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Serum β-endorphin level in patients with depression on fluvoxamine

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Abstract

The main interest of the present study was to determine possible alterations in β-endorphin serum levels in healthy volunteers and in patients with depression, as well as changes in β-endorphin serum levels caused by fluvoxamine treatment. Fluvoxamine maleate (Fevarin®) was administered orally at a dose of 200 mg/day for 4 weeks. The serum levels of β-endorphin were lower in patients with 'nonendogenous' depression (104.68 ± 5.29 pg/ml) and those with 'endogenous' depression (36.34 ± 2.23 pg/ml) than in healthy volunteers (125.19 ± 1.64 pg/ml). The endogenously depressed patients had significantly lower β-endorphin levels than the nonendogenous patients. A 4-week treatment of fluvoxamine (200 mg/day) caused a statistically significant increase in β-endorphin serum levels in all patients (nonendogenous depression 132.10 ± 2.38 pg/ml and endogenous depression 50.09 ± 2.45 pg/ml) in comparison to values found before the onset of the therapy. The efficacy of fluvoxamine was 11.0 (± 9.0) evaluated by the Hamilton Rating Scale for Depression (HAMD) in the patients with a diagnosis of depression. These results indicate that determination of β-endorphin serum levels could be a valuable laboratory test in the diagnosis of depression.

Keywords: Depression; Drug monitoring; Serotonergic systems; β-Endorphin; Serum levels; Immunometric analysis

1. Introduction

A number of neuropeptides present in the brain have been implicated in brain homeostatic control mechanisms [1]. It has been postulated that they are also involved in psychopathological conditions [1].

Abnormalities in serotonergic activity in depression could occur at one or more levels, e.g. diminished availability of L-tryptophan (L-TRP), a serotonin (5-HT) precursor, impaired 5-HT synthesis, release, re-uptake or metabolism, or 5-HT postsynaptic receptor disturbances [2]. Although much has been learned about serotonergic dysfunction in major depression since 1987, it is clear that there is no simple answer to the question of whether altered 5-HT activity is directly related to the pathogenesis or pathophysiology of major depression or whether it acts as a vulnerability factor in that illness. Future research on serotonergic activity in depression might focus on the following issues [2]. Disorders in both peripheral and central 5-HT metabolism and hypothalamic–pituitary–adrenal (HPA) axis hyperactivity may be interrelated phenomena, which participate in the pathophysiology of major depression [3,4]. Recently, clinical studies suggested that endogenous depression was due to a deficiency of monoamines, epinephrine and 5-HT at postsynaptic receptors [5].

Endogenic opiate peptides modulate brain noradrenergic, dopaminergic and serotonergic systems involved in both the etiology and pharmacotherapy of depression [6].

The hypothesis about the inclusion of the endogenic opiate system in the pathogenesis of depression is confirmed by data suggesting that β-endorphin agonists and opiates can be used in the treatment of depression [7]. Fluvoxamine is an antidepressant drug, a potent selective inhibitor of presynaptic 5-HT re-uptake with little or no effect on noradrenergic processes [8]. This agent

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has demonstrated antidepressant activity but is structurally quite different from the tricyclics, such as clomipramine [9].

The effect of fluvoxamine and other antidepressant drugs on the level of β-endorphin in the serum of patients with depression has not yet been fully explored. Furthermore, its mode of action in depression is far from being completely understood. Biogenic amines are intimately involved in the hypothalamic regulation of pituitary–adrenocortical function. Thus, enhancement of serotonergic neurotransmission (by inhibition of re-uptake) may be expected to cause neuroendocrine changes [9].

Having in mind all previously presented results, the aim of this study was to investigate variations in serum β-endorphin levels in patients with a diagnosis of depression after treatment with fluvoxamine.

2. Experimental

2.1. Drug

Fluvoxamine maleate tablets containing 100 mg of fluvoxamine (Fevarin®) were purchased from Solvay Duphar (Netherlands). All other chemicals used were of the highest purity obtainable from commercial sources.

2.2. Subjects

Thirty healthy volunteers (18 females and 12 males, mean age $\pm$ SD 27 ± 7 years) participated in the study and the body weight (kg) of each subject was measured. A second group consisting of 30 depressed patients (21 women, nine men, mean age $\pm$ SD 27 ± 5 years) during therapeutic monitoring also participated in the study. Patients were referred to the Psychiatric Clinic of the Clinical Center of Serbia in Belgrade. Informed consent was obtained from all the patients. Patients were studied whilst on a minimum of 4 weeks of double-blind cross-over, randomized clinical study with application of drug and placebo according to 'double dummy' procedure. Diagnosis of primary major depression was performed by two psychiatrists in separate interviews according to Diagnostic and Statistical Manual Criteria of Mental Disorders (DSM-IV) [10].

