缬草对慢性应激导致的抑郁大鼠体质量和行为的影响

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摘 要：【目的】探讨缬草对慢性应激导致的抑郁大鼠体质量和行为的影响。【方法】70只大鼠随机分为低、中和高剂量缬草模型组、阳性对照模型组、阴性对照模型组、未用药模型组和正常对照组各10只。给予各模型组大鼠慢性应激4周建立抑郁症模型。模型建立后除未用药模型组大鼠正常饲养外，其余6组相应灌服低、中和高剂量缬草、氟西汀(阳性对照)和羧甲基纤维素钠(阴性对照)等药物3周。每周测定大鼠的体质量、自来水摄取量和10 g/L糖水摄取量。【结果】灌服低、中和高剂量缬草以及阳性对照药氟西汀均不能促使抑郁大鼠的体质量恢复至正常大鼠水平。在整个实验期间，7组大鼠之间自来水摄取量的差异无统计学意义。氟西汀与低剂量缬草能够促使抑郁大鼠的糖水摄取量恢复性增加到正常大鼠水平。【结论】一定剂量的缬草能够促使抑郁大鼠恢复正常的行为活动。

关键词：慢性应激；抑郁症；缬草；体质量；行为学
中图分类号：R749 **文献标识码**：A **文章编号**：1672-3554(2008)05-0541-05

Effects of Valerian on Weight and Behavior of Depressive Rats Induced by Chronic Mild Stress

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Abstract: 【Objective】To explore the effects of *Valerian* on the weight and behavior of depressive rats induced by chronic mild stress. 【Methods】A total of 70 rats were divided randomly into low dose of *Valerian* model group, medium dose of *Valerian* model group, high dose of *Valerian* model group, positive control model group, negative control model group, untreated model group, and normal control group. Each group had 10 rats. Each model group of rats were induced into depressive disorder by chronic mild stress for 4 weeks. After that, except the untreated model group, the other six groups were administrated respectively by low, medium, and high dose of *Valerian*, fluoxetine, and sodium carboxymethycellulose for 3 weeks. The weight, tap water intake and 10 g/L sucrose intake were weekly examined for seven groups of rats. 【Results】After the intragastric administration of low, medium, and high dose of *Valerian*, and fluoxetine (a positive control drug), the weight of depressive rats did not recover to that of normal control group of rat. Tap water intake was not statistically different between seven groups of rats during the experimentation. However, 10 g/L sucrose intake in fluoxetine model group and low dose of *Valerian* model group was increased and recovered to that of normal control group of rat. 【Conclusion】A certain dose of *Valerian* may make behavior of depressive rats to recover to normal status.

Key words: chronic stress; depression; *Valerian*; weight; behavior
[J SUN Yat-sen Univ(Med Sci), 2008, 29(5): 541-545]

抑郁症(depression)是一组以显著而持久的心境障碍为主要表现的一种常见精神障碍，据世界卫生组织估计，到2020年抑郁症成为仅次于缺血性心脏病的第二大疾病[1-3]。缬草(Valerian)化学成

收稿日期：2007-10-11
基金项目：广东省中医药管理局科研基金(101139)
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分复杂,药理活性多样,具有镇静催眠、抗肿瘤、抗菌、抗病毒、抗抑郁等活性。Oshima 等[4]报道缬草提取物能够缩短小鼠强迫游泳实验不动时间,显示了缬草的抗抑郁活性。本实验旨在探讨缬草对慢性应激导致的抑郁大鼠体质量和行为的影响,为临床应用缬草防治抑郁症提供实验资料。

1 材料与方法

1.1 材 料

1.1.1 *动物* SD成年雄鼠80只,体质量180~200 g,由广东省实验动物中心(粤监证字2006A015)提供。

1.1.2 *药物* 阳性药物氟西汀购自美国礼来公司,缬草由Holistal International LTD提供,氟西汀和缬草溶液用5 g/L羧甲基纤维素钠配置而成。

1.2 实验方法

1.2.1 *动物分组及模型建立* 首先将80只大鼠正常饲养1周(本实验称为0周),在这段时间内,大鼠群养(每笼3~5只),且可以自由饮食和饮用自来水,同时给予10 g/L糖水进行训练。动物房温度控制在22 ℃±2 ℃,且保持12/12 h昼夜节律。在0周结束时,对所有大鼠禁食禁水20 h,然后测定其在1 h内对10 g/L糖水摄取量,从中筛选出糖水摄取量相近的大鼠70只,并将其分成以下7组:①低剂量缬草模型组;②中剂量缬草模型组;③高剂量缬草模型组;④阴性对照模型组;⑤阳性对照模型组;⑥未用药模型组;⑦正常对照组。本试验采用慢性应激抑郁模型[5],具体方法是:除正常对照组外,给予其余6组大鼠4周不可预测的中等强度刺激,包括强迫游泳(8 min)、禁水(20 h)、同笼饲养(16 h)、昼夜颠倒(12 h)、打湿垫料(20 h)、45°倾斜笼子(16 h)和放置异物(7 h)等。每天随机安排上述1种以上刺激方式。

