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Low plasma dopamine-b-hydroxylase activity in patients with panic disorder

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Decreased plasma dopamine-b-hydroxylase activity in a group of patients with panic disorder was found as compared with the groups of patients with generalized anxiety disorder and healthy controls.

Key words: panic disorder, plasma dopamine-β-hydroxylase

Introduction

Panic disorder, like most mental disorders, is of multifactor etiology. Genetic background as well as the factors connected with psychoaffective development form the basis [13], which is activated in a specific psychobiological situation of the patient. This is manifested in a panic attack, in the picture of which the symptoms connected with dysfunction of peripheral autonomous nervous system come to the foreground. The presence of these symptoms at so great an intensity and so large a number, is a distinctive feature of the panic disorder. Many of these symptoms correspond with activation of the peripheral noradrenergic (sympathetic) system [17]. Generally, it is assumed that activation of the peripheral sympathetic system in panic disorder is of central origin. Noradrenergic system of locus ceruleus [2] as well as the central serotoninergic system [6], or other systems (gabaminergic, cholecystokininergic) are supposed to be responsible for it. Some authors claim that changes in the peripheral sympathetic system should occur in patients with panic disorder. Numerous investigations regarding this system have been conducted. The examined area included physiological and metabolic effects of agonists and antagonists of catecholaminergic systems, adrenaline and noradrenaline concentration in blood plasma at rest and after a provoked panic attack. The results of these investigations are not univocal and do not allow for a definite opinion regarding the condition of the sympathetic system in

patients with panic disorder [12].

An important role in the noradrenergic system functioning is played by dopamine-β-hydroxylase (DBH), which is an enzyme catalyzing the process of dopamine transformation into noradrenaline. It is found in synaptic vesicles of noradrenergic neuron endings and in chromaffine cells of adrenal glands. Noradrenaline release from synaptic endings or adrenaline release from chromaffine granules is an exocytosis process, and is accompanied by secretion of dopamine-β-hydroxylase. This enzyme is transferred to blood plasma. Its concentration is considered to be an indicator of peripheral sympathetic nervous system activity [4]. This relation, however, is not always observed [5].

Increased activity of the enzyme was detected in blood plasma of patients in the initial phase of primary hypertension [14]; decrease of its activity was detected in endogenous depression [11]. In literature survey, we did not find any reports concerning activity of plasma dopamine-β-hydroxylase in patients with panic disorder.

Material and method

The examination covered the following groups of patients (diagnosed according to the DSM-III-R criteria):

1) patients with the diagnosis of panic disorder – 16 persons (7 women, 9 men);
2) patients with the diagnosis of generalized anxiety disorder – 10 persons (6 women, 4 men);
3) patients with the diagnosis of hypochondriasis – 16 persons (12 women, 4 men).

Control group consisted of 12 women and 8 men (20 persons), mentally and somatically healthy.

As regards age, there were no statistically significant differences between groups. Mean age in particular groups was as follows: 1) 29.4 ± 4.6; 2) 33.2 ± 5.8; 3) 34.3 ± 6.5 years; in the control group – 30.6 ± 7.2. Duration of illness in the patients with panic disorder was no longer than one year; in the patients with hypochondriasis it amounted to 2–4 years.

Only somatically healthy persons were qualified for the study. Special attention was paid to arterial blood pressure. All persons whose blood pressure assumed borderline values and those in whose families hypertension occurred were eliminated from the study. Only those persons who had not taken any drugs for two weeks prior to the examination (in case of fluoxetine – 5 weeks) were qualified for groups. The blood test was performed after at least four days from the latest panic attack.

Blood samples of 0.5 – 1.0 ml were taken before eating, at 8.00 a.m., from the elbow vein. DBH activity was determined in two blood samples using spectrophotometric method [8] with tyramine as a substrate. The activity was expressed in IU/l.

Results

Except the group of patients with panic disorder, in all remaining groups the distribution of the enzyme activity was normal (Kolmogorov-Smirnov test: $p < 0.05$). Mean values (± standard deviation) of plasma activity of DBH are presented in figure 1. The lowest enzyme activity was detected in the group of panic disorder (9.3 ± 12.5

IU/l). The activity was higher in the group of hypochondriasis (13.6 ± 10.6 IU/l), much higher in the patients with generalized anxiety disorder (17.6 ± 13.5 IU/l). The highest

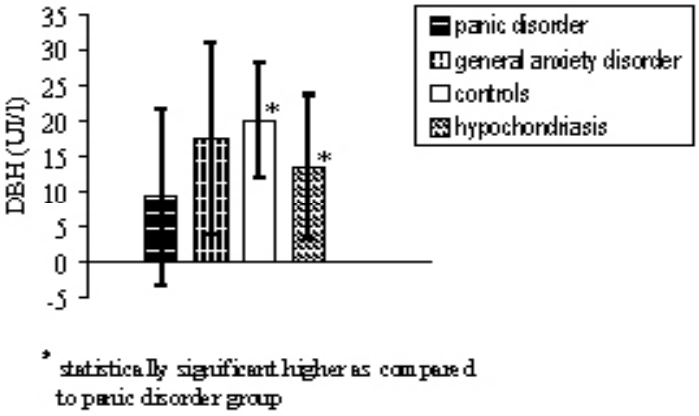

Fig. 1. **Plasma dopamine-β-hydroxylase (DBH) activity**

enzyme activity was found in the control group (20.1 ± 8.1 IU/l).

