

Plasma Neuropeptide Y Levels in Medication Naive Adolescents with Major Depressive Disorder

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ÖZET:

İlaç tedavisi almayan majör depresif bozukluklu ergenlerde plasma nöropeptid Y düzeyleri

Amaç: Neuropeptide Y (NPY), anksiyete ve depresyon patofizyolojisinde önemli bir maddedir. NPY'nin emosyonel düzenlemeyi sürdürmesi için kortikotropin salınımını sağlayan faktör (CRF) tarafından aracılık edilen stres etkilerini giderdiği ileri sürülmüştür. Bu çalışmada ilk kez depresyon tanısı alan ergenlerde NPY düzeyleri, hastaların intihar girişimi öyküleri gözününde bulundurularak araştırılmıştır.

Yöntem: Majör depresif bozukluk (MDB) tanılı 33 ergen çalışmaya alındı. 11 hasta, başka bir psikiyatrik hastalığın varlığı nedeniyle çalışma dışında tutuldu. MDB tanılı 22 ergende, NPY'nin plazma konsantrasyonları ölçüldü. Beck Depresyon Envanteri-Türkçe uyarlaması ve Beck Anksiyete Envanteri-Türkçe uyarlaması, depresyon ve anksiyete düzeylerini ölçmek için kullanıldı.

Bulgular: Depresyonlu ergenlerde sağlıklı kontrollere oranla anlamlı derecede düşük NPY düzeyleri bulundu. Hastalar intihar girişimi öykülerine göre sınıflandırıldığında her iki grup arasında NPY düzeyleri açısından anlamlı bir fark bulunmadı. NPY düzeyleri, hastalığın süresiyle ve suçluluk duyguları ile negatif yönde, anksiyeteye pozitif yönde korelasyon gösterdi. Anksiyete, bir eşdeğişken olarak alındığında zaman, NPY ile suçluluk duyguları arasındaki korelasyonlar kayboluyor, hastalığın süresi bir eşdeğişken olarak alındığında aradaki korelasyon anlamlılığını koruyordu.

Tartışma: Ergen depresif hastalar sağlıklı kontrollere oranla daha düşük NPY plazma düzeylerine sahipti. Plazma NPY düzeyleri, hastalığın süresiyle azalıyor, suçluluk duygusu ve anksiyetenin şiddetiyle artıyordu. NPY'nin, ergenlerde görülen MDB'de anksiyete ile ilgili depresyona bir eğilim için belirleyici olduğu ileri sürülebilir.

Anahtar sözcükler: Nöropeptid Y, emosyonel düzenleme, anksiyete, depresyon, ergenler

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ABSTRACT:

Plasma neuropeptide Y levels in medication naive adolescents with major depressive disorder

Objective: Neuropeptide Y (NPY) has been implicated in pathophysiology of anxiety and depression. It was proposed that NPY counteracts corticotropin-releasing factor-mediated stress effects to maintain emotional regulation. We investigated NPY concentrations in a sample of first episode medication-naive adolescent patients with MDD with regards to their history of suicide attempts.

Method: 33 adolescents with MDD were enrolled. 11 patients were excluded due to comorbidity of another psychiatric illness. In 22 adolescents with MDD patients, the plasma concentrations of NPY were assessed. The Beck Depression Inventory-Turkish Version and the Beck Anxiety Scale- Turkish Version were used to rate the severity of depressive and anxiety symptoms.

Results: Our sample of depressed patients showed lower levels of NPY compared to healthy controls. When the depressed patients were grouped with regards to suicidality, both groups did not show any significant differences. NPY levels were negatively correlated with duration of illness and feelings of guilt, and positively correlated with anxiety. When anxiety was taken as a covariate, significant correlations between NPY levels and feelings of guilt disappeared; whereas, when duration of illness was taken as a covariate correlations were still significant.

Conclusions: Adolescent depressed patients were found to have lower NPY plasma levels compared to healthy controls. Plasma NPY concentrations were decreasing with duration of illness, increasing with feelings of guilt and anxiety severity. Plasma NPY levels in adolescents MDD might indicate a predisposition to anxiety-related depression.

