ARTICLES

Effects of *Valeriana officinalis* extract on rat depression model

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[**Abstract**] **Objective** To investigate the effects of *Valeriana officinalis* extract on behaviors, 5-hydroxytryptamine level and cell proliferation at cerebral hippocampus of a depressive rat model induced by chronic mild stress. **Methods** Seventy male Sprague-Dawley rats were divided into 7 groups (10 per group) including normal control group, untreated depressive rat model group, negative control group, positive control group, low dosage *Valeriana officinalis* extract group, medium dosage *Valeriana officinalis* extract group and high dosage *Valeriana officinalis* extract group. All groups were examined by weight, tap water intake and 1% sucrose intake once a week. The rats were killed after week 7. The hippocampal tissues of brain for half of the groups were removed for detection of 5-hydroxytryptamine level. In the other half, the neural cells in hippocampus were detected by bromodeoxyuridine labelling and neutral red staining. **Results** low dosage *Valeriana officinalis* extract could make behaviors of depressive rats, the 5-hydroxytryptamine level and cell proliferation at hippocampus of these rats recovered to normal status. **Conclusion** *Valeriana officinalis* extract has high potential to be developed to be an effective antidepressant.

[**Key words**] *Valeriana officinalis* extract; depression; rat

INTRODUCTION

Depression is a group of syndromes characterized by notable and persistent mood disorders. It is the most prevalent psychiatric disorder world-wide, with 10% ~ 30% of women and 7% ~15% of men likely to suffer from depression in their life-time. Therefore it is important to study the definite pathogenesis and better therapeutic methods of depression. Extracts of *Valeriana officinalis* L. s. l., *Valerianaceae*, are used for treating mild sleep disorders and nervous tension. They are the most well recognized herbal sedatives. Controlled clinical trials have assessed the efficacy of various *Valeriana officinalis* extracts[1~3].

Despite intensive research efforts, the pharmacological actions accounting for the clinical efficacy of valerian remain unclear. The purpose of this study was to investigate the effects of *Valeriana officinalis* extract on behaviors, 5-hydroxytryptamine (5-HT) level and cell proliferation at cerebral hippocampus of depressive rats induced by chronic mild stress.

MATERIALS AND METHODS

Seventy male Sprague-Dawley rats, body weight 180 ~ 200 g, were divided into 7 groups (10 per group) including:

i) normal control group: no treatment for 4 weeks (weeks 0 ~4). Then received oral 0.5% sodium carboxymethylcellulose (solvent) 2 ml twice daily via intragastric administration for three weeks (weeks 5 ~ 7).

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ii) untreated depressive rat model group: prepared depressive rats, received chronic mild stress[4~6] for 4 weeks (weeks 0~4). After chronic mild stress, extent of weight increasing of prepared depressive rats was lower than that of normal control group above. Tap water intake of two groups did not change with the time passing. 1% sucrose intake of prepared depressive rats was decreased, but 1% sucrose intake of normal control group was increased (Table 1, weeks 0~4). Then no treatment for 3 weeks (weeks 5~7). 1% sucrose intake was used as an indicator for depression.

iii) negative control group: prepared depressive rats as in (ii) (weeks 0~4). Then received oral 0.5% sodium carboxymethylcellulose as in (i) (weeks 5~7).

iv) positive control group: prepared depressive rats as in (ii) (weeks 0~4). Then received oral 0.5% sodium carboxymethylcellulose as in (i) (weeks 5~7), dissolved with fluoxetine (Eli Lilly, USA), an antidepressive drug at dosage 2.2 mg/kg.

v) low dosage *Valeriana officinalis* extract group: prepared depressive rats as in (ii) (weeks 0~4). Then received oral 0.5% sodium carboxymethylcellulose as in (i) (weeks 5~7), dissolved with *Valeriana officinalis* extract (Holistal International Ltd., Hong Kong, China) at dosage 100 mg/kg.

vi) medium dosage *Valeriana officinalis* extract group: prepared depressive rats as in (ii) (weeks 0~4). Then received oral 0.5% sodium carboxymethylcellulose as in (i) (weeks 5~7), dissolved with *Valeriana officinalis* extract at dosage 200 mg/kg.

vii) high dosage *Valeriana officinalis* extract group: prepared depressive rats as in (ii) (weeks 0~4). Then received oral 0.5% sodium carboxymethylcellulose as in (i) (weeks 5~7), dissolved with *Valeriana officinalis* extract at dosage 400 mg/kg.

