Saudi Journal of Biological Sciences 14 (2) 201-214, December 2007
ISSN 1319 - 562 X
The Official Journal of the Saudi Biological Society
htt:www.saudibiosoc.com

Daily Dose effect of Valerian root extract on some Neurotransmitter contents in different Brain areas of male Albino Rats

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Abstract

The aim of the present study was to investigate the daily effect of *valerian* (*Valeriana officinalis* L .) root extract on epinephrine (E), norepinephrine (NE) , dopamine (DA) , serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) , and gamma-aminobutyric acid (GABA) contents in different brain areas (cerebellum , pons plus medulla oblongata , striatum , cerebral cortex , hypothalamus, midbrain and hippocampus) of male albino rats .The daily intraperitoneal (i.p.) injection of 300 mg/kg body wt valerian for 30 days caused a significant increase in epinephrine (E) content in pons plus medulla oblongata , cerebral cortex , hypothalamus and in midbrain . Norepinephrine (NE) content was significantly increased in all brain areas tested except in cerebellum and cerebral cortex . Dopamine (DA) content was significantly increased in all tested brain areas except in cerebral cortex and hippocampus . moreover , there was also a significant increase in serotonin (5-HT) and 5-hydroxyindol acetic acid (5-HIAA) contents in all tested brain areas . However, gamma-aminobutyric acid (GABA) content was significantly decreased in all tested brain areas . After the extract withdrawal, the increase in (E , NE , DA , 5-HT) contents and the decrease in GABA content persisted in pons plus medulla oblongata , striatum , midbrain and hippocampus , and this might be due to regional differences toward the effect. The increase in E , NE , DA , 5-HT and 5-HIAA contents , at the same time the decrease in GABA content in the different brain areas of albino rats may be due to the presence of both valepotriates and valerenic acid in the extract which mediated the GABA ergic mechanisms including the inhibition of GABA metabolism and the increase in GABA synthesis and release , although agonized the GABAA receptors which led to the inhibit of the neurotransmitter release. Valerian root extract may be useful as a herbal medicine having sedative effect and it is safe.

Key Words: Valerian , E, NE, DA, 5-HT, 5-HIAA, GABA, Brain, Rat.

Introduction

Valerian (*Valeriana officinalis* L.) is a member of the *Valerianaceae* family that includes up to 2000 species and the name itself originates from the Latin word "Valere", meaning courage or to be healthy (Gold *et al.,* 2001) . The plant is found throughout Europe and Northern Asia. It is also common in England in marshy thickets and on the borders of ditches and rivers, where its tall stems may generally be seen in the summer towering above the usual herbage (Houghton, 1999; Yager *et al.,* 1999). For more than 1,000 years , valerian has been valued for its many believed medical uses especially as a calmative for nervousness or hysteria (Hadley and Petry, 2004), sleep-aid dietary supplements (Leuschner *et al.,* 1993; Ang-Lee *et al.,* 2001; Pallesen *et al.,* 2002; Diaper and Hindmarch, 2004), hypnotic (Dominguez *et al.,* anticonvulsant (Eadie, 2004) diarrhea, colic, stomach cramps and irritable bowel (Hazellhoff *et al.,* 1982). The parts of the plant used for therapeutic purposes are the roots and rhizomes (Cionga, 1961; Navarrete *et al.*, 2006).

Valerian supplements contain a complex mixture of chemical constituents. The main constituents are valerenic acid and its derivatives contained in the volatile oil (Granicher *et al .,* 1995; Bose *et al.*, 1997; Blumenthal *et al.,* 2000; Shohet *et al.,* 2001). The valepotriates have also been investigated for pharmacologic activity

(Bos *et al.,* 2002). Minor constituents include various alkaloids, furanofuran lignans and free amino acids (Hazellhoff *et al.,* 1982; Houghton, 1999; Hadley and Petry, 2004). The widespread use of Valerian supplements suggests that it is use with conventional medications is inevitable, and the potential for drug interactions is undefined (Fugh-Berman and Ernst, 2001; Markowitz *et al.,* 2003; Huang *et al.,* 2004).

Valerian is listed by the USA, Food and Drug Administration as a food supplement and it is, therefore, not subjected to regulatory control beyond labeling requirements. according to Commission E monographs (Blumenthal, 1998).

Since valerian is commonly used in folk medicine in Saudi Arabia (plant known in Saudi Arabian as ' Nardin'), it is therefore deemed interesting to reexamine the effect of the root extract on CNS . So , the present work aimed to examine the daily administration of valerian root extract on epinephrine (E), norepinephrine (NE), dopamine (DA), serotonin (5-HT) and its metabolite 5-hydroxiindoleacetic acid (5-HIAA), and gamma-aminobutyric acid (GABA) contents in different brain regions, i.e. cerebellum, pons plus medulla oblongata, striatum, cerebral cortex, hypothalamus, midbrain and hippocampus, since these neurotransmitters are known to play an important role in brain function.