Key words: Neuropeptide Y, emotional regulation, anxiety, depression, adolescents

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INTRODUCTION

Neuropeptide Y (NPY) is a 36 aminoacid peptide which belongs to the pancreatic polypeptide family (1). NPY has a direct association with the hypothalamic pituitary adrenal (HPA) axis. The hypothalamic paraventricular nucleus is the main site of accumulation of nerve terminals of NPY neurons, and electron microscopy revealed synapses between NPY and corticotrophin-

releasing factor (CRF) neurons (2). It was proposed that NPY counteracts the corticotrophin-releasing factor (CRF)-mediated stress effects to maintain "emotional homeostasis" (3). High concentrations of NPY are particularly found in the limbic system, basal ganglia (caudate nucleus, putamen), cerebral cortex, and hypothalamus in the human brain (4). Limbic areas include the hippocampus, amygdala, cortical areas, and the bed nucleus of stria terminalis, all of which play a role

in the regulation of the stress response system and emotional behavior. Two other areas with high NPY expression that are involved in mediating fear and anxiety are the periaqueductal grey matter and the septum. High levels are also found in the hypothalamus, the primary area for origination of stress response (5). NPY is co-stored and co-secreted with noradrenaline in the brain and sympathetic nerve endings. It acts as a co-transmitter, neurohormone, and neuromodulator in the central and peripheral nervous systems (6). NPY and NPY receptors play an important role in the regulation of food intake (7), sexual behavior (8), information handling (9), cognition (10), learning and memory (11-13), control of blood pressure (14), sympathetic activity (15), modulation of emotional processing (3), and the regulation of stress and anxiety (13,16,17).

Exposure to acute traumatic and/ or chronic stress is central to both mood and anxiety disorders. Most affective and stress induced psychiatric disorders have major disturbances in the stress regulatory systems of the body. There is also a high comorbidity of alcoholism, addiction, and cognitive dysfunction with various psychiatric conditions (3). There are several clinical studies investigating the cerebrospinal fluid (CSF) and plasma NPY concentrations in psychiatric disorders such as anxiety disorders, depression, stress related disorders, alcohol dependence, and eating disorders (18-21).

NPY may have an important role in the pathophysiology of major depressive disorder. Many clinical studies have demonstrated decreased NPY levels in the CSF and plasma of depressed patients when compared to healthy control subjects (22-26). According to preclinical studies, three lines of evidence from animal work supported the relevance of NPY in depression: (1) animal models of depression and NPY levels; (2) potentiation of NPY expression by antidepressant treatments; (3) administration of NPY compounds reduce depressive behavior (3,27,28). All preclinical evidence discussed above supports a role of NPY and the Y1 receptor in the pathophysiology of depression (29). The stimulatory effects of central NPY on the HPA axis may appear contradictory to the anti-stress and anti-anxiety role of the peptide, especially in depression where both reduced NPY tone and hyperactive HPA activity coexist. However, in depression, HPA hyperactivity is primarily a result of impaired HPA feedback which might not involve

hypothalamic NPY responses. The amygdala is known to be the brain region intimately involved in mediation and processing of emotion and emotional memory. Reduced central NPY may in turn contribute to CRF hyperactivity in the amygdala which may induce elevated anxiety in depressed patients (3).

Lower plasma NPY and CRF concentrations in suicide attempters with depression have previously been reported (30-33). Human studies have also shown decreased NPY concentrations especially in the frontal cortex and caudate nucleus of suicide victims with major depression (34). Presently available evidence suggests that peripheral NPY is largely a marker of sympathetic nervous system activity, which is unrelated to central NPY-signaling of importance for emotionality and mood (16). In a recent study, Hou et al. showed that there were no differences between severe major depressive disorder and healthy controls in CSF NPY levels, however, significantly lower CSF NPY was found in first episode depressed patients compared with recurrent depressed patients. They concluded that NPY might be a marker for first episode of depression (23). It is possible that NPY contributes to the phenomenology of depression such as suicidality, psychophysiological, and emotional manifestations via different ways. Therefore, we thought plasma NPY concentrations might provide a valuable tool for prediction of suicidality and might be potential marker for evaluating adolescent depression.

To our knowledge, there are no studies in the literature investigating the possible role of NPY in adolescent depression. Adolescent depression may manifest itself with high risk of suicidality. Here, we investigated NPY concentrations in adolescents with MDD with regards to their history of suicide attempts. In this present study, we examined how NPY levels contributed the pathogenesis of major depressive disorder (MDD) and suicidality in a sample of first episode medication-naïve adolescent patients with MDD.

METHODS

Participants and procedure

Thirty three consecutive outpatients presented with first episode MDD were recruited from the Adolescent Outpatient Clinics of the Bakirkoy Mental Health

Table 1: Demographic and clinical variables between patient and control groups

	Patients (n=22)	Normal Healthy Control (n=41)	p
Gender (Female %)	36%	39%	N.S.
Age	16.4 (15-18)	16.6 (15-18)	N.S.
Neuropeptide Y (ng/ml)	0.291±0.12	0.393±0.1	0.003
Beck Anxiety Inventory	13.64±5.1	11.66±9.75	N.S.
Beck Depression Inventory	27.50±4.60	7.79±6.08	<0.0001