Mean activity of DBH in the group of patients with panic disorder was statistically significantly lower (Mann-Whitney test) as compared with the following groups: controls (p = 0.0001), generalized anxiety disorder (p = 0.0140) and hypochondriasis (p = 0.0379). In comparison with the control group, statistically significantly lower values of mean activity of DBH (t-Student test) were detected also in the group of patients with hypochondriasis (p = 0.045). No statistically significant differences were found (Mann-Whitney test) between females and males within any of the examined groups (table 1), though in all these groups enzyme activity was higher in females.

Table 1

Dopamine–β–hydroxylase activity (IU/l) vs. Sex

Group	Women	Men
Control	21.2 ± 10.2	16.5 ±6.4
Panic disorder	13.7 ± 16.3	5.9 ±3.1
Generalized anxiety disorder	19.4 ± 15.7	13.0 ±9.8
Hypochondriasis	15.1 ± 11.6	9.3 ±5.8

This difference was particularly related to the group of panic disorder.

Discussion

We detected a significant decrease of plasma DBH activity in the group of patients with panic disorder, as compared with the groups of healthy controls; patients with generalized anxiety disorder and patients with hypochondriasis. The significantly

different values of DBH activity in the group of patients with panic disorder and that with generalized anxiety disorder indicate biologically different character of these two disorders.

Interpretation of the detected decrease of DBH activity in patients with panic disorder in the light of other studies is not easy. We can pose three hypotheses.

Firstly, the decrease of enzyme activity may be a manifestation of the diminished function of the presynaptic part of the peripheral noradrenergic system. This statement seems to be surprising. With regard to symptoms, we are rather inclined to associate panic attacks with hyperfunction of the sympathetic system. This, however, need not apply to its presynaptic part. Presynaptic noradrenergic hypofunction may lead to adaptive hypersensitivity of postsynaptic receptors. These hypersensitive receptors would overreact to little changes in the synaptic transmission, or even to non-specific stimuli, which would lead to periodical occurrence of vegetative symptoms of panic attack. Thus panic attack need not necessarily be connected with the increase of noradrenergic presynaptic activity. Lack of catecholamine increase after a spontaneous panic attack (cit. after [2]) supports this view. An increase of peripheral postsynaptic β receptor sensitivity was observed [10]. The drugs effective against panic attacks cause a decrease of β receptor density [15]. It must be stressed, however, that a decrease of β receptor sensitivity was also observed in patients with panic disorder [9]. Besides, determination of adrenaline and its metabolites concentration in plasma, or their 24-hours secretion with urine, which are regarded as indicators of presynaptic noradrenergic activity, did not show any differences as compared with a group of healthy controls (cit. after [2]). This did not provide a proof of a decreased peripheral presynaptic noradrenergic activity. Therefore, the hypothesis discussed above does not have a complete confirmation.

Another interpretation is based on the observation [5] that a chronic hyperactivity of the sympathetic system may lead to DBH deficit in nerve endings, and, therefore, to a decreased concentration of this enzyme in the blood plasma. Its decrease in the group of patients with panic disorder, as we showed, would be a result of a long-term hyperactivity of the presynaptic part of the peripheral noradrenergic system. The decreased sensitivity of postsynaptic receptors : α_2 (decreased secretion of somatotrophic hormone after stimulation with clonidine – [3]) and β [9] (as it was mentioned before, an increase of receptor sensitivity was also reported) detected in some cases may be treated as a secondary adaptive change. However, the above mentioned normal values of adrenaline and its metabolites concentrations do not support the hypothesis of either increased or decreased presynaptic noradrenergic activity.

The facts presented above do not provide a clear and unambiguous picture of peripheral noradrenergic synapse functioning in patients with panic disorder. This is why some authors speak generally about the hard to define dysregulation of synaptic activity [3]. Maybe, the functional state of synapse depends on the phase of disorder or an extension of participation of particular factors in etiology of this undoubtedly multifactorial and probably heterogeneous syndrome.

Plasma DBH activity is under genetic control [7]. This is the basis for our third interpretation, which does not exclude any of the previous ones. The decreased enzy-

me activity was detected in depressive disorder [11]. In the present study we found it in patients with panic disorder as well as in those with hypochondriasis. Maybe, then, it could be treated as a non-specific marker of predisposition for occurrence of some psychiatric disorders. There is some relation between the panic disorder and the depressive disorder. They are often comorbid [1] and seem to be genetically interconnected [16]. In our group of patients with panic disorder we have not found comorbid depression (the group consisted of young persons with short duration of illness) or family history of affective disorder.

The examined group of patients with panic disorder was heterogeneous as regards plasma DBH activity – there was no normal distribution of enzyme activity. This concerns mainly the subgroup of women, where particularly high value of standard deviation was stated, and mean value was relatively high. Thus, we may assume that the decrease of plasma DBH activity is not a necessary and sufficient condition for the occurrence of panic disorder. This statement seems to refer, first of all, to women.

The decreased DBH activity in plasma of patients with hypochondriasis is an interesting finding. We know little about the biological determinants of this disorder. Detection of this dysfunction may be an essential starting point for further research.

Conclusions

1. The group of patients with panic disorder, particularly the subgroup of men, was characterized by a diminished dopamine-β-hydroxylase activity in plasma. The pathogenic meaning of this fact remains obscure.
2. The significant difference in plasma dopamine–β-hydroxylase activity between the groups of patients with panic disorder and those with generalized anxiety disorder indicates a biological difference between these disorders.
3. The diminished activity of plasma dopamine-β-hydroxylase in the group of patients with hypochondriasis inclines us to seek its biological determinants.

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