The Relationship Between Basal Plasma ß-Endorphin Levels and the Severity of Major Depressive Episode

Mustafa Baştürk M.D.[1], Sabahattin Muhtaroğlu M.D.[2], M.Fatih Karaaslan M.D.[1], Aslan Oğuz M.D.[1], Aytül Şimşek M.D.[1], Mustafa Reyhancan M.D.[1]

SUMMARY

THE RELATIONSHIP BETWEEN BASAL PLASMA ß-ENDORPHIN LEVELS AND THE SEVERITY OF MAJOR DEPRESSIVE EPISODE

Objective: Although several studies performed in depressed patients have shown a deficiency in endorphin activity, plasma studies of ß-Endorphin (ß-EP) in depressive disorders have produced conflicting results so far. The aim of the present study was to test the hypothesis that possible changes in basal ß-EP levels are related to severity of major depressive episode. **Methods:** 36 patients (17 females, 19 males) who were diagnosed to have major depressive episode according to the DSM-IV criteria (mean age±SD:48.6±13.2) and admitted to the psychiatric ward of our university teaching hospital and 13 healthy subjects (mean age 38.70±10) participated in the study. They had HAM-D and MADRS scores above 15 and 8, respectively, at the time of evaluation. Morning plasma ß-EP levels were determined with standart RIA kits. **Results:** Basal plasma values of ß-EP were significantly higher in the patients than in the control subjects ($t=2.66$ $p<0.05$). Furthermore, there was a significant correlation between basal plasma ß-EP levels and HAM-D and MADRS scores ($r=0.59$ $p<0.05$ and $r=0.57$ $p<0.05$, respectively). **Conclusion:** Our data support the hypotheses that: 1) Significantly higher plasma ß-EP levels in patients with major depressive episode compared to controls reflect a central limbic disturbance. 2) Significantly correlated plasma ß-EP levels with severity of depressive symptoms also reflect magnitude of central limbic disturbance during major depressive episode.

Key words: ß-endorphin, major depressive episode.

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ÖZET

BAZAL PLAZMA ß-ENDORPHIN SEVİYELERİ İLE MAJOR DEPRESSİF EPIZODUN AĞIRLIĞI ARASINDAKİ İLİŞKİ

Amaç: Depresyonlu hastalarda yapılmış olan çalışmalar endorfin aktivitesinde değişikliği göstermekle beraber, şimdiye kadar olan plazma ß-EP seviyesi çalışmaları çelişkili sonuçlar vermiştir. Bu çalışmanın amacı plazma bazal ß-EP seviyelerindeki muhtemel değişikliklerin major depressif epizodun ağırlığı ile ilişkili olabileceği hipotezini test etmektir. **Metod:** DSM-IV kriterlerine göre major depressif epizod teşhisi konmuş ve üniversite hastanesinin psikiyatri servisine kabul edilmiş olan 36 hasta (17 kadın, 19 erkek) (ortalama yaş ±SD: 48.6±13.2) ve 13 sağlıklı kontrol (ort.yaş 38.70±10) çalışmaya dahil edildi. Değerlendirme esnasında onların HAM-D ve MADRS skorları sırasıyla 15 ve 8'in üstündeydi. Sabah plazma ß-EP seviyeleri standart RIA kitleri ile ölçüldü. **Bulgular:** Hastalarda bazal plazma ß-EP değerleri kontrollerdekine göre önemli şekilde yüksekti ($t=2.66$ $p<0.05$). Ayrıca bazal plazma ß-EP seviyeleri ile HAM-D ve MADRS skorları arasında önemli bir korelasyon tesbit edildi. (Sırasıyla $r=0.59$ $p<0.05$ ve $r=0.57$ $p<0.05$). **Sonuç:** Bulgularımız şu hipotezleri desteklemektedir: 1) Major depressif epizodda kontrollere göre önemli şekilde yüksek olan plazma ß-EP seviyeleri merkezi limbik bozukluğu yansıtmaktadır. 2) Depressif semptomların ağırlığı ile plazma ß-EP seviyelerinin korelasyon göstermesi major depressif epizod esnasındaki merkezi limbik bozukluğun büyüklüğünü yansıtmaktadır.

