, 中国)。

3) Animal

ICR小鼠 (SPF级), 雌雄兼用, 体重为 18-20 g, 购自北京华阜康生物科技股份有限公司, 动物合格证号: 11401300086884, 使用许可证号: SCXK (京) 2015-0041。

2. Experimental method

1) Animal grouping and treatment

将ICR小鼠分为5组, 每组20只, 雌雄各半。正常组、模型组、女仕牌固体饮料大 (1.65 g/kg/d)、中 (0.83 g/kg/d)、小剂量组 (0.41 g/kg/d), 分别相当于成人日用量的 2 倍, 1倍, 0.5倍。除正常组外, 各组小鼠给予左甲状腺素钠 50 μ g/kg ig, 0.1 mL/10 g, 每天 1 次, 连续 10 天, 造成肾阴虚证候小鼠模型。每日给予左甲状腺素钠后间隔 2 小时给予相应药物 0.2 mL/10

g ig, 连续 10 天, 正常组和模型组在同等条件下给予蒸馏水。

2) Detection of index

每天观察大鼠饮食饮水情况、精神状态、毛色、体态, 末次给药后称取体质量。观察小鼠一般体征。第 11 天称重后眼眶取血, 离心分离血清, -20℃保存待测, 采用ELISA方法检测甲状腺素 (thyroxine, T4)、三碘甲状腺原氨酸 (triiodothyronine, T3)、促甲状腺激素 (thyroid-stimulating hormone, TSH)、睾酮 (testosterone, T)、雌二醇 (estradiol, E2)、环磷酸腺苷 (cyclic Adenosine monophosphate, cAMP)、环磷酸鸟苷 (cyclic guanosine monophosphate, cGMP) 的表达。

3. Statistical analysis

各组所得数据均以 (mean $\pm$ standard deviation) 表示, 组间比较采用单因素方差分析。

Results

1. Effect of Nv Shi solid drink on general physical signs in mice with kidney-yin deficiency

正常组小鼠毛发润泽、活动自如; 连续给予左甲状腺素钠10天后, 模型组小鼠出现躁动、易惊、体毛粗糙无光泽等表现, 体重增长缓慢, 与正常组比较有极显著性差异 ($p < 0.01$)。灌胃给予女仕牌固体饮料后小鼠毛色和光泽度有所改善, 易惊表现有改善趋势。女仕牌固体饮料大剂量、中剂量组小鼠体重增加, 与模型组比较均有显著性差异 ($p < 0.05$)。见Table 1。

2. Effect of Nv Shi solid drink on hyperthyroidism in mice with kidney-yin deficiency

给予左甲状腺素钠后, 模型组小鼠血清TSH含量降低, T3、T4含量升高, 与正常组比较均有显著性差异 ($p < 0.01$); 女仕牌固体饮料各剂量组血清TSH含量升高, 与模型组比较有显著性差异 ($p < 0.01$, $p < 0.05$); 女仕牌固体饮料大剂量、中剂量组血清T3含量均降低, 与模型组比较有显著性差异 ($p < 0.01$, $p < 0.05$); 女仕牌固体饮料各剂量组血清T4含量降低, 与模型组

Table 1. Effect of Nv Shi solid drink on body mass in mice with kidney-yin deficiency (N=20)

Group	Dosage (g/kg/d)	After model establishment (g)
Normal group	—	28.50 $\pm$ 1.27 ¹⁾
Model group	—	24.80 $\pm$ 1.40 ^{##}
High dose group	1.65	26.70 $\pm$ 2.11 [*]
Middle dose group	0.83	26.60 $\pm$ 2.17 [*]
Low dose group	0.41	25.89 $\pm$ 2.80

¹⁾Mean $\pm$ standard deviation; Compared with normal group, ^{##} $p < 0.01$; Compared with model group, ^{*} $p < 0.05$.

比较有极显著性差异 ($p<0.01$)。见Table 2。

3. Effect of Nv Shi solid drink on the level of sex hormone in mice with kidney-yin deficiency

对于雌性小鼠：模型组血清E2含量升高，T含量降低，E2/T升高，与正常组比较均有显著性差异 ($p<0.01$, $p<0.05$)；给予女仕牌固体饮料后，各剂量组雌鼠E2水平降低，大剂量组雌鼠E2/T水平降低，与模型组比较均有显著性差异 ($p<0.05$)。

对于雄性小鼠：模型组血清T含量降低，E2/T升高，与正常组比较均有显著性差异 ($p<0.05$)，模型组血清E2含量无显著改变，与正常组比较均无显著性差异 ($p>0.05$)；给予女仕牌固体饮料后，大剂量和小剂量组雄鼠血清E2/T有降低趋势，但与模型组比较无显著性差异 ($p>0.05$)。见Table 3。

