

Levels of Adenosine Deaminase and Dipeptidyl Peptidase IV in Patients with Panic Disorder

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Abstract

Objective: Adenosine deaminase and dipeptidyl peptidase IV are enzymes connected to T cells that play an important role in immune system functioning. In this study, in order to understand the immune processes in panic disorder, we determined the serum levels of adenosine deaminase and dipeptidyl peptidase IV in medication-free panic disorder patients and compared them to those of healthy controls.

Method: Enzymes levels were determined in blood samples of 24 healthy controls and 33 panic disorder patients diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-IV that were medication free during the previous month and medically healthy.

Results: Levels of both enzymes were significantly higher in panic disorder patients than in the controls ($P < 0.001$ for adenosine deaminase and $P < 0.05$ for dipeptidyl peptidase IV). The levels of the enzymes did not correlate with sociodemographic variables, duration of the disorder, presence of agoraphobia, presence of stressors, number of panic attack symptoms, and Hamilton depression and anxiety rating scale scores. In addition, the 2 enzymes' levels did not correlate with each other. There was a correlation between Hamilton anxiety rating scale score and the number of panic attack symptoms ($P < 0.001$); however, Hamilton anxiety rating scale scores were not correlated with the other variables.

Conclusion: Our results suggest that there may be a primary or secondary impaired immune state in the course of panic disorder, as there is in many other psychiatric disorders, such as major depression. Future studies with larger samples are needed to clarify the relationship between the immune system and panic disorder.

Key Words: Panic disorder, adenosine deaminase, dipeptidyl peptidase IV, immune system

INTRODUCTION

Panic disorder (PD) is an anxiety disorder characterized by spontaneous, unexpected, recurrent panic attacks, which cause severe impairment in social and occupational functioning. Current hypotheses do not address the etiology of PD; however, some suggest the cause is related to multiple neurotransmitter and functional disturbances in different areas of the brain, which influence each other (Aydın et al., 2001).

Psychoneuroimmunology (PNI) investigates normal and pathological development, and central nervous system (CNS) functioning using immunological techniques. Studies in this field suggest that the CNS and the immune system affect each other reciprocally (Aydın et al., 2001; Schwarz et al., 2001). Stress causes neuro-

immunomodulatory instability and its effects on the immune system depend on the type of stressor and ability to control the stress (Galinowski, 1993).

Neuroendocrine and immunological changes are seen in some psychiatric disorders, such as depression and schizophrenia (Schiepers et al., 2005; Maes et al., 2000, 1996). Whether these changes are related to pathophysiology and are a cause of the disorder or a result of abnormal brain functioning is still a matter of debate. Nonetheless, there are similarities between CNS cells and lymphocytes in the expression of receptors and transduction processes, and changes in the metabolism and cellular functioning of the CNS resemble changes in the metabolism and functioning of blood lymphocytes observed in some psychiatric disorders (Gladkevich et al., 2004). Therefore, it is suggested that lymphocytes

are indicative of brain cell metabolism and can be used in studies related to psychiatric disorders.

PD has a high comorbidity with immunological diseases, such as allergy and asthma (Kovalenko et al., 2001). In addition, PD has similarities with major depression (in terms of biological, clinical, and therapeutic characteristics), which is often accompanied by immunological responses, and the rate of comorbid depression in PD cases is as high as 50% (Schleifer et al., 2002). Previous studies have shown that there are vast and consistent changes in the immune system of PD patients. On the other hand, studies in which the relationship between PD and the immune system were investigated are rare and their results are inconsistent. It was reported that PD patients have decreased polymorphonuclear leukocytes (PMNL) activity (O'Neill et al., 1990), increased IgA level (Ramesh et al., 1991), no alteration in the proliferation response of T lymphocytes to phytohemagglutinin mitogen (Brambilla et al., 1992), increased IgE-mediated type 1 allergic response (Schmidt-Traub et al., 1997), an increase in the number of B lymphocytes positive for CD16 (natural killer cell) and CD19 (Rapaport et al., 1998), a decrease in the number of B lymphocytes positive for CD19 (Schleifer et al., 2002), an increase in the ratio of CD4 (helper = Th) positive T cells to CD8 (suppressor = Ts) positive T cells, and a decrease in the number of T cells despite no change in the number of immunological cells (Park et al., 2005). In studies that compared cytokines in PD patients and controls it was shown that levels of interleukin-2 (IL-2) were higher in PD patients, and levels of interleukin-1 α (IL-1 α) and interleukin-1 β (IL-1 β) were the same in both groups (Rapaport et al., 1994), that levels of IL-2 and IL-3 were the same in both groups (Weizman et al., 1999), that there was an increase in IL-18 levels in PD patients (Kokai et al., 2002), and that there was a decrease in the proliferation response of lymphocytes with production of IL-2 (Koh et al., 2004) in PD patients. Andreoli et al. (1992) reported that mitogen response to phytohemagglutinin and the numbers of T cells were higher in patients with depression and PD than in those with only depression. They also proposed that comorbid PD in depression caused significant changes in immunological parameters. Kim et al. (2004) reported there were no differences among lymphocyte subtypes before treatment with antidepressants despite an increase in the number of T lymphocyte subtypes, including CD3, CD4, and CD8. Additionally, they reported a decrease in the number of B lymphocyte subtypes, including CD19, after 3 months of antidepressant treatment in PD pa-