Anahtar sözcükler: ß-endorfin, major depressif epizod.

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INTRODUCTION

Endomorphines are involved where pain, cerebral ageing, behavior with respect to feelings, food and emotions and psychiatric disorders are concerned. These endorphines are found in many areas of the brain and can behave as modulators or hormones or mediators (1). ß-endorphin (ß-EP) has a two-fold action: firstly a peripheral hormone action and secondly a neuroregulating action via interference with other neurotransmitters (1). Circulating ß-EP is supposed to produce a major effect in the central nervous system because it is able to cross blood-brain barrier (2). ß-EP secretion at the cerebral level influences plasma ß-endorphin levels through the portal blood flow (3).

The role of endorphins in the pathogenesis of psychiatric disorders has stimulated considerable interest in recent years. It has been that ß-EP may reflect pain, stress or mood disturbance as a trait or state marker (4). Although several studies performed in depressed patients have shown a deficiency in endorphin activity, plasma studies of ß-EP in depressive disorders have produced conflicting results so

Departments of Psychiatry[1] and Biochemistry[2], Erciyes University School of Medicine, Kayseri - Turkey

Yazışma Adresi / Address reprint requests to: Doç. Dr. Mustafa Baştürk, Erciyes Üniversitesi Tıp Fak. Psikiyatri Anabilim Dalı, Kayseri- Turkey
Telephone :+90 412 2488001
Fax:+ 90 412 2488520 E-Mail: scureoglu@hotmail.com

far. Some authors reported plasma ß-EP levels to have increased in patients with depressive disorders (5, 6) but others found no difference between depressed and normal subjects (7). The aim of the present study was to test the hypothesis that changes in ß-endorphin levels are related to severity of major depressive episode.

METHODS

Subjects

Thirtysix patients (17 females, 19 males) diagnosed to have major depressive episode according to the DSM-IV criteria (mean age±SD: 48.6±13.2; range: 30-56 years) and admitted to the psychiatric ward of our university teaching hospital participated in the study (8). None of the patients had bipolar depression or psychotic features. Thirteen age and sex-matched healthy subjects (6 females, 7 male; mean age±SD: 38.7±10.0; range: 28-58 years) chosen among the hospital staff served as control subjects. Patients were assessed with the 21-item Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS). They had HAM-D and MADRS scores above 15 and 8, respectively at the time of evaluation.

The clinical examination of the subjects was performed by a physician before the endocrine tests. All subjects were free of medical disorders or the other Axis Idiagnoses, and their ECG, EEG, radiograph heart and lungs and laboratory tests including urine analysis, blood chemistry, thyroid, kidney and liver function tests were within the normal limits. None of the patients had a history of substance use disorder or had been treated with ECT in the 6 months preceding their admission to the study. All psychotropic drugs were discontinued on admission, and consequently these subjects underwent a wash-out period of 2 weeks before blood sampling. The patients gave their written informed consent and the study protocol was approved by the ethics committee of our hospital.

Procedures

A heparinized catheter was inserted into antecubital vein to collect fasting blood samples at 08.00 a.m. under the stress-free condition, as possible. Venous blood drawn into ice-cold vacutainer tubes containing a mixture of EDTA and aprotinin was immediately centrifuged at 4°C and plasma was stored at –70°C until ß-EP assayed. Plasma levels of ß-EP were determined with standard RIA kits (Nichols Institute Diagnostics ß-EP B.N kits ND). The lowest limit of sensitivity was 14 pg/ml, intra-assay and inter-assay coefficients of variation were 213 pg/ml- %4.1, 190 pg/ml- %9.0 respectively. Both assays were performed by clinicians who were blind to subject diagnosis.

