



# Plasma catecholamine levels before and after paroxetine treatment in patients with panic disorder



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## ABSTRACT

Catecholamines such as norepinephrine, epinephrine, and dopamine are closely related to the autonomic nervous system, suggesting that panic disorder may involve elevated catecholamine levels. This study investigated basal and posttreatment catecholamine levels in patients with panic disorder. A total of 29 patients with panic disorder and 23 healthy controls participated in the study. Panic disorder patients received paroxetine treatment for 12 weeks after clinical tests and examination had been conducted. We investigated the difference in basal levels of catecholamine and measured the changes in catecholamine levels before and after drug treatment in panic disorder patients. The basal plasma epinephrine ( $48.87 \pm 6.18$  pg/ml) and dopamine ( $34.87 \pm 3.57$  pg/ml) levels of panic disorder patients were significantly higher than those ( $34.79 \pm 4.72$  pg/ml and  $20.40 \pm 3.53$  pg/ml) of the control group. However, basal plasma norepinephrine levels did not show statistically significant differences between patients and controls. After drug therapy, plasma catecholamine levels were nonsignificantly decreased and norepinephrine levels showed a tendency toward a decrease that did not reach significance. In conclusion, this study suggests the possibility of a baseline increase of plasma catecholamine levels and activation of sympathetic nervous systems in patients with panic disorder which may normalize after treatment with paroxetine.

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## 1. Introduction

Panic disorder is a kind of anxiety disorder that is characterized by unexpected and repeated panic attacks which are abrupt surges of intense fear or intense discomfort that reach a peak within minutes, and that are followed by anticipatory anxiety and phobic avoidant behavior as characterized in the DSM-5 (American Psychiatric Association, 2013). Although abnormalities in various neurotransmitter systems have been found in panic disorder, catecholamines such as norepinephrine, epinephrine, and dopamine are regarded as the key neurotransmitters involved in the pathophysiology of panic disorder.

Previous studies that directly measured plasma levels of catecholamine and urinary levels of the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG) in patients with panic

disorder found inconsistent results. Some studies reported an increase in plasma epinephrine (Nesse et al., 1984; Villacres et al., 1987) and urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels (Garvey et al., 1987) in patients with panic disorder, whereas other studies showed no change in baseline plasma norepinephrine (Stein et al., 1992) and MHPG levels (Uhde et al., 1988). Regarding the role of dopamine in panic disorder, previous studies that examined the plasma dopamine level (Roy-Byrne et al., 1986; Schneider et al., 1987) and cerebrospinal fluid levels of the dopamine metabolite homovanillic acid (HVA) (Eriksson et al., 1991; Johnson et al., 1994) did not find significant results. However, studies using dopamine agonists including apomorphine (Pitchot et al., 1992) and cocaine (Anthony et al., 1989) suggested abnormalities in the dopamine neurotransmitter system as a possible etiology of panic disorder. As far as we know, no previous studies have investigated plasma catecholamine levels before and after treatment of panic disorder.

The present study assessed whether the basal levels of catecholamines, such as epinephrine, norepinephrine, and dopamine, were higher in panic disorder patients, compared with levels in normal

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control subjects, and whether the abnormal catecholamine levels in panic disorder patients were significantly decreased after 12 weeks of paroxetine treatment.

## 2. Methods

### 2.1. Subjects

Twenty-nine patients, aged 20–60 years (14 men, 15 women; mean age 41.40 years) who met the criteria for panic disorder using the Anxiety Disorder Interview Schedule for DSM-IV (ADIS-IV) (Brown et al., 1994) were recruited for the study. All patients had scores < 17 on the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and their onset of illness was less than 1 year. Major medical illnesses (uncontrolled hypertension and diabetes, myocardial infarction, and stroke) or major psychiatric illnesses (schizophrenia, bipolar disorder, alcohol and drug dependence, organic mental disorder, and personality disorder), high risk of suicide, pregnancy, and lactation were exclusion criteria. Twenty-three normal healthy subjects, aged 20–60 years (10 men, 13 women; mean age 42.04 years), were recruited by a local advertisement. After participants were given a complete description of the study, written informed consent was obtained. This study was approved by the Institutional Review Board of Samsung Medical Center.

### 2.2. Efficacy assessment and medication

The psychological assessment scales administered in the patient group included the HAM-D, HAM-A (Hamilton Rating Scale for Anxiety) (Hamilton, 1959), and PDSS (Panic Disorder Severity Scale) (Shear et al., 1997). After being evaluated with the psychological scales, the patients were treated with controlled release paroxetine for 12 weeks and were permitted to receive alprazolam for 1 month. The dosage of paroxetine was adjusted by a clinician from 12.5 mg to 50 mg per day according to the degree of clinical symptoms and side effects in each patient. After 12 weeks of treatment, the mean daily dose of paroxetine used in the patients was 29 mg. Other treatment modalities such as cognitive behavioral therapy and psychotherapy were not administered.