tients. Hence, they suggested that pharmacological treatment may have affected the immunological functioning in the PD patients.

Adenosine deaminase (ADA) and dipeptidyl peptidase IV (DPP IV), which are involved in the activation of T lymphocytes and formation of cellular immunity, are enzymes needed to maintain normal immune responses. DPP IV is an exopeptidase that catalyzes the hydrolysis of the N terminal dipeptides of peptide chains, which contain proline or alanine next to the last position of the chain. DPP IV is found in nearly all mammalian tissues, such as the thyroid gland, lungs, spleen, liver, bone marrow, and intestines, but its activity mainly takes place in Th lymphocytes. Lymphocytic DPP IV is indicative of total serum DPP IV activity and serum DPP IV originates in T lymphocytes (Elgün et al., 1999a). Many cytokines, chemokines, and growth factors have N terminal sequences that contain proline or alanine next to the last position of their chains, which are sensitive to DPP IV; therefore, DPP IV has a role in the hydrolysis of many biological peptides involved in T cell-mediated immune response. The hydrolysis of peptides by DPP IV may result in an increase, decrease, or other changes in the activity of the peptide (Van West et al., 2000; Elgün et al., 1999a; Maes et al., 1991). Inhibition of DPP IV inhibits the production of IL-2, IL-10, IL-12, and interferon- γ (IFN γ), which in turn impairs the activation and proliferation of T cells (Elgün et al., 1999b). DPP IV is called CD-26 when it is bound to the cell membranes of lymphocytes, and it plays a role in the activation of T cells and the production of cytokines (IL-2 and IFN α). That is to say, DPP IV is recognized as CD-26 in the hematopoietic system (Van West et al., 2000). DPP IV levels were lower in immune-suppressed patients and those with autoimmune diseases, such as rheumatoid arthritis, autoimmune chronic hepatitis, and systemic lupus erythematosus (Van West et al., 2000; Elgün et al., 1999b; Maes et al., 1996).

ADA is an enzyme involved in purine metabolism and it catalyzes the hydrolytic deamination of adenosine and deoxyadenosine into inosine and deoxyinosine, respectively. It plays a role in the development and functioning of T lymphomonocytes (Da Cunha, 1991). Levels of this enzyme increase during the mitogenic and antigenic response of lymphocytes, whereas ADA inhibitors limited the blastogenesis of lymphocytes; thus, ADA levels are higher in T cells than in B lymphocytes (Herken et al., 2006). ADA was previously recognized as a cytosolic enzyme; however, it is currently known to be present at the surfaces of cells, in particular T lymphocytes, to interact

Table I. Sociodemographic characteristics of the patients and controls.

	Patient (n=33)	Control (n=24)	
Age (Mean $\pm$ SD)	39.3 $\pm$ 12.9	32.9 $\pm$ 9.1	p<0.05
Duration of the education (years) (Mean $\pm$ SD)	11.0 $\pm$ 4.2	12.7 $\pm$ 3.4	p>0.05
Gender			
Female	22 (66.7%)	15 (62.5%)	p>0.05
Male	11 (33.3%)	9 (37.5%)	
Marital status			
Married	22 (66.7%)	17 (70.8%)	
Single	9 (27.3%)	7 (29.2%)	p>0.05
Widower/divorced	2 (6.1%)	0 0	
Occupational status			
Housewife/not working	13 (39.4%)	5 (20.8%)	
Working	14 (42.5%)	14 (58.4%)	p<0.05
Student	3 (9.1%)	2 (8.3%)	
Other	3 (9.1%)	3 (10.5%)	

with some membrane proteins, including CD-26/DPP IV, and is considered an ecto-enzyme. This co-localization of DPP IV/CD-26 and ADA at T cells is important for the activation of T cells because the interaction of ADA and CD-26 at the T cells results in co-stimulatory signs responsible for the activation of the T cell receptor (Elgün et al., 2001).