4. Effect of Nv Shi solid drink on cyclic nucleotide level in mice with kidney-yin deficiency

模型组小鼠血清cAMP含量升高，cAMP/cGMP升高，与正常组比较均有显著性差异 ($p<0.05$)，cGMP无显著变化 ($p>0.05$)；给予女仕牌固体饮料后，各剂量组小鼠血清cAMP含量降低，与模

型组比较均有显著性差异 ($p<0.05$)；女仕牌固体饮料各剂量组cGMP含量，与模型组比较均无显著差异 ($p>0.05$)；女仕牌固体饮料小剂量组cAMP/cGMP降低，与模型组比较均有显著性差异 ($p<0.05$)。见Table 4。

Discussion

肾阴虚是中医学虚证的基本证型之一，是指由于肾阴亏损，失于滋养，虚热内生所表现的证候，肾阴虚证见腰膝酸痛，失眠多梦，头晕耳鸣，咽干颧红，五心烦热，遗精早泄，潮热盗汗，舌红少津无苔，脉细数等(Fu *et al.*, 2017)。临床肾阴虚患者多见体形消瘦、皮肤干燥、心烦易怒，模型组小鼠体重减轻一定程度上说明虚损的程度。肾阴虚主要与甲状腺轴、性腺轴、能量代谢、免疫力下降等有关((Fu *et al.*, 2017; Dai *et al.*, 2016; Zou *et al.*, 2015)。中医认为，甲状腺机能亢进属阴虚证范畴(Huang *et al.*, 2008)，T3、T4升高多见于五心烦热，咽干口渴，舌红少苔，脉细数的肾阴虚型患者(Fang, 2008)。甲状腺功能亢进可出现血清 T3、T4含量明

Table 2. Effect of Nv Shi solid drink on serum TSH, T3, T4 level in mice with kidney-yin deficiency (N=20)

Group	TSH (uIU/mL)	T3 (ng/mL)	T4 (ng/mL)
Normal group	6.29±1.61 ¹⁾	4.02±0.87	227.40±68.55
Model group	1.59±0.29 ^{##}	5.45±0.93 ^{##}	594.05±91.15 ^{##}
High dose group	2.53±0.67 ^{**}	4.11±0.88 ^{**}	379.72±62.88 ^{**}
Middle dose group	2.16±0.65 [*]	4.38±0.67 [*]	422.98±65.65 ^{**}
Low dose group	2.14±0.76 [*]	4.78±0.79	442.44±78.91 ^{**}

¹⁾Mean±standard deviation; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; Compared with normal group, ^{##} $p<0.01$; Compared with model group, ^{*} $p<0.05$, ^{**} $p<0.01$.

Table 3. Effect of Nv Shi solid drink on serum E2, T level and ratio of E2/T in mice with kidney-yin deficiency (N=20)

Group	TSH (uIU/mL)		T3 (ng/mL)		T4 (ng/mL)	
	Female	Male	Female	Male	Female	Male
Normal group	184.57±9.31 ¹⁾	170.33±19.49	0.84±0.09	2.75±0.35	221.47±30.72	63.10±13.82
Model group	226.75±23.30 ^{##}	167.24±9.32	0.69±0.07 [#]	1.79±0.66 [#]	334.50±60.83 ^{##}	102.55±33.18 [#]
High dose group	191.04±23.06 [*]	165.44±38.67	0.74±0.10	1.73±0.15	261.75±32.96 [*]	95.96±22.44
Middle dose group	190.26±26.28 [*]	178.11±26.48	0.62±0.10	1.69±0.24	221.47±30.72	63.10±13.82
Low dose group	188.72±15.91 [*]	0.65±0.06	0.84±0.09	2.75±0.35	334.50±60.83 ^{##}	102.55±33.18 [#]

¹⁾Mean±standard deviation; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; Compared with normal group, [#] $p<0.05$, ^{##} $p<0.01$; Compared with model group, ^{*} $p<0.05$.

Table 4. Effect of Nv Shi solid drink on serum cAMP and cGMP level and the ratio of cAMP/cGMP in mice with kidney-yin deficiency (N=20)

Group	cAMP (nmol/L)	cGMP (nmol/L)	cAMP/cGMP
Normal group	139.52±22.28 ¹⁾	159.62±24.77	0.89±0.18
Model group	160.45±15.42 [#]	143.35±28.36	1.16±0.25 [#]
High dose group	145.46±15.01 [*]	141.58±21.43	1.02±0.19
Middle dose group	143.38±21.80 [*]	149.25±31.86	1.00±0.22
Low dose group	145.84±13.09 [*]	154.93±12.60	0.94±0.09 [*]

¹⁾Mean±standard deviation; Compared with normal group, [#] $p<0.05$; Compared with model group, ^{*} $p<0.05$.