N.S.: Non Significant

Training and Research Hospital. The mean age of the patient group was 16.4 years (SD = 1.0), within a range of 15-18 years (Table 1). Adolescents had no prior psychiatric history nor received any treatments with psychotropics before their visit to the hospital. All patients met criteria for a current major depressive disorder of unipolar subtype. The diagnoses of MDD was made with a trained clinician by using the Structured Clinical Interview for DSM-IV (SCID-I). A total of eleven patients with Axis I disorder other than MDD, including patients with bipolar disorder, and current substance abuse or dependence (n=3) were excluded from the study. Twenty two adolescents with MDD; 8 (36.4%) males and 14 (63.6 %) females, were included in the study. The Beck Depression Inventory-Turkish Version and the Beck Anxiety Scale- Turkish Version were used to rate the severity of depressive and anxiety symptoms. Patients were free of any major physical illnesses and medical treatments. Forty one age- and- gender matched healthy controls (HC); 16 (39%) males and 25 (61%) females, were recruited from the children of hospital staff and their acquaintance (Table 1). The mean age of the control group was 16.6 years (SD = 1.1) within an age range of 15-18. All control participants were interviewed with the SCID-I in order to exclude any Axis I disorders. They were also in good physical health and had no first degree relatives with known psychiatric disorders. The study was approved by the Ethics Committee of the Bakirkoy Mental Health Training and Research Hospital. Written informed consent was obtained from adolescent patients and healthy volunteers and also from their parents or legal guardians prior to the start of the study procedures.

Blood samples (7 ml) were drawn from the antecubital vein between 7:00 and 8:00 A.M. after 15 minutes rest and after an overnight fast. They were collected into the Lavender Vacutainer tubes containing EDTA and

centrifuged at 1600 x g for 15 minutes at 4°C. Next the samples were stored at -70°C for six weeks. Plasma neuropeptide Y concentrations were measured by radioimmunoassay with commercial kits (Phoenix Pharmaceuticals, Belmont, CA). Regarding the characteristics of the kit used, the rabbit NPY antibody had a 100% cross-reactivity with human, rat and porcine NPY. The NPY antisera did not recognize pancreatic polypeptide. Sensitivity of the NPY assay was 0.27 ng/ml, and the interassay and intraassay coefficients of variation were <14% and <5%, respectively.

Psychological Assessments

Structured Clinical Interview (SCID) for DSM-IV Axis I Disorders. SCID-I is a semi-structured clinical interview developed for the major diagnosis of DSM-IV Axis I disorders (35). The reliability and validity of the Turkish version of the SCID has been conducted by Sorias et al. (36).

Beck Depression Inventory (BDI). This scale measures somatic, emotional, cognitive, and motivational symptoms related to depression (37). The goal of this scale is not to diagnose depression but to provide objective assessment about the severity of depressive symptoms. It includes 21 symptom categories, each having 4 items. Each item is scored from 0 to 3. The sum of these scores provides the final score for depression; with a higher score indicating a more severe illness. It was shown to be valid and reliable in Turkish samples (38,39).

Beck Anxiety Inventory (BAI). This instrument is a self-report scale revealing the frequency of anxiety symptoms experienced by the individual (40). It is a Likert-type scale composed of 21 items scored from 0 to 3. Higher total scores correlate with greater severity of anxiety symptoms. The validity and reliability of the BAI in a Turkish sample was done by Ulusoy et al. (41).

Table 2: Demographic and clinical variables between patients in terms of to suicidality

	Patients with suicide history (n=7)	Patients without suicide history (n=15)	p
Age	16.4 ±1.28	16.6±0.91	N.S.
Illness Duration (months)	6.57±4.58	5.93±3.28	N.S.
Neuropeptide Y (ng/ml)	0.30±0.07	0.29±0.08	N.S.
Beck Anxiety Inventory	15.14±5.04	12.93±5.13	N.S.
Beck Depression Inventory	28.57±5.38	27.00±4.29	N.S.

N.S.: Non Significant

Table 3: Correlations between clinical variables in patients with MDD

	Illness of duration	BAI	BDI-1	BDI-2	BDI-3	BDI-4	Suicidality
NPY	-0.521 0.013	0.709 <0.0001	-	-	-	-0.654 0.001	-
Illness of duration		-0.480 0.024	-	-	-	-	-
BAI			-	-	-	-0.465 0.029	-
BDI-1				-	0.507 0.016	-	-
BDI-2					-	-	-
BDI-3						-	-
BDI-4							-
Suicidality							

Table 4: Partial correlations between the NPY levels and the illness duration, BDI, and BAI scores

	Illness duration		BDI*		BAI	
	r1	p	r2	p	r3	p
Neuropeptide Y	-0.3422	N.S.	-0.3422	N.S.	0.4485	0.047

*feelings of guilt; with BAI controlled for r:-0.4073, p<0.05, with duration of illness controlled for r:-0.5250, p:0.015

r1: partial correlation coefficient controlling for BDI, and BAI scores.

r2: partial correlation coefficient controlling for illness duration and BAI scores.

r3: partial correlation coefficient controlling for illness duration and BDI scores.