1.2.2 *给药* 模型建立后,7组大鼠分别灌服不同的药物。①正常对照组和阴性对照模型组大鼠灌服5 g/L羧甲基纤维素钠;②阳性对照模型组大鼠灌服氟西汀溶液(2.2 mg/kg);③低剂量缬草模型组大鼠灌服低剂量缬草溶液(100 mg/kg);④中剂量缬草模型组大鼠灌服中剂量缬草溶液(200 mg/kg);⑤高剂量缬草模型组大鼠灌服高剂量缬草溶液(400 mg/kg);以上药物的剂量均是4 mL/d,分早晚两次灌服,每次2 mL,灌药周期为3周。⑥未用药模型组不灌服任何药物,正常饲养。

1.2.3 *体质量和行为学检测* 本实验周期为8周,每周对各只大鼠进行一次体质量、自来水摄取量、10 g/L糖水摄取量的测量。具体方法是在禁食禁水20 h后,同时给予大鼠自来水和10 g/L糖水(需预先称自来水瓶和糖水瓶的重量),1 h后,拿去自来水瓶和糖水瓶并称其重量,前后两次称量的差值分别为大鼠的自来水摄取量和10 g/L糖水摄取量。体质量称量在检测自来水摄取量和10 g/L糖水摄取量后进行。

1.2.4 *统计学分析* 采用SPSS12.0统计软件,组间各数据比较均用单因素方差分析,结果用 $\bar{x}\pm s$ 表示。

2 结 果

2.1 制备模型期间7组大鼠体质量和行为学结果

表1显示,在实验的第3周和第4周,与正常对照组大鼠相比,其余6组大鼠体质量增加的幅度明显减小。表2显示7组大鼠在同一测定时间内,两两之间比较各组大鼠的自来水摄取量差异无统计学意义($P>0.05$)。表3显示,在实验的第3周和第4周,与相同测定时间的正常对照组大鼠相比,其余6组大鼠的10 g/L糖水摄取量明显减少($P<0.05$)。这些结果提示,应用慢性应激能够成功制备抑郁症大鼠模型。

2.2 灌服药物期间大鼠体质量和行为学结果

表4显示,与正常对照组大鼠比较,灌服低、中和高剂量缬草以及阳性对照药氟西汀均不能明显恢复抑郁大鼠的体质量,这提示缬草和氟西汀对改善抑郁大鼠的体质量状况没有明显作用。表5显示7组大鼠在同一测定时间内,两两之间比较各组大鼠的自来水摄取量差异无统计学意义($P>0.05$)。表6显示,在实验的第6周和第7周,阳性对照模型组和低剂量缬草模型组大鼠的10 g/L糖水摄取量恢复性增加到正常水平。上述结果提示,应用低剂量缬草能改善大鼠抑郁症状,具有抗抑郁的作用。

3 讨 论

慢性应激抑郁模型是目前最为公认、应用最

表 1　7 组大鼠制备模型期间体质量的比较

Table 1　Comparison of the weight in seven groups of rats during the periods of establishing model　($\bar{x}\pm s$, g)

Group	n	Experimental period				
		0 week	1 week	2 week	3 week	4 week
Low dose of *Valerian* model	10	260 ± 9	291 ± 7	309 ± 9	320 ± 8[1)]	325 ± 12[1)]
Medium dose of *Valerian* model	10	262 ± 12	293 ± 9	309 ± 7	322 ± 10[1)]	327 ± 11[1)]
High dose of *Valerian* model	10	263 ± 11	294 ± 7	311 ± 10	324 ± 10[1)]	326 ± 9[1)]
Negative control model	10	260 ± 7	287 ± 16	307 ± 11	322 ± 7[1)]	332 ± 11[1)]
Positive control	10	262 ± 10	292 ± 9	311 ± 10	322 ± 9[1)]	327 ± 11[1)]
Untreated model	10	261 ± 8	293 ± 5	312 ± 9	322 ± 9[1)]	331 ± 9[1)]
Normal control	10	262 ± 10	293 ± 11	316 ± 8	331 ± 8	343 ± 14

1) Compared with normal control group, by oneway ANOVA, $P < 0.05$

表 2　7 组大鼠制备模型期间的自来水摄取量变化的比较

Table 2　Comparison of the tap water intake in seven groups of rats during the periods of establishing model　($\bar{x}\pm s$, g)