The patients were further classified as endogenous (four men, 11 women) according to both the Research Diagnostic Criteria (RDC) [11] and the Newcastle Depression Scales (NDS) criteria [12] with a cut-off point of six, and as nonendogenous (five men, ten women) when showing a score of five or less on the NDS.

A score of 25 or more on the 26-item version of the Hamilton Rating Scale for Depression (HAMD) was required at the end of the wash-out period [13].

Exclusion criteria were: pregnancy, non-stabilized organic illnesses. EEG and ECG abnormalities, serious abnormalities of the laboratory test results and structured psychotherapy started within the last 2 months.

The study protocol was approved by the Ethical Committee of the University School of Medicine, Belgrade, Yugoslavia.

2.3. Drug treatment

The patients received fluvoxamine maleate 200 mg per day, per os (p.o.), given in two equal doses at 12 h intervals during the study period (28 days). Blood samples were collected before fluvoxamine administration and after 28 days of administration (p.o. once daily for 28 days) by venipuncture into glass tubes. Samples were immediately centrifuged (3000 rpm, 10 min). The serum was separated and stored in glass at -20°C until use.

2.4. Determination of β-endorphin

Levels of β-endorphin were determined in the serum samples by immunometric analysis (IRMA-β-Endorphin Allegro™ human, Nichols Institute, Paris, France, Diagnostic San Juan Capistrano). The concentration of β-endorphin was calculated in each serum sample.

The antibody had 16% cross-reactivity with human β-lipotropin and $< 0.001\%$ with leucine–enkephalin and methionine–enkephalin. The inter- and intra-assay coefficients of variation for the method were 4.1% ($\bar{x} = 213$ pg/ml; $n = 12$) and 9% ($\bar{x} = 190$ pg/ml; $n = 20$), respectively.

2.5. Psychometric tests

The efficacy of both drugs was measured by means of the modified 26-item HAMD [13]. In addition, the Clinical Global Impression Scale (CGI) was used [14]. Clinical global impression was noted after 4 weeks of treatment which continued throughout the initial 8-week assessment period.

2.6. Statistical analysis

Obtained data were expressed as mean values $\pm$ SEM. The difference of the sample mean values (of the β-endorphin's serum levels) between groups was evaluated by Student's t-test. The $P < 0.05$ changes were considered significant.

In order to determine the significance of the difference between groups (depressed patients and comparison subjects) in the continuous variables (12 clinical characteristics of depression), we used t-tests and the Mann–Whitney U/Wilcoxon rank sum W-test.

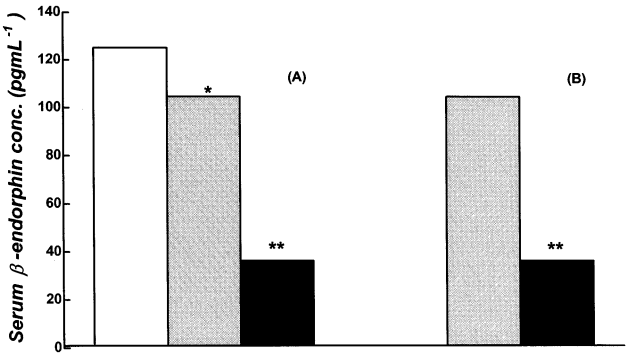

Fig. 1. Serum β-endorphin levels (mean ± SEM) in the patients before fluvoxamine treatment and in the controls (healthy volunteers). (A) □, healthy volunteers; ▩, patients with nonendogenous depression (in comparison with normal control, * $P < 0.01$); ■, patients with endogenous depression (in comparison with normal control, ** $P < 0.005$). (B) ▩, patients with nonendogenous depression; ■, patients with endogenous depression (in comparison between two groups of patients, ** $P < 0.005$).

3. Results and discussion

Determinations of serum β-endorphin levels of the healthy volunteers (control) and the patients with nonendogenous depression and endogenous depression currently receiving no drugs, demonstrated significantly lower levels of β-endorphin in the patients compared to the control (Fig. 1).