All groups were examined by weight, tap water intake and 1% sucrose intake once a week. The rats were killed after week 7. The hippocampal tissue of brain for half of the groups (n=5) were removed for high-performance liquid chromatography (HPLC) (Waters 1525, USA) detection of 5-HT[4,7].

In other half of the groups (n=5), the neural cells in hippocampus were detected by immunohistochemistry using bromodeoxyuridine (BrdU) (Sigma, USA) labelling, the cross sectional area of hippocampus was assessed using neutral red staining (Shanghai Chemical Reagent Company, China)[4,8].

Statistical testing of difference between groups was performed using one way ANOVA with the level of significance set at $P < 0.05$. Data were analyzed with a statistical analysis computer software (SPSS v12.0, Chicago, USA).

RESULTS

After the application of sodium carboxymethylcellulose, fluoxetine, valerian, extent of weight increasing of prepared depressive rat model groups was lower than that of normal control group. Tap water intake of 7 groups did not change with the time passing. 1% sucrose intake in low dosage *Valeriana officinalis* extract group rats increased and recovered to normal level (Table 1, weeks 5~7).

The 5-HT content at hippocampus in low dosage *Valeriana officinalis* extract group and medium dosage *Valeriana officinalis* extract group rats increased and recovered to normal status.

After the administration of low dosage *Valeriana officinalis* extract for 3 weeks, BrdU positive cells and neurons in the hippocampus recovered to normal status (Table 2).

Table 1 Comparison of the body weight, tap water intake, and 1% sucrose intake in seven groups of rats