Material and methods

1. Valerian extract

Commercially available dried roots of *valeriana officinallis* were obtained from the Arkopharma (Saudi Arabia) marketplace from local growers. The root were ground in blender at low speed for five minutes with 100 ml distilled water. The mix was left to stand for 48 hours and filtered through filter paper . The extract was stored at room temperature (Ortiz *et al.,* 1999).

2. Animals

The experimental animals used in this study were adult male albino rats, *Rattus rattus* with an average body weight 120-150 g . The animals were supplied with food and water ad *libitum* under standard conditions of light, humidity and temperature. The treated animals were randomly divided into tow group.

The first group (n=36) was divided into 6 subgroups each of 6 rats. The rats were daily injected (i. p.) with 300 mg/kg of Valerian root extract (Diaper and Hindmarch , 2004; Oliva *et al.,* 2004; Arce *et al.*, 2005) and one subgroup was decapitated at the end of each week up to 4 weeks. To examine the withdrawal effect, the remaining tow subgroups were decapitated after one and two weeks from the withdrawal of extract. The second group was divided as the first group, they were injected with saline vehicle and served as control.

The rats were killed by sudden decapitation at the designed times. The brain was rapidly and carefully excised and then dissected on dry ice glass plate, according to the method of Glowinski and Iversen (1966), into the following regions: cerebellum, pons plus medulla oblongata, striatum, cerebral cortex, hypothalamus, midbrain and hippocampus. The brain tissues were wiped dry with a filter paper, weighed, wrapped in plastic films and then in aluminum foil, and quickly frozen in dry ice pending analysis.

E, NE, DA and 5-HT were extracted and estimated according to the method of Chang (1964) modified by Ciarlone (1978). The 5-HIAA was estimated according to the method described by Miller *et al.,* (1970). The GABA was estimated according to the method of Sutton and Simmondes (1973). The fluorescence was measured in Jenway 6200 fluorometer.

4 . Statistical analysis

The data in Tables 1-6 are presented as mean $\pm$ S.E. The statistical analysis between control and treated animals were performed using paired ''*t*''-test (Armitage, 1974). All statistical analysis were computed by SPSS version 14.

Result

The single daily i.p. injection of 300 mg/kg of valerian root extract significantly increased the E content in all tested areas after 1 , 2 , 3 and 4 weeks except in cerebellum

after 3 and 4 weeks , striatum and hippocampus after 4 weeks. The E content still significantly increased two weeks after the withdrawal of the extract in pons +medulla oblongata and after one week in hypothalamus and midbrain (Table 1).

Data in Table 2 show that the treatment induced a significant increase in NE content in all tested areas after 1, 2, 3 and 4 weeks except in cerebellum and cerebral cortex after 3 and 4 weeks. The NE content persisted in its significant increase two weeks after the withdrawal of the extract in pons+medulla oblongata and midbrain and after one week in striatum.

There was a significant increase in DA content in all tested brain areas after 1, 2, 3 and 4 weeks except in cerebral cortex after 3 and 4 weeks , and in hippocampus after 4 weeks. The significant increase in DA content persisted for the two weeks of the withdrawal in pons + medulla oblongata , striatum and midbrain only (Table 3).

Moreover, the treatment significantly increased the 5-TH and 5-HIAA content in all tested brain areas at all tested intervels. The significant increase in 5-HT and 5-HIAA contents persisted for two weeks of the withdrawal in all brain areas tested except cerebellum, cerebral cortex and hypothalamus (Tables 4 and 5).

However, the treatment significantly decreased the GABA content in all tested areas after 1, 2, 3 and 4 weeks. The GABA remained significantly decreased after the two weeks withdrawal of the extract in pons +medulla oblongata, cerebral cortex and midbrain, and after one week in striatum and hypothalamus (Table 6).

Discussion

Several clinical studies have shown that valerian is effective in the treatment of states of psychological and sensorial excitability such as insomnia, neuroasthenia, hysteria, distress, and epilepsy (Allport, 1943; Leathwood *et al.,* 1982 ; Leathwood and Chauffard, 1983, 1985; Stevinson and Ernst, 2000; Krystal and Ressler, 2001; Fernandez *et al.,* 2004; Komori *et al.,* 2006; Doghramji, 2006). One of the earlier papers (Cionga, 1961) stated that valerian had a depressant action on the central nervous system . Eight clinical studies conducted between 1977 and 1996 have shown that valerian is not a suitable herb for the acute treatment of insomnia. Rather, its principal utility lies in its ability to promote natural sleep after several weeks of use, without risk of dependence or adverse health effect (Robbers *et al.,* 1996; Blumenthal, 1998). Bent *et al.* (2006) suggested that valerian might improve sleep quality without producing side effects.