显升高,基础代谢增强(Huang *et al.*, 2011),负反馈抑制腺垂体分泌TSH,二者互相拮抗,T3、T4、TSH表达异常能反映甲状腺轴功能紊乱(Dai *et al.*, 2016)。在临床检查中,性激素E2、T和E2/T比值异常能反映性腺轴功能紊乱,是阴阳失调的重要指标(Xu *et al.*, 2007)。但各类肾虚类型的T与E2水平及变化不尽相同(Qiu *et al.*, 1999)。有研究将E2含量上升、T含量下降,E2/T作为肾阴虚大鼠模型造模成功的评判标准(Peng & Zhang., 2003)。环核苷酸cAMP、cGMP是调节细胞功能活动的重要物质,二者相互制约、相互拮抗,其对生物细胞的双向调节作用与中医阴阳学说相似(Cheng, 2016; Li *et al.*, 2017)。cAMP/cGMP升高可反映肾阴虚动物模型造模成功(Luo, 2006)。本实验中,左甲状腺素钠诱导肾阴虚模型小鼠出现躁动、易惊、体毛粗糙无光泽,体重增长缓慢等状态,表现虚损症状。肾阴虚小鼠血清T3、T4含量上升,TSH含量下降,T含量下降、E2/T比值上升,cAMP/cGMP比值升高,均表明肾阴虚模型造模成功。

女仕牌固体饮料由黑木耳、茯苓、枸杞子、桑椹、龙眼肉、玉竹、薏苡仁、莲子、大枣等药食同源的中药组成,其中以黑木耳、枸杞子、桑椹为君,可滋阴补血、补肝益肾、生津止渴,缓解头晕眼花、潮热盗汗;茯苓、龙眼肉、莲子为臣,可宁心安神,清心除烦、缓解失眠心烦、汗出;玉竹、薏苡仁为佐,可健脾益气、养阴润燥,缓解口干口渴;大枣为使,可补气养血,调和口味,全方共奏滋肾阴、补阴血的功效。本研究采用左甲状腺素钠诱导肾阴虚模型评价女仕牌固体饮料干预肾阴虚的作用,分为低、中、高剂量组,在造模后给予女仕牌固体饮料干预,不仅观察女仕牌固体饮料干预肾阴虚的功效,同时初步探讨对肾阴虚的作用机制。

机体处于甲亢状态与下丘脑-垂体-甲状腺轴(hypothalamic-pituitary-thyroid, HPT)相关(Duan *et al.*, 2016),甲亢型肾阴虚小鼠的甲状腺功能亢进、基础代谢增多,躁动、易惊扰,体毛干枯、体重下降,血清T3、T4含量升高,TSH含量降低。本实验结果显示,女仕牌固体饮料可改善肾阴虚模型动物毛色和光泽度,在一定程度上改善模型动物的易惊状态,并可增加模型动物体重,具有降低肾阴虚动物模型血清T3、T4、升高TSH作用。研究从分子水平提示,女仕牌固体饮料能改善甲状腺功能亢进,改善HPT轴功能。

中医认为“肾藏精,主生长发育与生殖”,肾气的盛衰直接影响着人体的生殖功能,而现代医学也发现生殖系统的功能受下丘脑-垂体-性腺(hypothalamic-pituitary-gonadal axis, HPG)轴神经内分泌调节,肾阴虚与HPG轴功能密切相关(Zhang *et al.*, 2017)。本实验结果显示女仕牌固体饮料可降低雌性肾阴虚动物模型血清E2含量,降低E2/T比值,研究提示女仕牌固体饮料能在一定程度上调节性激素平衡,改善HPG轴功能。

机体处于正常状态下,血清的cAMP, cGMP水平不会发生变

化,一旦机体持续处于亢奋状态,通过激活腺苷酸环化酶的活性,诱导cAMP, cGMP的合成。cAMP和cGMP是调节物质代谢和生物学功能的重要物质,对细胞功能处于稳定状态具有双向控制调节作用(Pan *et al.*, 2014),且与中医学的阴阳学说有相似之处,研究表明, cAMP含量升高是肾阴虚的特征之一(Chen, 2011),本实验结果显示女仕牌固体饮料可降低肾阴虚动物模型血清cAMP含量,降低cAMP/cGMP比值,研究提示女仕牌固体饮料在一定程度上具有平衡环核苷酸系统的作用。

Conclusion

女仕牌固体饮料能在一定程度上改善肾阴虚小鼠虚损状态,调节肾阴虚证的相关物质基础促甲状腺激素(TSH)、三碘甲状腺原氨酸(T3)、甲状腺素(T4)、环磷酸腺苷(cAMP)以及雌性小鼠雌二醇(E2)水平,从而改善甲状腺功能亢进,调节雌性肾阴虚模型性激素,平衡环核苷酸系统。研究提示,女仕牌固体饮料可能通过改善肾阴虚动物模型神经内分泌HPT轴和HPG轴功能,平衡环核苷酸系统,从而发挥滋阴补肾功效。

Author's contribution

SL, YJS and HM designed the experiment and YJS, WYZ and JL operated the animal experiment. SL and SYM analyzed the data and YJS and HM wrote the article.