Group	Parameter (Mean ± sx, g)	Time (week)				
		0	4	5	6	7
Normal control	body weight	262.00 ± 10.33	342.50 ± 13.79	356.00 ± 12.42[a]	368.50 ± 7.83[h]	382.50 ± 7.90[o]
	tap water intake	0.96 ± 0.27	2.77 ± 0.52	3.32 ± 0.38	3.35 ± 0.48	3.30 ± 0.30
	1% sucrose intake	11.06 ± 1.34	13.63 ± 1.19	13.76 ± 0.89[aa]	13.80 ± 0.79[hh]	14.13 ± 1.29[oo]
Counter lateral depressive rat model	body weight	261.00 ± 7.75	331.00 ± 9.06	345.50 ± 8.31[b]	359.50 ± 7.97[i]	376.00 ± 6.58[p]
	tap water intake	0.94 ± 0.29	3.04 ± 0.59	3.54 ± 0.52	3.30 ± 0.49	3.34 ± 0.38
	1% sucrose intake	11.18 ± 1.27	10.31 ± 0.65	10.65 ± 0.41[bb]	11.14 ± 0.64[ii]	10.76 ± 0.90[pp]
Negative control	body weight	259.50 ± 7.25	331.50 ± 10.81	344.50 ± 11.41[c]	357.00 ± 7.53[j]	365.00 ± 9.12[q]
	tap water intake	0.97 ± 0.36	2.85 ± 0.53	3.37 ± 0.46	3.13 ± 0.66	3.10 ± 0.34
	1% sucrose intake	11.28 ± 1.27	10.64 ± 0.75	11.15 ± 1.12[cc]	11.49 ± 1.13[jj]	11.34 ± 1.30[qq]
Positive control	body weight	261.50 ± 9.44	327.00 ± 10.85	346.50 ± 10.21[d]	358.50 ± 9.73[k]	374.50 ± 6.85[r]
	tap water intake	1.02 ± 0.30	3.22 ± 0.54	3.53 ± 0.71	3.19 ± 0.52	3.21 ± 0.57
	1% sucrose intake	11.04 ± 1.10	10.74 ± 0.85	12.09 ± 0.94[dd]	13.92 ± 0.94[kk]	14.02 ± 0.79[rr]
Low dosage group	body weight	260.00 ± 9.13	325.00 ± 12.01	340.00 ± 11.30[e]	354.00 ± 10.48[l]	370.50 ± 8.95[s]
	tap water intake	0.99 ± 0.33	2.98 ± 0.52	3.52 ± 0.68	3.13 ± 0.55	3.09 ± 0.58
	1% sucrose intake	11.10 ± 1.22	11.01 ± 0.80	12.09 ± 0.91[ee]	13.58 ± 0.95[ll]	13.75 ± 0.44[ss]
Medium dosage	body weight	262.00 ± 12.06	327.00 ± 11.35	343.50 ± 10.81[f]	357.00 ± 10.59[m]	368.50 ± 8.51[t]
	tap water intake	0.97 ± 0.27	3.02 ± 0.55	3.36 ± 0.55	3.22 ± 0.57	3.13 ± 0.33
	1% sucrose intake	10.81 ± 1.36	10.76 ± 0.98	12.08 ± 0.61[ff]	12.88 ± 0.90[mm]	12.21 ± 0.70[tt]
High dosage	body weight	263.00 ± 10.85	325.50 ± 9.27	345.50 ± 9.21[g]	358.50 ± 9.73[n]	358.50 ± 9.14[u]
	tap water intake	0.98 ± 0.19	3.10 ± 0.59	3.55 ± 0.49	3.25 ± 0.71	3.25 ± 0.71
	1% sucrose intake	11.26 ± 1.39	10.53 ± 0.63	11.33 ± 0.86[gg]	11.74 ± 1.08[nn]	11.60 ± 1.22[uu]

For body weight: One way ANOVA; aVSb, aVSc, aVSd, aVSe, aVSf, aVSg, hVSi, hVSj, hVSk, hVSl, hVSm, hVSn, oVSq, oVSr, oVSs, oVSt, oVSu, pVSq, pVSt, pVSu, qVSr, $P < 0.05$; bVSc, bVSd, bVSe, bVSf, bVSg, cVSd, cVSe, cVSf, cVSg, dVSe, dVSf, dVSg, eVSf, eVSg, fVSg, iVSj, iVSk, iVSl, iVSm, iVSn, jVSk, jVSl, jVSm, jVSn, KVSl, kVSm, kVSn, lVSm, lVSn, mVSn, oVSp, pVSr, pVSs, qVSs, qVSt, qVSu, rVSs, rVSt, rVSu, sVSt, sVSu, tVSu, $P > 0.05$; For tap water intake: Oneway ANOVA, $P > 0.05$. For 1% sucrose intake: Oneway ANOVA aaVSbb, aaVScc, aaVSdd, aaVSee, aaVSff, aaVSgg, bbVSdd, bbVSee, bbVSff, ccVSdd, ccVSee, ccVSff, hhVSii, hhVSjj, hhVSmm, hhVSn, iiVSkk, iiVSl, iiVSmm, jjVSkk, jjVSll, jjVSmm, kkVSmm, kkVSnn, llVSnn, mmVSnn, ooVSpp, ooVSqq, ooVStt, ooVSuu, ppVSrr, ppVSss, ppVStt, qqVSrr, qqVSss, rrVStt, rrVSuu, ssVStt, ssVSuu, $P < 0.05$; bbVScc, bbVSgg, ccVSgg, ddVSee, ddVSff, ddVSgg, eeVSff, eeVSgg, ffVSgg, hhVSkk, hhVSll, iiVSjj, iiVSnn, jjVSnn, kkVSll, llVSmm, ooVSrr, ooVSss, ppVSqq, ppVSuu, qqVStt, qqVSuu, rrVSss, ttVSuu, $P > 0.05$