The results of animal experiments indicated that several compounds in valerian root extract (valepotriates, valerenal, valerenic acid) are capable of inducing depressant effects on the central nervous system (CNS) (Hendriks *et al.,* 1985; Veith and Schneider, 1986; Oshima and Matsuoka, 1995; Boyadzhiev, 2004; Navarrete *et al.,* 2006). Wagner *et al.* (1998) believed that a combination of valerenic acid, valepotriates, and unidentified aqueous constituents may contribute to the sedative properties of *valerian*.

Valerenic acid inhibits the enzyme system responsible for the central catabolism of GABA (Riedel *et al,* 1982; Houghton, 1999) and it also depresses the central nervous system (CNS) activity (Hendricks *et al.,* 1985; Anderson *et al.*, 2005).

Valepotriates, a class of iridoid from *valeriana* first isolated in 1966, contribute to the valerian overall activity by possessing sedative activity based on the CNS although their mode of action is not clearly known (Fursa *et al.,* 1985). They themselves act as prodrugs and are transformed into homobaldrinal which has been shown to reduce the spontaneous activity of mice (Krieglstein and Grusla, 1988).

In vitro studies found that the valerian aqueous extracts inhibit the uptake and stimulate the release of gamma-aminobutyric acid (GABA), which may increase the extracellular concentration of GABA in the synaptic cleft, thereby contributing to the herb's sedative effect (Kuhlmann *et al.,* 1999).

Malva *et al.,* (2004) and Yuan *et al.,* (2004) concluded that valerian acts via gamma-aminobutyric acid (GABA) ergic mechanisms. A possible effect of Valeriana officinalis on GABA transaminase has been proposed (Bruneton, 1993; Cavadas *et al.,* 1995).

Table 1 :Effect of daily administration of *valerian* (*Valeriana officinalis*) root extract (300mg/kg , i.p.) on epinephrine (E)content (µ g/g) in different brain areas of albino rat.

Time of area Decapitation (week)			Cerebellum µ g/g	Pons+medulla oblongata µ g/g	Striatum µ g/g	Cerebral cortex µ g/g	Hypothalamus µ g/g	Midbrain µ g/g	Hippocampus µ g/g
Treatment	1st %	C	385.72±6.35	462.16±11.49	764.19±10.87	124.70±1.11	840.63±8.79	457.59±8.83	645.03±11.75
		T	555.44±13.84 43.99*	641.68±9.63 *38.84	956.18±13.48 *25.12	150.31±0.57 *20.05	959.78±9.21 *14.17	647.04±8.68 *41.40	833.17±4.95 *29.16
	2nd %	C	382.50±8.49	364.62±8.74	761.09±10.11	125.60±1.40	840.88±9.39	459.16±5.65	653.55±11.31
		T	441.47±7.18 *16.72	528.51±11.47 *13.99	898.17±4.99 *18.01	141.01±0.66 *22.57	947.40±10.23 *12.66	527.00±6.34 *14.77	756.06±10.24 *15.68
	3rd %	C	383.04+10.50	452.59±10.24	760.68±10.10	±0.86_124.32	857.35±12.81	444.33±8.64	643.83±8.70
		T	405.85±5.57 5.94	549.35±10.57 *21.37	842.68±4.99 *10.77	139.09±1.74 *11.88	946.68±7.44 *10.41	550.71±8.24 *23.94	725.33±5.34 *12.65
	4th %	C	367.50±8.00	462.16±11.49	753.10±11.90	123.92±0.86	847.65±5.54	459.14±11.83	635.39±6.52
		T	392.31±6.60 4.30	556.81±8.22 *20.47	777.74±6.26 3.27	138.92±1.20 *12.10	962.47±7.13 *13.54	556.27±6.53 *21.15	652.56±8.06 2.70
withdrawal	1st %	C	±11.34 364.40	±7.91 449.34	±9.58 749.72	±0.90 123.56	±4.36 845.50	±8.72 450.72	±10.05 644.06
		T	383.12±10.16 5.13	554.98±11.25 *24.62	761.69±9.14 1.59	120.30±1.32 -2.63	943.54±5.91 *11.59	548.17±7.99 *21.62	639.48±5.70 -0.71
	2nd %	C	8.00 ± 367.50	11.49 ± 462.16	11.90 ± 753.10	0.80 ± 122.92	5.54 ± 847.65	5.41 ± 422.93	6.52 ± 635.39
		T	357.33± 10.54 -2.76	560.55 ± 9.58 21.28*	787.52 ± 5.15 4.57	123.63 ± 1.94 0.57	853.77 ± 6.00 0.72	460.36 ± 7.84 8.85	636.81 ± 5.55 0.22

Data are expressed as Mean ± SE
Statistical analyses were performed between control and treated for six animals.
% : percentage of change from control. * significant at p <0.01 .