Group	n	Experimental period				
		0 week	1 week	2 week	3 week	4 week
Low dose of *Valerian* model	10	0.99 ± 0.33	1.65 ± 0.45	2.28 ± 0.64	2.76 ± 0.88	2.98 ± 0.52
Medium dose of *Valerian* model	10	0.97 ± 0.27	1.65 ± 0.55	2.23 ± 0.68	2.53 ± 0.74	3.02 ± 0.55
High dose of *Valerian* model	10	0.98 ± 0.19	2.01 ± 0.62	2.63 ± 0.75	2.68 ± 0.67	3.10 ± 0.59
Negative control model	10	0.97 ± 0.36	1.50 ± 0.47	2.24 ± 0.93	2.45 ± 0.69	2.85 ± 0.53
Positive control	10	1.02 ± 0.30	1.76 ± 0.52	2.30 ± 0.68	2.96 ± 0.85	3.22 ± 0.54
Untreated model	10	0.94 ± 0.29	1.78 ± 0.49	2.32 ± 0.65	2.96 ± 0.80	3.04 ± 0.59
Normal control	10	0.96 ± 0.27	1.67 ± 0.54	2.47 ± 0.90	2.49 ± 0.61	2.77 ± 0.52

Compared with normal control group, by oneway ANOVA, $P > 0.05$

表 3　7 组大鼠制备模型期间的 1%糖水摄取量变化的比较

Table 3　Comparison of 10 g/L sucrose intake in seven groups of rats during the periods of establishing model　($\bar{x}\pm s$, g)

Group	n	Experimental period				
		0 week	1 week	2 week	3 week	4 week
Low dose of *Valerian* model	10	11.1 ± 1.2	112.1 ± 1.2	12.3 ± 1.1	11.3 ± 1.2[1)]	11.0 ± 0.8[1)]
Medium dose of *Valerian* model	10	10.8 ± 1.4	12.1 ± 1.0	12.3 ± 0.9	11.3 ± 0.5[1)]	10.8 ± 1.0[1)]
High dose of *Valerian* model	10	11.3 ± 1.4	12.3 ± 1.2	12.1 ± 1.4	11.0 ± 1.1[1)]	10.5 ± 0.7[1)]
Negative control model	10	11.3 ± 1.3	12.1 ± 1.4	11.6 ± 1.9	11.1 ± 1.0[1)]	10.6 ± 0.8[1)]
Positive control	10	11.0 ± 1.1	12.0 ± 1.4	12.3 ± 1.3	11.3 ± 1.1[1)]	10.8 ± 0.9[1)]
Untreated model	10	11.2 ± 1.3	11.7 ± 1.1	11.6 ± 1.1	10.8 ± 0.8[1)]	10.3 ± 0.7[1)]
Normal control	10	11.1 ± 1.3	11.8 ± 1.1	12.2 ± 0.7	12.5 ± 0.7	13.6 ± 1.2

1) Compared with normal control group, by oneway ANOVA, $P < 0.05$

多、最经典的抑郁模型之一。它是通过模拟人们在日常生活中所遇到的"困难"而建立起来的动物模型。在给予动物 3 ~ 4 周的中等强度刺激后,动物表现出兴趣丧失,糖水消耗量减少,这与临床上抑郁症患者最常见的症状快感丧失有一定程度的相似性。但是该模型也具有一些缺点,如造模耗时,费力,尤其是结果不太稳定。因此,如何制备出稳定的慢性应激抑郁模型一直是研究的焦点。在本研究中,为了降低因为大鼠个体差异造成的实验结果不稳定性,在给予大鼠慢性中等强度刺激之前,正常饲养大鼠一段时间,让其适应环境。同时,按照 Angela 等报道的方法,用摄取 1%糖水来训练大鼠[6]。在适应环境后,对所有大鼠禁食禁水一段时间,然后测定其糖水摄取量,从中筛选出糖水

表4 7组大鼠灌服药物期间体质量的变化比较

Table 4 Comparison of the body weight in seven groups of rats during the periods of administrating drugs

($\bar{x}\pm s$, g)

Group	n	Experimental period		
		5 week	6 week	7 week
Low dose of *Valerian* model	10	340±11[1)]	354±10[1)]	371±9[1)]
Medium dose of *Valerian* model	10	344±11[1)]	357±11[1)]	369±9[1),2)]
High dose of *Valerian* model	10	346±9[1)]	359±10[1)]	369±9[1),2)]
Negative control model	10	345±11[1)]	357±8[1)]	365±9[1),2)]
Positive control model	10	347±10[1)]	359±10[1)]	371±7[1),3)]
Untreated model	10	346±8[1)]	360±8[1)]	376±7
Normal control	10	356±12	369±8	383±10[1)]

1)Compared with normal control group, by oneway ANOVA, $P<0.05$; 2)Compared with untreated model group, by oneway ANOVA, $P<0.05$; 3)Compared with negative control group, by oneway ANOVA, $P<0.05$