### 2.3. Plasma catecholamine measurements

All subjects were requested to maintain their regular eating patterns for the study period. However, they were prohibited from drinking caffeinated beverages and alcohol for at least a day before the blood test. Subjects also fasted for 12 h before the test and were not allowed to smoke on the test day. Blood sampling for women was timed to avoid the menstrual period, to eliminate interference of female sex hormones with plasma catecholamine levels. Measurements were conducted at the same time to control the effect of possible daytime variations of catecholamine levels. To reduce changes in catecholamine levels due to external factors such as stress, an intravenous heparin lock was placed for the blood test at 8:00 am on the day of the visit, and subjects were told to rest by lying down and listening to music for 30 min before blood sampling was conducted.

### 2.4. Statistical analyses

We applied  $\chi^2$  test, Student's *t*-test, and Mann–Whitney *U*-test to determine differences between demographic variables and psychological rating scales between the patient group and the control group (two-tailed). Analysis of covariance (ANCOVA) was applied to determine differences between catecholamine levels between the patient group and the control group for purposes of adjusting the potential confounding variables such as age, sex and body-mass index. Student's paired *t*-test was used to compare the plasma epinephrine and norepinephrine levels in the patients before and after 12 weeks of paroxetine treatment. Because plasma dopamine levels were not normally distributed, Wilcoxon's signed rank test was used. Pearson's correlation analysis and Spearman's correlation analysis were performed to examine the correlation between scores of psychological scales and plasma catecholamine levels. All statistical tests were conducted using SPSS version 16.0 (SPSS, Chicago, IL, USA). A *p*-Value of < 0.05 was considered significant.

## 3. Results

### 3.1. Baseline characteristics of subjects

There was no difference in age, gender and body-mass index between the patient group and the control group (Table 1). The panic disorder patients had significantly higher mean scores on

the HAM-A and HAM-D than the control subjects (Table 1). Among the 29 patients, 18 patients (62.1%) completed the study, while 11 patients dropped out during the study (one patient withdrew agreement for study participation, another dropped out due to an underlying heart disease, and another nine patients omitted their follow-up visit without any notice). The completers showed no significant difference in basal serum catecholamine levels, demographic variables, and scores on the HAM-A and HAM-D, and PDSS psychological scales compared with the dropout patients.

### 3.2. Baseline catecholamine levels

The mean of basal plasma epinephrine level was significantly higher in the patient group than the control group ( $48.87 \pm 6.18$  vs.  $34.79 \pm 4.72$  pg/ml,  $p=0.032$ ). The mean basal plasma dopamine level was also higher in the patient group than the control group ( $34.87 \pm 3.57$  vs.  $20.40 \pm 3.53$  pg/ml,  $p=0.008$ ). The mean basal plasma norepinephrine levels tended to be higher in the patient group than the control group ( $263.58 \pm 18.35$  vs.  $215.09 \pm 17.28$  pg/ml,  $p=0.051$ , NS) (Table 1).

### 3.3. Changes of catecholamine levels and psychological scales after treatment

Panic disorder patients showed significant improvement on the HAM-A ( $15.50 \pm 1.82$  vs.  $6.72 \pm 0.94$ ,  $p < 0.0001$ ), HAM-D ( $11.67 \pm 1.24$  vs.  $4.67 \pm 0.82$ ,  $p < 0.0001$ ), and PDSS ( $12.17 \pm 1.28$  vs.  $2.50 \pm 0.55$ ,  $p < 0.0001$ ) after paroxetine treatment (Table 2). After paroxetine treatment, panic disorder patients tended toward a decrease in mean plasma norepinephrine levels ( $262.61 \pm 24.71$  vs.  $209.84 \pm 22.19$  pg/ml,  $p=0.06$ , NS), but did not show even a trend toward a significant decrease in the mean plasma epinephrine and dopamine levels (Table 2).

## 4. Discussion

In this study, we measured peripheral catecholamines. It is known that peripheral catecholamines do not cross the blood–brain barrier in physiologically significant amounts (Oldendorff, 1971; MacKenzie et al., 1976; Oleson et al., 1978) and they result from sympathetic nervous system activation (Wallin, 1984). Maas et al. (1984) suggested a close coupling of functional activity of the sympathetic nervous system and the catecholamine systems in the central nervous system (Maas et al., 1984). Thus, we considered peripheral catecholamines as a reflection of the activity of central catecholamine neurons.

In this study, the mean basal plasma epinephrine level in panic disorder patients was higher than that in control subjects, a difference that remained after 12 weeks of paroxetine treatment. However, the basal plasma norepinephrine level did not differ between panic disorder patients and control subjects. These findings are similar to the results of earlier studies (Villacres et al., 1987; Wilkinson et al., 1998). Considering the fact that epinephrine is mainly released from the adrenal medulla into the bloodstream, whereas norepinephrine is released from postganglionic sympathetic nerves into the bloodstream, these findings suggest a possibility that the sympathetic nervous system in the adrenal medulla is more activated, compared with postganglionic sympathetic nerves in panic disorder patients (Villacres et al., 1987; Wilkinson et al., 1998).

The mean basal plasma dopamine level in the panic disorder patients was also higher than that of control subjects, a difference that did not change after the treatment. There have been a few studies on the role of dopamine in panic disorder. Stein et al. reported a high incidence of panic disorder in patients with Parkinson's disease (Stein et al., 1990). Panic attacks are known to usually occur in the off phase of fluctuations in Parkinson's

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