Table 2 : Effect of daily administration of *valerian* (*Valeriana officinalis*) root extract (300mg/kg , i.p.) on norepinephrine (NE) content (μ g/g) in different brain areas of albino rat.

Time of area Decapitation (week)			Cerebellum μ g/g	Pons+medulla oblongata μ g/g	Striatum μ g/g	Cerebral cortex μ g/g	Hypothalamus μ g/g	Midbrain μ g/g	Hippocampus μ g/g
Treatment	1st	C	368.83±15.26	449.08±7.98	743.63±13.04	123.90±1.11	811.52±16.05	429.70±12.11	522.56±21.11
		T	520.00±6.69	551.83±13.48	925.05±5.33	146.87±1.21	894.80±13.80	590.76±9.63	710.37±8.72
	%		40.98*	22.88*	24.39*	18.53*	10.26*	37.48*	35.94*
	2nd	C	351.80+14.03	437.05±5.96	735.05±11.97	121.82±1.06	837.62±8.19	449.03±12.37	633.17±9.14
		T	436.69±9.01	528.51±11.47	825.84±11.08	137.47±1.04	947.88±9.04	530.81±10.76	735.93±8.87
	%		24.13*	20.92*	12.35*	12.84*	13.16*	18.21*	16.22*
	3rd	C	376.88±10.12	444.08±12.71	744.01±12.06	122.69±1.46	851.03±13.06	455.18±10.05	565.10±11.92
		T	389.67±6.65	545.50±12.70	830.92±9.26	118.03±1.05	963.98±10.28	545.64±14.44	627.164±8.99
	%		5.92	22.83*	11.68*	-3.81	13.27*	19.87*	10.98*
	4th	C	343.74±11.70	445.23±13.42	744.65±11.81	124.54±1.25	839.03±11.57	438.18±12.66	547.34±12.30
		T	348.24±13.39	541.91±11.72	840.52±13.35	123.06±0.96	935.73±11.30	531.48±8.81	653.18±12.32
	%		1.30	21.71*	12.87*	-1.18	11.52*	21.29*	19.33*
withdrawal	1st	C	±11.95 338.36	±12.31 446.60	±9.33 737.39	±0.96 114.47	±13.38 839.82	437.19±10.03	±10.05 644.06
		T	352.49±10.34	541.48±13.24	837.65±10.12	110.80±1.53	827.73±10.80	532.97±6.72	646.49±13..16
	%		4.17	21.24*	13.59*	-3.20	-1.43	21.90*	0.37
	2nd	C	12.11 ± 356.70	15.41 ± 453.34	11.06 748.31±	0.94 ± 122.71	9.68 ± 834.32	12.64 ± 438.77	12.00 ± 639.01
		T	346.31 ± 14.04	529.83 ± 5.62	753.00 ± 12.02	121.77 ± 1.17	841.67 ± 9.929	557.01± 10.31	641.51 ± 9.70
	%		-2.91	16.87*	0.62	-0.76	0.88	26.94*	0.70

Data are expressed as Mean ± SE
Statistical analyses were performed between control and treated for six animals.
% : percentage of change from control. * significant at $p < 0.01$.

Table 3 : Effect of daily administration of *valerian* (*Valeriana officinalis)* root extract (300mg/kg , i.p.) on dopamine (DA) content (µ g/g) in different brain areas of albino rat .