Table 2 Comparison of the contents of 5-HT at hippocampus, the number of BrdU positive cells at hippocampal DG, the cross-sectional area at hippocampus of brain and the number of neuron at hippocampus of brain in seven groups of rats (Mean ± sx,)

Group		5-HT(ng/g)	Hippocampal DG BrdU positive cells	Hippocampus cross-sectional area(cm^2)	Hippocampus neuron
	n	5	5	10	10
Normal control	left side	0.268 ± 0.03^{a}	33.00 ± 9.87^{aa}	1.3100 ± 0.0244	1230 ± 60
	right side			1.3190 ± 0.0563	1219 ± 64
Counter lateral depressive rat model	left side	0.182 ± 0.03^{b}	18.00 ± 3.39^{bb}	1.3360 ± 0.0636	1108 ± 34
	right side			1.3325 ± 0.0594	1115 ± 44
Negative control	left side	0.214 ± 0.03^{c}	19.20 ± 3.42^{cc}	1.3390 ± 0.0502	1129 ± 38
	right side			1.3370 ± 0.0455	1134 ± 36
Positive control	left side	0.396 ± 0.06^{d}	35.00 ± 6.32^{dd}	1.3535 ± 0.0576	1194 ± 48
	right side			1.3375 ± 0.0658	1217 ± 38
Low dosage group	left side	0.312 ± 0.04^{e}	32.60 ± 5.41^{ee}	1.3360 ± 0.0497	1232 ± 47
	right side			1.3405 ± 0.0568	1247 ± 43
Mmedium dosage	left side	0.306 ± 0.04^{f}	18.40 ± 3.65^{ff}	1.3350 ± 0.0433	1138 ± 31
	right side			1.3430 ± 0.0469	1117 ± 28
High dosage	left side	0.218 ± 0.03^{g}	18.20 ± 2.70^{gg}	1.3355 ± 0.0439	1105 ± 36
	right side			1.3400 ± 0.0418	1117 ± 35

For 5-HT: One way ANOVA; aVSb, aVSc, aVSd, aVSg, bVSd, bVSe, bVSf, cVSd, cVSe, cVSf, dVSe, dVSf, dVSg, eVSg, fVSg, $P < 0.05$; aVSe, aVSf, bVSc, bVSg, cVSg, eVSf, $P > 0.05$. For hippocampus cross-sectional area: One way ANOVA, $P > 0.05$; For BrdU positive cells: One way ANOVA; aaVSbb, aaVScc, aaVSff, aaVSgg, bbVSdd, bbVSee, ccVSdd, ccVSee, ddVSff, ddVSgg, eeVSff, eeVSgg, $P < 0.05$; aaVSdd, aaVSee, bbVScc, bbVSff, bbVSgg, ccVSff, ccVSgg, ddVSee, ffVSgg, $P > 0.05$

DISCUSSION

Recent research showed that depression was associated with suppressed proliferation and apoptotic changes hippocampal tissue[9,10]. Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. Hippocampal neurogenesis is required for the behavioral effects of antidepressants[8]. Therefore, a measurement of BrdU positive cells and neurons in the hippocampus can be an indicator to measure the effectiveness of an antidepressive agent. In addition, Banasr, *et al.*[7] showed 5-HT was related to hippocampal neurogenesis and this were mediated through different and common 5-HT receptor subtypes. Grippo, *et al.*[5] showed chronic mild stress induced behavioral and physiological changes, and may alter serotonin 1A receptor function. An increase in

5-HT level can increase the neurogenesis in hippocampus and thus causing an improvement in depression, causing a change in depressive behavior to normal status. The result of the present study showed that low dosage *Valeriana officinalis* extract could make behaviors of depressive rats recover to normal status. At the same time, the 5-HT level and cell proliferation at hippocampus of these rats recovered to normal status. Therefore *Valeriana officinalis* extract has high potential to be developed to be an effective antidepressant.

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