DPP IV activity in psychiatric patients was previously investigated and reported to be lower in patients with depression (Herken et al., 2006; Rapaport et al., 1994; Maes et al., 1991; Livnat et al., 1985). In addition, it was reported that in patients receiving interferon treatment DPP IV levels decreased, symptoms of depression were observed, and the severity of depressive symptoms were negatively correlated to DPP IV levels (Maes et al., 2004, 2001a, 2001b). Studies related to ADA levels in psychiatric patients are virtually non-existent. Elgün et al. (1999b) reported that ADA levels decreased in patients with depression, whereas Herken et al. (2006) reported that ADA levels increased in PD patients.

To the best of our knowledge, the present study is the first to investigate the level of both ADA and DPP IV in PD patients; therefore, we consider the study important because it is unique, facilitates additional research, and clears the path for further exploration of the immunopathogenesis of PD. This study aimed to explore whether the levels of ADA and DPP IV (enzymes related to T cells) are different in PD patients with panic disorder and whether the immune systems in these patients are impaired.

METHOD

Sample

The study sample consisted of 33 patients that presented to the psychiatry department of the medical faculty of Ankara University between June 2004 and December 2005, and were diagnosed with PD according to the DSM-IV. Inclusion criteria were 18-65 years of age, no use of psychotropic drugs during the previous month, and no use of any drugs during the previous 15 days. Patients with an Axis-I disorder were excluded from the study after a psychiatric evaluation. The control group consisted of 24 healthy individuals that were age-, gender-, and sociodemographically-matched with the patient group.

Instruments

A sociodemographic data collection form, and the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I), Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) were administered to both the patients and the controls.

The sociodemographic data collection form gathered such information as name, age, gender, marital status, occupation, place of residence, etc.

The SCID-I is used for diagnosing major DSM-IV Axis-I disorders and is a structured clinical interview scale. This scale, developed by First et al. (1997), was adapted to Turkish by Çorapçıoğlu et al. (1999) who

Table II. ADA and DPP IV levels in the patients and controls.

	Patient	Control	
ADA	17.98 ± 3.43	13.79 ± 2.86	P < 0.001
DPP IV	30.48 ± 26.50	26.50 ± 4.36	P < 0.05

then studied its reliability. SCID-I was developed in order to standardize assessment, to increase the reliability of diagnoses, to facilitate the application of DSM-IV diagnostic criteria, to increase the validity of diagnoses, and to systematically explore some symptoms that would otherwise could be overlooked.

HAM-D is a scale that measures the level and severity of depression. It contains 17 items, each of which is scored between 0 and 4 points. HAM-D was developed by Hamilton (1967), and the validity and reliability study of its Turkish form was carried out by Akdemir et al. (1996).

HAM-A measures the level of anxiety, symptom variation, and changes in the severity of anxiety. HAM-A was developed by Hamilton (1959), and the validity and reliability study of its Turkish form was carried out by Yazıcı et al. (1998). The scale contains 14 items, each of which is scored between 0 and 4 points.

PROCEDURE

The aims and procedures of the study were explained to the subjects, and those that gave informed consent were included in the study. The ethical review board of the Medical Faculty of Ankara University approved the study. After all the subjects were psychiatrically evaluated and administered the scales by the first author of this article, blood samples were collected for routine laboratory examinations (complete blood count, biochemical parameters, thyroid function) and electrocardiograms (ECGs) and urine examinations were performed. The psychiatric evaluations and blood collection were carried out after a panic attack. Venous blood samples (5 cc) were taken into test tubes containing citrate, centrifuged at 3500 rpm for 5 min, and then the plasma was extracted for biochemical examination. Blood plasma was frozen at -20 °C. After the all samples were collected, the measurements were carried out between June 2004 and December 2005. Serum levels of ADA and DPP IV were measured spectrophotometrically and the results are expressed in IU/l (Oosthuizen et al., 1993; Nagatsu et al., 1976).