Statistical Analysis

Comparisons among the groups were made using the Mann Whitney U test. Correlations were examined using the Spearman's test. Spearman's correlation coefficients were obtained between the NPY score and the illness duration and psychological factors such as anxiety and depression (total and all sub-dimensions). In order to determine the relationship between the NPY scores and the depression score, partial correlation analysis was also used to adjust for the duration of the illness and anxiety. Partial correlation analyses with similar covariates were

applied where appropriate to determine the relationship between the NPY levels and depression and anxiety scores, respectively. All statistical analyses were performed using the SPSS Version 9.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Sociodemographic and clinical variables such as NPY levels, BDI, and BAI scores between patient and control groups are shown in Table 1. There were significant differences between depressed patients and controls in

NPY levels and BDI scores, however, BAI scores were not found significantly different.

When the major depressed patients were separated by history of suicide attempt, there were no significant differences in age, duration of illness, BDI, BAI, and NPY levels (Table 2).

Correlations between duration of illness, suicidality, NPY, BAI, and BDI total and subscales were shown in Table 3. NPY levels were found to be negatively correlated with duration of illness and feelings of guilt, and positively correlated with anxiety.

Partial correlation analyses with similar covariates were applied where appropriate to determine the relationship between the NPY levels and depression and anxiety scores, respectively. Partial correlations between the NPY levels and the illness duration, BDI and BAI scores were shown in Table 4. When anxiety was taken as a covariate, partial correlations between NPY levels and feelings of guilt were $r = -.4073$, $p = .067$; when duration of illness was taken as a covariate partial correlations were found as $r = -.5250$, $p = .015$.

DISCUSSION

NPY is widely distributed in the human brain and varying concentrations found in limbic system have been repeatedly implicated in the regulation of affective and emotional processing, as well as in the pathogenesis of MDD (29). Our sample of depressed patients showed lower levels of NPY compared to healthy controls. However, when the depressed patients were grouped with regards to suicidality, both groups did not show any significant differences. NPY levels were found to be negatively correlated with duration of illness and feelings of guilt and positively correlated with anxiety. When anxiety was taken as a covariate, significant correlations between NPY levels and feelings of guilt disappeared; whereas, when duration of illness was taken as a covariate correlations were still significant.

Several studies have shown that plasma and cerebrospinal (CSF) NPY levels were found to be lower in MDD patients compared to healthy controls (22-26). Our results were consistent with this finding. Lower levels of NPY in brain tissue were also reported in suicide victims who has evidence to suggest presence of major depression prior to their death (33). Heilig and Widerlov showed that

CSF NPY levels to be negatively correlated to anxiety scores in MDD patients, suggesting a possible link between low NPY levels and predisposition to anxiety-related or stress-induced depression (42). We speculated that lower NPY levels in our sample were perhaps indicating a phenomenological role rather than etiopathological role in depression.

Plasma NPY concentrations were found to be lower in suicidal patients with major depression (29,31,32). When the depressed patients in our sample were grouped with regards to presence of suicidality, both groups did not show any significant differences. This finding was not consistent with previous reports in the literature. Our sample has only 7 suicide attempters, it is difficult to make a conclusive statement.

Plasma NPY concentrations were found to be negatively correlated with duration of illness and feelings of guilt, and positively correlated with anxiety. The finding that NPY levels were decreasing while the duration of depression was getting longer might indicate the contribution of NPY system to the clinical symptomatology of depression. Since anxiety scores were decreasing while duration of illness was getting longer and also NPY concentrations had positive correlations with anxiety scores, these finding seemed to suggest that NPY was perhaps a marker for anxiety-related or stress-induced depression. When anxiety was taken as a covariate, partial correlations between the NPY concentrations and the illness duration, BDI and BAI scores also supported this possible link.

Plasma NPY concentrations were found not to be correlated with the BDI subscale scores except for feelings of guilt subscale. Additionally, a negative correlation was found between NPY concentrations and feelings of guilt. These findings might be attributed to specific features of adolescent depression symptomatology. Since this relationship remained significant in partial correlations where duration of illness was taken as covariate and disappeared when anxiety levels was taken as a covariate, it might indicate the importance of NPY system in anxiety-related adolescent depression research.

In conclusion; adolescent depressed patients were found to have lower NPY plasma levels compared to healthy controls. When the depressed patients were grouped with regards to presence of suicidality, no significant differences were found. NPY levels were

decreasing with duration of illness, increasing with feelings of guilt and anxiety severity. When adolescents were stress intolerant, plasma NPY levels were indicating a predisposition to anxiety-related depression. Our findings warrant further research in larger samples and

patients with different clinical features.

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