Lower serum β-endorphin levels in patients with endogenous depression in comparison with the levels of the healthy volunteers determined in this study are in accordance with previously reported data [15,16].

These results indicate that the disturbances at the level of β-endorphin secretion could be one of the factors associated with pathogenesis of depression.

A decrease of β-endorphin in the serum of the patients suffering from depression probably results from disturbed serotonergic activity [2]. It has been previously concluded that 5-HT stimulates the release of corticotrophin-releasing hormone (CRH), which in turn triggers the secretion of proopiomelanocortin (POMC), a β-endorphin precursor, from the anterior pituitary of rats. It is generally accepted that concentrations of β-endorphin in rat serum reflect its release from pituitary tissues [17]. The changes of β-endorphin in the serum levels are likely to be due to the HPA-axis hyperactivity in patients with depression.

The hyperactivity of the sympathoadrenomedullary system and the HPA-axis in depressed patients is probably caused by the increased hypothalamic CRH secretion, which is occurring under the influence of either the negative feedback by glucocorticoid receptors or disorders in connection with neurotransmitters [18,19]. The decrease in the serum levels of β-endorphin recorded in the present study could be explained by a lower rate of β-endorphin biosynthesis and release in anterior and intermediate lobes of pituitary tissues [20].

Our data show that serum β-endorphin concentrations are significantly lower in subjects with endogenous depression than in patients with nonendogenous depression (Fig. 1).

These findings are in accordance with previously reported results [15] that serum β-endorphin level is decreased in patients with endogenous depression. This suggests that measurement of serum β-endorphin levels is one of the possible complementary markers in differentiating between endogenous and nonendogenous depression.

The administration of fluvoxamine (200 mg/day for 28 days) leads to a statistically significant increase in serum β-endorphin level of the patients with nonendogenous and endogenous depression in comparison with the level before the onset of therapy (Table 1). Serum β-endorphin levels in patients before and after the treatment with fluvoxamine are listed in Table 1.

We have found that per os administration of fluvoxamine provoked changes in serum β-endorphin levels of the patients with depression, which were similar to the effect of evaluated serum levels of opioids, obtained after administration of psychotropic drugs [19].

Also, an increase in rat plasma concentrations of β-endorphin after a single dose of fluvoxamine was observed in an experimental study by Petraglia et al. [21].

Antidepressive treatments were found to induce a gradual development of increased 5-HT activity by different mechanisms [22].

Table 1
Levels of β-endorphin in the blood sera of the patients before and after administration of fluvoxamine

Patients	Concentration of β-endorphin (pg/ml)[a]	
	Before the treatment (control)	After administration of fluvoxamine (200 mg/day for 28 days)
Nonendogenous depression ($n = 15$)	104.68 ± 5.29	132.10 ± 2.38*
Endogenous depression ($n = 15$)	36.34 ± 2.23	50.09 ± 2.45**

[a] Each value represents the mean ± SEM of 15 test samples.
* $P < 0.01$.
** $P < 0.005$ ($P < 0.05$ changes were considered significant).

The changes in serum levels of β-endorphin recorded in the present study after 28-day administration of fluvoxamine could be the result of an increased 5-HT metabolism. Our findings suggest that antidepressant drugs could modulate β-endorphin concentrations in the serum of patients with depression.

Findings of psychometric tests were represented by the mean total score on the HAMD and CGI. At the final assessment the mean total score ($\pm$SD) in the fluvoxamine groups was 11.0 ($\pm$9.0), equivalent to a mean improvement of 67.2% compared with a reduction of 27% after placebo, evaluated by HAMD. The patients' condition as judged on the CGI also improved gradually. The median severity score in the fluvoxamine groups was 5.5 which meant that the majority of patients were markedly to severely ill.

Based upon global impression ratings, HAMD and CGI scores, fluvoxamine was more effective than placebo. It seems that increases in serum levels of the β-endorphin observed in patients with major depression treated with fluvoxamine initiate a possibility of correlation between fluvoxamine and β-endorphin level, which may also be associated with a patient's positive (beneficial) response to the applied drug.

In the light of these findings, we speculate that a relative deficiency of β-endorphin or a change in the ratios of endogenous opiate peptides may play a role in etiology of some forms of depression, probably by modulating neuronal activity.

These results indicate that determination of serum β-endorphin levels could not only be a valuable laboratory test in the diagnosis of depression, but also a useful tool in research and therapeutic strategy.

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