Analysis

Data analysis was carried out using the SPSS for Windows v.11.5 software package. We used Student's t-test for metric data and the chi-square test for categorical data when comparing the patient and control groups; in the analyses of the factors affecting the values of HAM-D, HAM-A, ADA, and DPP IV, we used Student's t-test for categorical data and Pearson's correlation analysis for metric data. Statistical significance was determined to be P = 0.05.

RESULTS

The sociodemographic characteristics of the patient and the control groups are presented in Table I. While there was a significant difference in age and occupational status between the patients and the controls (P < 0.05), the differences in education, gender, and marital status were not significant (p>0.05).

The duration of PD varied between 1 and 120 months. In all, 13 (40.6%) of the PD patients presented during their first panic attack and 19 (59.4%) presented during recurrent attacks. Agoraphobia was associated with PD in 25 patients (75.8%). Mean HAM-D and HAM-A scores of the PD patients were 3.09 ± 1.940 and 9.81 ± 5.899, respectively.

The levels of both enzymes were significantly higher in the PD patients than in the controls (P < 0.001 for ADA and P < 0.05 for DPP IV). The values of both enzymes in the patient and control groups are shown in Table 2, and their distributions are shown in Figures I and II.

There were no significant differences between the sociodemographic variables (age, gender, and education years) and the levels of the enzymes (P > 0.05).

The levels of the enzymes did not correlate with duration of PD, the presence of agoraphobia, the presence of stressors, total number of panic attack symptoms, or HAM-D and HAM-A scores (P > 0.05). Furthermore, the enzymes' levels did not correlate with each other (P > 0.05).

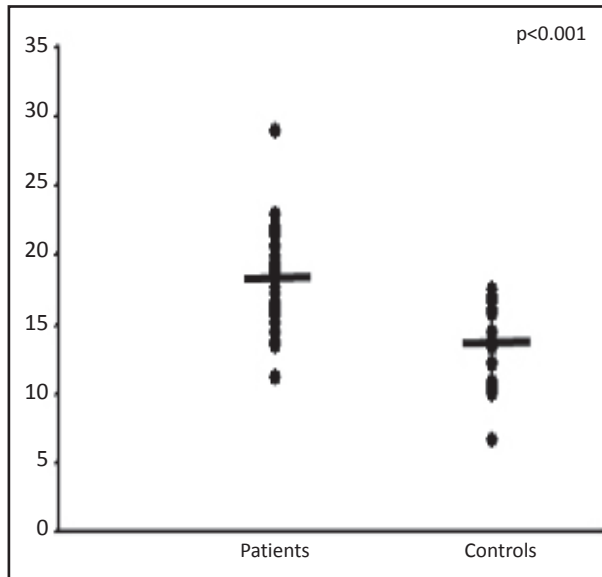


Figure I. Distribution of ADA levels in the patients and controls.

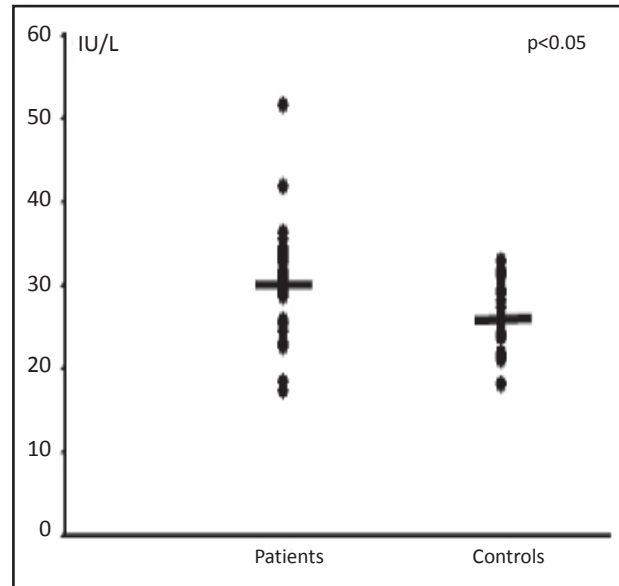


Figure II. Distribution of DPP IV levels in the patients and controls.

DISCUSSION

In the present study we examined ADA and DPP IV levels in PD patients and healthy controls, and investigated the relationships between the enzymes' levels, and sociodemographic variables, PD symptoms, and HAM-D and HAM-A scores. The goal of the study was to determine the levels of ADA and DPP IV, which both play important roles in the development of normal immune responses in PD patients, particularly cellular immunity. Thus, it was thought that the study would contribute to the understanding of the pathophysiology of PD.