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中文摘要

女仕牌固体饮料对左甲状腺素钠诱导肾阴虚小鼠模型内分泌系统的影响

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目的: 观察女仕牌固体饮料对左甲状腺素钠致肾阴虚模型小鼠体内甲状腺激素、性激素及环核苷酸的影响。**方法:** ICR小鼠随机分为正常组、模型组、女仕牌固体饮料大、中、小剂量组, 雌雄各半, 采用左甲状腺素钠片灌胃造成小鼠肾阴虚模型, 造模当天灌胃给予样品, 每天1次, 连续10天。末次给药后1天, 观察小鼠体征及体重, 取血, 采用Elisa方法检测血清中甲状腺素(thyroxine, T4)、三碘甲状腺原氨酸(triiodothyronine, T3)、促甲状腺激素(thyroid-stimulating hormone, TSH)、睾酮(testosterone, T)、雌二醇(estradiol, E2)、环磷酸腺苷(cyclic Adenosine monophosphate, cAMP)、环磷酸鸟苷(cyclic guanosine monophosphate, cGMP)的表达。**结果:** 与模型组比较, 女仕牌固体饮料大剂量组和中剂量组小鼠体重显著升高($p<0.05$); 大剂量和中剂量组T3显著降低($p<0.01$, $p<0.05$), 各剂量组血清T4、cAMP均显著降低($p<0.01$, $p<0.05$), TSH均显著升高($p<0.01$, $p<0.05$), 小剂量组cAMP/cGMP比值降低($p<0.05$), 各剂量组雌鼠E2表达显著降低, 大剂量组雌鼠E2/T比值降低, 各剂量组雄鼠性激素表达无显著改变($p>0.05$)。**结论:** 女仕牌固体饮料可能通过调整机体内神经分泌系统中T3、T4、TSH、cAMP、雌鼠E2这些共同的潜在物质基础, 改善HPT轴和HPG轴功能、平衡环核苷酸系统, 从而改善肾阴虚证, 发挥滋阴补肾功效。

关键词: 女仕牌固体饮料, 肾阴虚证, 性激素, 甲状腺激素, 环核苷酸

국문초록

Levothyroxine Sodium에 의해 유발 된 신장음질 결핍 마우스의 내분비 조절에 대한 여성브랜드 고형 음료의 효능

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목적: Levothyroxine sodium에 의해 유발 된 신장 음질 결핍 마우스에서 갑상선 호르몬, 성 호르몬 및 사이 클릭 뉴클레오티드에 대한 여성 브랜드 고형 음료의 효능을 확인하고자 한다. **방법:** ICR 마우스를 정상 대조군, 모델 군, 여성브랜드 고형 음료 고용량 군, 중간 용량 군 및 저용량 군, 수컷 및 암컷으로 무작위로 그룹화 하였다. 신장음질 결핍 마우스 모델은 10 일 연속으로 하루에 한 번 levothyroxine sodium을 위내 투여에 의해 형성되었다. 마지막 투여 1 일 후, 체중을 측정함으로써 그 효과를 관찰 하였다. ELISA 법으로 혈청 내 thyroxine (T4) triiodothyronine, (T3), thyroid-stimulating hormone (TSH), testosterone (T), estradiol (E2), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP)의 발현을 측정하였다. **결과:** 모델 그룹과 비교하여, 여성브랜드 고형 음료의 고용량 및 중간 용량 그룹에서 마우스의 체중은 유의하게 증가하였고($p < 0.05$); 고용량 및 중간 용량 그룹에서 T3는 유의하게 감소 하였다($p < 0.01$, $p < 0.05$). 혈청 T4 및 cAMP는 유의하게 감소하였고($p < 0.01$, $p < 0.05$), TSH는 유의적으로 증가하였고($p < 0.01$, $p < 0.05$), 저용량 그룹 cAMP/cGMP 비율은 감소 하였다($p < 0.05$), 각 용량 그룹 암컷 쥐에서 E2의 발현은 유의하게 감소하였고 고용량 군에서 암컷 쥐의 E2/T 비율은 감소하였으나, 각 용량 군에서 수컷 쥐에서 성 호르몬의 발현에는 유의 한 변화가 없었다($p > 0.05$). **결론:** 여성브랜드 고형 음료는 신체의 내분비 계에서 T3, T4, TSH, cAMP 및 E2 수준을 조절하여 신장 음질 결핍 증후군을 개선할 수 있다.

핵심어: 여성 브랜드 고형 음료, 신음 결핍 증후군, 성 호르몬, 갑상선 호르몬, 사이클릭 뉴클레오티드