Time of area Decapitation (week)			Cerebellum µ g/g	Pons+medulla oblongata µ g/g	Striatum µ g/g	Cerebral cortex µ g/g	Hypothalamus µ g/g	Midbrain µ g/g	Hippocampus µ g/g
Treatment	1st	C	335.15±13.06	434.02±7.75	751.89±12.91	123.31±1.26	790.99±10.25	445.33±13.07	517.66±11.02
		T	422.62±8.29	523.00±8.54	930.17±10.96	144.46±1.49	916.54±9.00	594.60±7.01	706.12±7.20
	%		26.09*	20.50*	23.71*	17.03*	15.87*	33.51*	36.40*
	2nd	C	343.41±15.54	443.19±14.24	745.39±12.70	124.16±1.28	839.40±9.44	451.01±13.80	653.47±9.74
		T	425.59±12.35	538.71±9.80	849.63±12.11	138.59±1.13	944.53±8.50	531.64±8.50	737.51±9.99
	%		23.93*	21.55*	13.98*	11.62*	12.52*	17.87*	12.86*
	3rd	C	360.56±10.32	452.83±14.17	732.83±9.71	124.95±1.28	828.78±7.10	439.52±11.07	547.63±15.40
		T	440.48±8.04	563.68±6.45	840.09±12.38	124.66±0.88	936.15±4.60	520.67±16.85	632.63±9.09
	%		28.80*	24.47*	14.63*	-0.23	12.95*	18.46*	15.52*
	4th	C	368.81±16.17	432.77±15.13	737.52±13.67	124.32±1.45	822.69±5.94	441.85±12.66	549.01±9.89
		T	448.50±11.41	538.54±7.05	834.63±9.00	120.76±0.97	939.73±14.04	555.00±11.93	543.56±8.95
	%		21.60*	24.44*	13.16*	-2.86	14.22*	25.23*	-0.99
withdrawal	1st	C	345.93 ±13.24	437.24 ±10.82	734.05±8.96	118.54 ±1.58	829.99 ±9.05	439.50±10.69	639.90 ±12.60
		T	352.30±11.37	570.49±4.58	861.16±3.52	119.29±1.46	820.70±8.73	555.18±10.62	635.68±9.78
	%		1.84	30.47*	17.31*	0.63	-1.11	26.32*	-0.65
	2nd	C	346.52 ± 14.78	443.83 ± 11.87	725.49 ± 6.80	120.33 ± 1.31	823.13 ± 3.83	431.30 ± 13.13	630.47 ± 14.81
		T	328.32 ± 10.79	546.18 ± 11.03	838.62 ± 9.78	121.07 ± 1.24	831.01± 10.32	553.15 ± 14.51	646.16 ± 14.28
	%		-5.25	23.06*	15.59*	0.61	0.83	28.25*	2.48

Data are expressed as Mean ± SE
Statistical analyses were performed between control and treated for six animals.
% : percentage of change from control. * significant at p <0.01 .

Table 4 : Effect of daily administration of *valerian (Valeriana officinalis*) root extract (300mg/kg , i.p.) on serotonin (5-TH)content(μ g/g) in different brain areas of albino rat .

Time of area Decapitation (week)			Cerebellum μ g/g	Pons+medulla oblongata μ g/g	Striatum μ g/g	Cerebral cortex μ g/g	Hypothalamus μ g/g	Midbrain μ g/g	Hippocampus μ g/g
Treatment	1st	C	338.84±15.28	418.79±7.98	723.20±6.79	117.95±1.37	822.48±5.21	418.46±7.32	623.47±5.14
		T	434.90±9.16	534.61±8.10	838.15±12.50	137.12±1.32	930.77±8.71	528.15±11.12	727.47±7.07
	%		28.34*	27.65*	15.89*	16.25*	13.16*	26.15*	16.68*
	2nd	C	350.47±14.97	431.21±9.62	743.14±12.02	123.96±1.31	810.77±9.88	435.34±9.91	635.39±6.52
		T	432.32±10.47	532.00±9.48	832.66±7.94	137.10±1.49	919.67±5.03	540.36±7.40	718.04±10.63
	%		23.35*	23.37*	12.04*	10.60*	13.43*	24.12*	13.00*
	3rd	C	344.01±9.30	440.47±12.09	739.19±8.81	115.79±1.34	822.73±6.50	423.30±7.63	516.80±6.07
		T	439.87±8.27	532.93±7.34	852.03±14.03	135.40±1.18	930.35±7.40	537.93±7.17	607.40±12.09
	%		27.86*	21.67*	15.26*	16.93*	13.00*	27.08*	17.53*
	4th	C	340.23±12.66	436.95±7.09	762.72±10.53	118.27±1.71	797.34±11.72	435.85±9.03	619.13±7.25
		T	421.16±12.95	540.28±7.07	843.13±11.00	133.23±1.34	900.736±11.88	550.40±11.36	733.75±10.28
	%		23.78*	23.64*	10.54*	12.64*	12.96*	26.28*	18.51*
withdrawal	1st	C	332.63 ±10.31	419.19 ±10.34	722.21 ±6.87	119.66 ±1.49	770.71 ±15.37	444.44 ±14.16	644.35 ±10.77
		T	358.12±15.96	507.54±9.26	836.78±13.72	133.47±1.16	796.49±13.74	532.77±9.26	740.82±11.35
	%		7.66	21.07*	15.866*	11.54*	3.34	19.87*	14.97*
	2nd	C	315.63 ± 5.75	455.70 ± 9.82	738.09 ± 14.07	122.88 ± 0.69	828.03 ± 10.57	434.95 ± 12.53	635.64 ± 9.92
		T	334.31±13.75	535.64±9.92	835.09±8.47	123.67±1.35	825.13±8.88	541.46±9.49	722.63±6.35
	%		5.91	17.54*	13.14*	0.64	-0.35	24.48*	13.68*

Data are expressed as Mean ± SE
Statistical analyses were performed between control and treated for six animals.
% : percentage of change from control. * significant at $p < 0.01$.