We found that the levels of ADA and DPP IV in PD patients were significantly higher than in healthy controls. This finding is similar to Herken et al.'s (2006), who reported that the levels of ADA were high in PD patients. On the other hand, Elgün et al. (1999b) reported that ADA levels were low in patients with depression, whereas DPP IV levels were low in patients with major depression (Herken et al., 2006; Rapaport et al., 1994; Maes et al., 1991; Livnat et al., 1985) and in those that developed depression following interferon treatment (Maes et al., 2004, 2001a, 2001b).

The studies that found the DPP IV levels to be low in patients with depression suggest that their immune systems were impaired. In this respect it is possible that the increased DPP IV levels in PD patients observed in the present study is indicative of increased cellular immunity, but we do not have appropriate data to support this thesis. Much of the immunological changes in hu-

man organism are nonspecific and reflect an intermediate period of immune response, rather than the last point. For this reason, any changes in a particular segment of the immune cascade may not solely be evidence of a significant change in immune processes. For instance, Hildebrandt et al. (1999) noted that the increase in serum levels of DPP IV they observed in anorectic patients compensated for a decrease in the number of CD-26 positive cells. Therefore, further studies are needed to determine which segments of the immune system are reflected by increased levels of these enzymes.

In the present study we did not find any significant relationships between the levels of the enzymes, and age, gender, level of education, duration of PD, presence of agoraphobia, presence of stressors, or HAM-D and HAM-A scores; however, it was determined that the decreased levels of DPP IV correlated with the severity of depression (Maes et al., 2001a, 1991; Elgün et al., 1999).

The reason for the low HAM-D scores in the patient group was that we excluded patients with depression. The reason for the low HAM-A scores in the patient group was that we evaluated the patients after panic attacks and that the patients negatively answered the questions related to symptoms of perceived general anxiety. As such, it may be advised that future studies use scales specific to PD. Another reason for the decreased anxiety scores in our study is that the scales were administered after psychiatric assessments, and these assessments could reduce the severity of anxiety symptoms, to some degree.

In the present study a significant difference between the ages of the patient and the controls was observed ($P < 0.05$). When we searched the literature for evidence of relationships between the 2 enzymes and age, we found 2 studies; one of which showed that ADA levels did not changed with age in rats (Mackiewicz et al., 2006) while the other showed that DPP IV levels measured in the dental plaque of patients who refer dentists, increased with age (Hu et al., 1999). Since we did not find more comprehensive and detailed information about this topic, the difference between our study groups was considered a confounding variable.

One of the limitations of the present study is that we did not consider smoking. It is suggested that smoking can affect the immune system and it was found that smoking was related to B lymphocytes and other measures of the immune system (Schleifer et al., 2002). Another limitation is that the assessments and blood collection were carried out when the patients presented to the hospital and that the circadian rhythm was not considered similar to controls, therefore, the levels of the enzymes in the collected samples from the individuals being constant for 24 hours are debatable. Furthermore, the studies conducted with PD patients were carried out in the absence of panic attacks, in contrast to studies on mood and other anxiety disorders. For this reason it is not known whether the temporary changes in the immune systems of the PD patients were the direct result of panic attacks.

We encountered some difficulties during the study. One of these is that PD patients often have comorbid depression and the fact that we excluded patients with

depression it was hard to find PD patients without depression. PD patients with a medical illness that could affect the levels of the enzymes were not included in the study. Both conditions limited the number of cases included in the study. Another factor that limited the number of patients in the study was the exclusion of patients that used any drug that could affect the immunological parameters we measured. Patients previously diagnosed with PD often apply to hospital after using anxiolytic drugs after a panic attack. Because we did not know how these drugs affect the levels of the enzymes these patients were not included in the study; however, the use of a patient sample diagnosed only with PD and no additional medical illnesses or drug use could be characterized as the strength of the study.

Consequently, we explored whether serum levels of ADA and DPP IV (enzymes related to T cells) were different in PD patients and determined that the levels of both enzymes were higher in these patients than in the controls. These results suggest that there might be a disturbance related to cellular immune system functioning in PD patients. The high levels of the 2 enzymes may be indicative of changes in immune response in PD, but in order to completely explain the role of these changes in the process of PD further studies are needed. For future studies it is suggested that they: include larger study populations, control the smoking (both in patients and controls), and collect blood samples from subjects at appropriate times, preferably in the morning, consistent with the diurnal rhythm. We think that studies aimed at exploring the immunopathology of PD will result in the emergence of data useful to the field of psychoneuroimmunology.

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