表5 7组大鼠灌服药物期间的自来水摄取量的变化比较

Table 5 Comparison of the tap water intake in 7 groups of rats during the periods of administrating drugs

($\bar{x}\pm s$, g)

Group	n	Experimental period		
		5 week	6 week	7 week
Low dose of *Valerian* model	10	3.52±0.68	3.13±0.55	3.09±0.58
Medium dose of *Valerian* model	10	3.36±0.55	3.22±0.57	3.13±0.33
High dose of *Valerian* model	10	3.55±0.49	3.25±0.71	3.25±0.71
Negative control model	10	3.37±0.46	3.13±0.66	3.10±0.34
Positive control model	10	3.53±0.71	3.19±0.52	3.21±0.57
Untreated model	10	3.54±0.52	3.30±0.49	3.34±0.38
Normal control	10	3.32±0.38	3.35±0.48	3.30±0.30

Compared with normal control group, by oneway ANOVA, $P>0.05$

摄取量相近的大鼠参与本实验。在造模过程中,为了降低大鼠对刺激的耐受,提高造模的有效性,本文参考了 Angela[6]、Lin[7]、Janne[8]和 Ipek[9]等的造模方法。并在此基础上,不断地对模型的刺激进行调整改进,最终确立了一套造模程序。例如,随机使用各种刺激,同一种刺激在实验中不能连续重复使用3次或以上,这使得大鼠对刺激不可预知。通过上述的造模方法,致使被造模的动物体质量增加的幅度比正常大鼠的要明显减小,其1%糖水摄取量也明显降低,这些都表明本实验成功建立了抑郁大鼠模型。

目前,大部分国外学者采取液体消耗实验中的糖水消耗量来判断抑郁模型是否成功。糖水摄取量的变化可以反映动物对"奖励"的反应。患有抑郁症的大鼠,其"情绪低落",对奖励淡漠,其糖水摄取量是明显减少的。本研究也发现,在造模的第3周和第4周,制备模型组大鼠的糖水摄取量是明显减少的。这表明给予慢性应激能够使大鼠发生抑郁。

本文还观察到,一定剂量的缬草可以使抑郁大鼠的糖水摄取量恢复性增加到正常大鼠的水平,从而逆转了快感消失的症状。缬草是如何促使抑郁大鼠恢复正常的行为活动?其机制目前还不清楚。有研究发现,出现抑郁行为的动物和人,其大脑海马神经元是减少的[10-12]。一些研究表明,缬草可以明显降低因脑缺血引起的海马神经元死亡数量,提示缬草有保护脑细胞的作用[13,14]。我们另一项实验也显示[15],应用缬草可促使抑郁大鼠海马神经元恢复性增加,并且达到正常大鼠水平。表明缬草可以保护抑郁大鼠海马受损伤神经元,不让它们死亡,从而稳定了海马结构。因此,本文认

表6 7组大鼠灌服药物期间的10 g/L糖水摄取量变化的比较

Table 6 Comparison of the 10 g/L sucrose intake in 7 groups of rats during the periods of administrating drugs ($\bar{x}\pm s$, g)

Group	n	Experimental period		
		5 week	6 week	7 week
Low dose of *Valerian* model	10	12.1±1.0[1),2),3)]	13.6±1.0[2),3)]	13.7±0.4[2),3)]
Medium dose of *Valerian* model	10	12.1±0.6[1),2),3)]	12.9±0.9[1),2),3),4)]	12.2±0.7[1),2),4),5)]
High dose of *Valerian* model	10	11.3±0.9[1)]	11.7±1.1[1),4),5)]	11.6±1.2[1),4),5)]
Negative control model	10	11.2±1.1[1)]	11.5±1.1[1)]	11.3±1.3[1)]
Positive control model	10	12.1±1.0[1),2),3)]	14.0±0.9[2),3)]	14.0±0.8[2),3)]
Untreated model	10	10.7±0.4[1)]	11.1±0.6[1)]	10.8±0.9[1)]
Normal control	10	13.8±0.9	13.8±0.8	14.1±1.3

1) Compared with normal control group, by oneway ANOVA, $P<0.05$; 2) Compared with untreated model group, by oneway ANOVA, $P<0.05$; 3) Compared with negative control group, by oneway ANOVA, $P<0.05$; 4) Compared with positive control group, by oneway ANOVA, $P<0.05$; 5) Compared with low dose of Valerian group, by oneway ANOVA, $P<0.05$

为，一定剂量的缬草促使抑郁大鼠恢复正常的行为活动可能与抑郁大鼠海马神经元恢复性增加有关,这一推测还有待于研究证实。本研究不清楚不同剂量的缬草有不同作用的原因，推测与缬草含有多种活性成分有关。据认为,天然植物药中某一种成分在一定的剂量范围内可能对某一器官、组织具有保护作用，但是另一剂量可能会产生相反的效果[16]。

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(编辑　张恩健)