Table 5 : Effect of daily administration of *valerian* (*Valeriana officinalis*) root extract (300mg/kg , i.p.) on 5-hydroxyindoleacetic acid (5-HIAA) content (µ g/g) in different brain areas of albino rat .

Time of area Decapitation (week)			Cerebellum µ g/g	Pons+medulla oblongata µ g/g	Striatum µ g/g	Cerebral cortex µ g/g	Hypothalamus µ g/g	Midbrain µ g/g	Hippocampus µ g/g
Treatment	1st	C	385.29±10.38	440.60±9.87	740.15±9.57	123.38±0.51	817.20±8.88	437.24±10.65	626.61±8.26
		T	447.74±7.91	547.20±10.58	835.63±12.16	138.27±1.92	938.40±10.19	529.36±6.28	732.50±13.02
	%		16.20*	24.19*	12.90*	12.06*	14.83*	21.06*	16.89*
	2nd	C	362.81±14.44	435.83±7.96	763.45±12.01	118.35±0.77	832.09±12.12	441.44±13.50	633.49±3.62
		T	415.64±14.56	528.07±7.38	842.36±9.87	130.90±1.44	933.76±8.65	523.97±6.91	739.95±4.53
	%		16.20*	21.16*	10.33*	10.60*	12.21*	18.69*	16.80*
	3rd	C	378.57±11.21	419.54±8.22	728.09±9.79	115.62±0.88	839.72±8.87	437.60±8.22	524.45±9.51
		T	454.82±9.71	529.34±5.65	829.14±13.22	129.50±1.32	929.72±6.15	529.70±8.86	637.40±12.09
	%		20.14*	26.17*	13.87*	12.50*	10.71*	21.04*	21.53*
	4th	C	324.10±11.16	434.41±10.79	734.29±10.38	115.60±1.24	821.35±16.23	422.92±4.97	614.66±5.66
		T	390.55±16.01	530.50±8.86	823.15±8.56	131.74±0.77	914.26±9.00	502.06±8.50	721.36±4.36
	%		20.50*	22.11*	12.10*	13.96*	11.32*	18.71*	17.35*
withdrawal	1st	C	±10.61 324.63	±11.45 432.58	±12.99 744.98	±1.85 121.26	±7.49 795.27	±9.33 446.54	±8.43 627.68
	%	T	341.99±19.77	530.41±9.29	849.67±15.19	135.21±1.10	820.82±16.63	532.11±12.41	724.91±7.78
			5.34	22.61*	14.05*	11.50*	3.21	19.16*	15.49*
	2nd	C	8.86 ± 327.55	12.21 ± 447.21	12.38 ± 745.52	1.08 ± 123.88	4.36 ± 816.13	11.20 ± 420.35	8.39 ± 616.26
	%	T	318.53 ± 9.32	532.76 ± 9.35	842.50 ± 7.74	123.65 ± 4.36	825.13 ± 8.88	491.85 ± 10.70	705.67 ± 8.09
			-2.75	19.19*	13.00*	-0.18	1.00	17.00*	14.50*

Data are expressed as Mean ± SE
Statistical analyses were performed between control and treated for six animals.
% : percentage of change from control. * significant at $p < 0.01$.

Table 6 : Effect of daily administration of *valerian* (*Valeriana officinalis)* root extract (300mg/kg , i.p.) on gamma-aminoburyric acid (GABA) content (µ g/g) in different brain areas of albino rat .