Data analysis

Comparison of the values obtained from both the patients and the controls was made by using Student's t-test (unpaired, two tailed). Spearman's rank correlations were performed by SPSS to study the relationship between plasma ß-EP values and the severity of clinical symptoms.

RESULTS

Table presents clinical variables and the mean values of the ß-EP of the groups studied. Basal plasma values of b-endorphin were significantly higher in the patients than in the control subjects ($t=2.66$ $p<0.05$). Furthermore, there was a significant correlation between basal plasma ß-EP levels and HAM-D and MADRS scores ($r=0.59$ $p<0.05$ and $r=0.57$ $p<0.05$, respectively). But no correlation was observed between ß-EP levels and the age, the length of illness or the number of depressive episodes.

Table - Clinical variables and plasma b-endorphin values of the patients with major depressive disorder and of the controls.

VARIABLES	Patients with MDD (n=36)		Control subjects (n=13)		COMPARISON	
Age	Mean	SD	Mean	SD	t	p
Length of illness	48.60	13.20	38.70	10.00		
Number of episodes	7.13	5.87	-	-		
HAM-D score	4.33	2.49	-	-		
MADRS score	23.40	3.07	-	-		
Plasma B endorphin	10.60	2.15	-	-		
Level (pmol/L)	132.76*	28.78	116.21	21.26	2.66	<0.05

*Significantly different from the control subjects.

DISCUSSION

ACTH, as well as ß-EP, are derivatives of precursor molecule pro-opiomelanocortin (POMC), and ß-EP is a product of ß-lipotropin. Under normal circumstances these hormones are synthesised in and released from pituitary cells. Production and releasing process of them is regulated by CRH. Cortisol is synthesised and released from the adrenal cortex under the influence of ACTH.

Both ACTH and ß-EP immunoreactivity are found to have similar anatomical distributions in the central nervous system and they may act as co-neurotransmitters and co-neuromodulators (9). As Brambilla and co-workers (10) have also noted, altered neuronal ratio of ß-EP to ACTH might have behavioral effects and these could be involved in the pathogenesis of depression and/or dysphoric mood. However, plasma ß-EP studies yielded inconsistent findings, and inconsistencies of the results may be attributed to the study of different depressive subtypes or use of different methods of blood collection, because it has been known that ß-EP secretion has a 24 hr circadian pattern (11) and a brief half-life (12).

Two neuropeptide systems, ß-EP and ACTH, are intimately associated with responsiveness to stress, not only at an endocrine level, but also within the brain (13). Furthermore, results on the release of ß-EP from hypothalamus indicate that CRH is a potent releaser of brain ß-EP (14). Therefore, the elevation of CRH in depressed patients may be associated with a concomitant increase in ß-EP release. Supporting this idea, it has previously been demonstrated that increases in plasma ß-EP immunoreactivity occur during stress process (12). It has also been demonstrated that correlated increases in plasma and ß-EP and cortisol immunoreactivity in humans occur under stressful conditions as an index of arousal (12). Taking these considerations into account, although we did not measured the cortisol and ACTH levels in our study, significantly higher plasma ß-EP levels in the patients with major depressive episode compared to the normal controls that we found may represent a stress manifestation in major depressive episode. Furthermore, based on our finding that there was a correlation between ß-EP levels and depression rating scale scores, one may speculate that progressive HPA axis disinhibition induced by stress may cause a more severe depressive episode and that higher plasma ß-EP levels during major depressive episode may reflect a more severe limbic disturbances occur at that time span.

In conclusion our data support the hypotheses that:

1. Significantly higher plasma ß-EP levels in patients with major depressive episode compared to controls reflects a central limbic disturbance.

2. Significantly correlated plasma ß-EP levels with severity of depressive symptoms also reflects magnitude of central limbic disturbance during major depressive episode.

However, since HPA axis and ß-EP have circadian secretory patterns (Gianoulakis 1996), estimation of ß-endorphin levels based on more frequent blood sampling in the future studies may confirm this association between ß-EP and the severity of symptomatology during major depressive episode emerges.

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