Time of area Decapitation (week)			Cerebellum µ g/g	Pons+medulla oblongata µ g/g	Striatum µ g/g	Cerebral cortex µ g/g	Hypothalamus µ g/g	Midbrain µ g/g	Hippocampus µ g/g
Treatment	1st	C	14.44 ± 362.81	4.91 ± 422.53	10.35 ± 721.59	0.69 ± 122.58	10.47 ± 749.25	9.62 ± 428.30	7.08 ± 625.92
		T	11.11 ± 235.93	6.23 ± 352.73	10.57 625.83±	±1.55 100.13	8.05 ± 620.27	7.82 ± 321.52	10.66 ± 531.27
	%		*-34.79	*-22.90	*-13.27	*-18.31	*-17.21	*-24.93	*-15.12
	2nd	C	309.52+3.14	420.65±5.19	727.28±8.00	116.66±1.30	10.35 ± 734.34	420.75±6.48	612.56±3.91
		T	13.04 ± 247.80	9.45 ± 342.180	6.02 ± 634.04	2.53 ± 98.55	4.47 ± 615.92	10.84 332.88±	11.58 ± 540.83
	%		*-19.94	*-18.64	*-12.82	*-15.52	*-16.12	*-20.88	*-11.70
	3rd	C	320.01±6.40	417.13±7.02	4.42 ± 712.64	114.28±0.85	742.00±14.04	431.58±8.90	626.14±7.19
		T	11.66 ± 466.36	12.34 ± 354.23	15.72 ± 631.38	1.41 ± 100.45	9.75 ± 635.61	12.90 ± 343.13	12.06 ± 532.28
	%		*-27.51	*-15.07	*-11.40	*-12.10	*-14.33	*-20.49	*-14.99
	4th	C	339.64±12.97	369.92±20.27	727.61±10.50	115.44±1.10	766.64±19.27	416.93±4.96	622.25±7.70
		T	16.15 ± 252.95	14.65 ± 275.47	22.40 627.88±	1.72 98.49±	8.89 ± 637.91	14.43 ± 332.11	11.37 ± 540.48
	%		*-25.52	*-25.53	*-13.70	*-14.68	*-16.79	*-20.34	*-13.14
withdrawal	1st	C	±10.88 327.92	±13.35 360.62	±11.54 725.64	±1.39 114.97	±13.90 751.99	±3.83 411.14	±6.87 623.86
		T	16.54 ± 323.18	11.85 ± 288.38	± 650.437 13.22	2.08 ± 99.11	13.29 ± 639.53	9.30 ± 353.27	8.28 ± 630.71
	%		-1.44	*-20.03	*-10.36	*-13.79	*-14.95	*-18.45	1.09
	2nd	C	11.59 328.00±	11.50 ± 356.77	12.40 ± 741.74	1.07 ± 115.12	19.99 ± 761.44	3.27 ± 412.79	7.85 ± 620.42
		T	9.77 ± 319.72	11.13 ± 291.35	13.78 ± 742.25	1.39 ± 97.71	13.36 ± 794.11	14.02 ± 354.89	11.17 ± 639.17
	%		-2.52	*18.33	0.06	*-15.12	4.29	*-14.02	3.02

Data are expressed as Mean ± SE

Statistical analyses were performed between control and treated for six animals.

% : percentage of change from control. * significant at p <0.01 .

GABA is generally considered the major inhibitory neurotransmitter within the mammalian CNS and plays a crucial role in the pharmacology of stress and anxiety. Termination of its postsynaptic action is effected predominantly by its reuptake into presynaptic terminals by a Na^+ -dependent high – affinity transport system. It has been proposed that this system may also contribute to the GABA release in Ca^{2+} -independent manner by several of the GABA carrier in the plasma membrane (Santos *et al.,* 1994).

From the present result, it is clear that the daily injection of 300 mg/kg of valerian root extract caused a significant increase in neurotransmitter (E, NE, DA, 5-HT, 5-HIAA) and in a significant decrease in GABA contents in most of the tested brain areas at the different time intervals used.

These results are in agreement with the previous study carried out by De Feo and Faro (2003) which indicated that the extract of valerian showed a significant effect in inhibiting GABA uptake and in decreasing the intracellular content of amino acid neurotransmitters in rat.

Cavadas *et al.,* (1995) reported that the aqueous valerian extracts inhibit the uptake and induced the release of GABA by Ca^{2+} mediated exocytosis. When GABA binds to its receptors, the influx of Cl^- into the cell is increased leading to membrane hyperpolaraization and decreased cell excitability (Kupfer and Reynolds, 1997). Santos *et al.,* (1994) reported that the valerian extract increases GABA release in a Ca+2 independent way through the reversal of the transporter system.

Many in vivo effects of valerian are consistent with activation of $GABA_A$ receptors (Ketter *et al.,* 1999; Fields *et al.,* 2003; Abourashed *et al.,* 2004; Yuan *et al.*, 2004; Dietz *et al.,* 2005; Granger *et al.,* 2005). Cavadas *et al.* (1995) proposed interactions of valerian with $GABA_A$ receptors based on displacement of [^{3}H] muscimol binding. $GABA_A$ receptors are coupled to chloride ion channels and the activation of $GABA_A$ receptors induce an increase inward chloride ion flux resulting in membrane hyperpolarization and neural inhibition (Twyman *et al.,* 1989; Fields *et al.,* 2003; Malva *et al.,* 2004; Simmen *et al.,* 2005; Ortiz *et al.,* 2006). This can be affected by increasing either the frequency or the duration of opening of the chloride ion channels (Ketter *et al.,* 1999).

From the previous studies and present results , it could be concluded that the daily administration of valerian root extract caused changes in neurotransmitter contents which may be due to the presence of both valepotriates and valerenic acid which are mediated through the GABA ergic mechanisms including the inhibition of GABA metabolism and the increase in GABA synthesis and release, as a result GABA content is increased in the brain. Moreover, the agonized $GABA_A$ receptors, which led to inhibit neurotransmitter release (via opening Cl^- or K^+ channels), and reduction the release of vesicles of the innervated cell (via closing Ca^{2+} channels) could be responsible for the decrease in GABA and the increase the neurotransmitter (E, NE, DA and 5-HT) contents, at the same time. The increase in 5-HIAA content may be due to the increase in 5-HT content.

From the present results, it is also clear that after the withdrawal of valerian root extract, there are regional difference in the effect . The most affected areas are, pons + medulla oblongata which is responsible for the essential reflexive acts, midbrain which is responsible for the regulation of sleep, wakefulness and level of arousal as well as for coordination of eye movements , striatum which is the brain region responsible for motor activity and hippocampus which is responsible for memory (Bloom, 2001; Fox, 2004). These result are agreement with the study carried out by Ortiz *et al*. (1999) and Yuan *et al.,* (2004).

In conclusion, the daily administration of Valeriana officinalis root extract produces sedative effect which is probably related to both the presence of valepotriates and valerenic acid which are mediated through GABA ergic activity and to the agonized $GABA_A$ receptors . Valerian root extract may be useful as an herbal medicine having sedative effect and it is safe.

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تأثير الجرعة اليومي لمستخلص جذور النارادين على المحتوى الكلي لبعض الموصلات العصبية في المناطق المختلفة من مخ ذكور الجرذان البيضاء

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ص.ب ١٠٤٨ ، جدة ، ٢١٤٣١

الملخص

تهدف هذه الدراسة إلى معرفة تأثير الجرعة اليومي من مستخلص جذور النارادين على محتوى الإبينفرين والنورإبينفرين والدوبامين والسيرتونين و٥-هيدروكسي إندول حمض الخليك وجاما أمينو حمض البيوتريك في مناطق الدماغ المختلفة (المخيخ ، القنطرة والنخاع المستطيل ، الجسم المخطط ، القشرة المخية ، تحت المهاد البصري ، المخ المتوسط و قرين آمون) لذكور الجرذان البيضاء .

أدى الحقن اليومي داخل التجويف البطني بالجرعة ٣٠٠ مجم/كجم من وزن الجسم من مستخلص جذور النارادين ولمدة ٣٠ يوماً إلى زيادة ذات دلالة إحصائية ($p<0.01$) في محتوى الإبينفرين في القنطرة والنخاع المستطيل والقشرة المخية وتحت المهاد البصري والمخ المتوسط . كما تسبب ذلك الحقن في زيادة المحتوى الكلي للنورإبينفرين في جميع المناطق المختبرة ماعدا منطقتي المخيخ والقشرة المخية وفي زيادة محتوى الدوبامين في جميع مناطق المخ المختبرة ماعدا منطقتي القشرة المخية وقرين آمون وفي زيادة محتوى السيرتونين و٥-هيدروكسي إندول حمض الخليك في جميع المناطق المختبرة . لكن ذلك الحقن أدى إلى إنخفاض ذي دلالة إحصائية ($p<0.01$) في المحتوى الكلي للجاما أمينو حمض البيوتريك في جميع مناطق المخ المختبرة . وبعد انسحاب المستخلص من الجسم ظل المحتوى الكلي للموصلات العصبية متأثراً في مناطق القنطرة والنخاع المستطيل والجسم المخطط والمخ المتوسط وقرين آمون حتى نهاية فترة الانسحاب . وربما يكون هذا ناتجاً عن إختلافات مناطقية تجاه تأثير المستخلص .

الزيادة في محتوى الإبينفرين والنورإبينفرين والدوبامين والسيرتونين و٥-هيدروكسي إندول حمض الخليك وفي نفس الوقت الانخفاض في المحتوى الكلي للجاما في مناطق الجهاز العصبي المركزي المختلفة لمخ الجرذ الأبيض قد تكون نتيجة عن وجود كل من حمض الفاليرنيك والفلبيوترايتس في المستخلص اللذان تسببا في تثبيط أيض الجاما وفي نفس الوقت زيادة تصنيع الجاما وزيادة تحررها و تعزيز عمل مستقبلات الجاما (أ) التي أدت إلى انخفاض تحرر الموصلات العصبية . من الممكن استخدام جذور النارادين كعلاج عشبي مهدئ فعال وآمن .