ORIGINAL ARTICLE

Dopamine beta hydroxylase (DBH) plasma activity in childhood mental disorders

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Abstract

BACKGROUND: Developmental study of dopaminergic and noradrenergic systems in child psychiatric disorders are rare. DBH activity is one of noradrenergic biochemical marker that is correlate in psychiatry to clinical and genetic data.
OBJECTIVES: The main aim of the present study was to measure DBH activity at the onset of acute schizophrenia and depressive disorder in children and adolescents without pharmacological treatment and to compare these values with DBH activity in healthy controls. The authors also investigated untreated ADHD children.
METHODS: We examined 42 control healthy children, 15 children non-treated with acute schizophrenia, 15 non-treated children with acute depressive disorders and 30 non-treated ADHD children, all in age 7–14. Plasma DBH level was provided by Nagatsu (1972; 1974). Depressed children were reexamined after clinical remission.
RESULTS: DBH activity is statistically significantly decreased in non-treated depressive disorder and ADHD in children and adolescents. DBH activity is normalised during antidepressant therapy in child depression. Child schizophrenia patients present with normal DBH activity.
CONCLUSION: These results are similar to the results that have been observed in adult patients with schizophrenia and depression and in previous studies of DBH activity in children with ADHD. These results also indicate hypoactivity of the noradrenergic system in children with ADHD and depression.

Abbreviations :

5-HIAA	- 5-hydroxyindoleacetic acid
CDI	- Children Depression Inventory
CPQ	- questionnaire for parents
CPRS	- Children Psychiatric Rating Scale
DBH	- dopamine-beta-hydroxylase
HMA	- homovanillic acid
VMA	- vanillylmandelic acid

INTRODUCTION

As previously described in primates by Lewis *et al.* (1992), only noradrenergic neurons in the cortex contain dopamine beta hydroxylase (DBH) enzyme. Dopaminergic neurons do not contain this enzyme. DBH is an enzyme responsible for the conversion of dopamine into noradrenaline. Noradrenaline inhibits tyrosine hydroxylase, which reduces the production of dopamine. The DBH holoenzyme is a homotetramer composed of 602 amino acids. Its gene (9q34) exists as a single gene in the genome. The level of DBH in plasma and cerebrospinal fluid (CSF) is a stable, heritable trait. The DBH gene has been shown to be the major locus influencing the level of DBH (Cubells *et al.* 2000; Wigg *et al.* 2002). The alleles of several polymorphisms identified for the DBH locus have been found to be associated with serum DBH levels, suggesting that these alleles condition DNA variants controlling the function or expression of this gene. In the DBH gene, the G444A, G910T, C1603T, C1912T, C-1021T, 5´-ins/del and TaqI polymorphisms occur frequently and may affect the function of gene products or modify gene expression. Thus, these polymorphisms influence the level and activity of DBH. Reduced DBH activity is caused by decreased levels of circulation of the DBH protein, rather than by decreased activity of the enzyme. However, which polymorphisms play the main role in this process remains unknown. It could be the ones in the coding region (C-1021T, 5´-ins/del), or those in the regulation (G444A, G910T, C1603T, C1912T) or non-coding region (TaqI) (Cubells *et al.* 1998; Ishii *et al.* 1991; Tang *et al.* 2005; Zabetian *et al.* 2001).

Genetic determination of DBH activity is one of the main factors influencing its activity. Acquired neurobiological or psychosocial risk factors could also cause the same or similar abnormalities (Gerring *et al.* 1998). One related question is the correlation between low DBH activity and prenatal hypoxia. Koudelová *et al.* (1989) found that hypoxia achieved in a hyperbaric chamber decreased DBH activity in experimental animals, namely rats, particularly in very young ones (5 days after delivery).This time period is considered important in theories of aetiology of ADHD and other neurodevelopmental disorders in child psychiatry.

In response to stimulation of sympathetic nerves and the adrenal gland, DBH and catecholamines are released. It has been observed that subjecting experimental animals and humans to stress causes an increase of this enzyme's activity in the blood (Weinshilboum *et al.* 1973b).

Some authors have reported correlations between decreased DBH plasma activity and a diagnosis of severe depressive disorder (Shopsin *et al.* 1972; Lamprecht *et al.* 1974; Levitt *et al.* 1976; Melzer *et al.* 1976; Lerner *et al.* 1978; Strandman *et al.* 1978; Yu *et al.* 1980; Honecker *et al.* 1981; Puzynski *et al.* 1983a; Puzynski *et al.* 1983b) and increased DBH plasma activity after pharmacological therapy with tricyclic antidepressants (Puzynski *et al.* 1983a; 1983b). The results obtained by Schatzberg *et al.* (1992) and Meyer *et al.* (1999), i.e. low DBH activity in serum of patients with depressive disorders and psychotic symptoms were repeatedly assessed. Similar results were obtained by Sapru *et al.* (1989) in patients with psychotic depression, who have never undergone drug treatment. Meltzer *et al.* (1984) found low DBH levels in the central nervous system (CNS) of patients with depression and atrophy. Rihmer *et al.* (1984) indentified reduced DBH activity in individuals with bipolar disorder type I during a depressive phase. Sofuoglu *et al.* (1995) reported normalization of DBH activity in remitted bipolar patients treated with lithium.

Most studies have not shown any differences in plasma DBH levels between schizophrenic patients and normal controls (Shopsin *et al.* 1972; Wetterberg *et al.* 1972; Dunner *et al.* 1973; Golstein *et al.* 1974; Meltzer *et al.* 1976). Other authors, however, have found elevated (Markianos *et al.* 1976; Wei *et al.* 1992), or reduced values (Baron *et al.* 1980; Fujita *et al.* 1978). In addition, in some schizophrenic patients increased arousal of the sympathetic nerves. It is associated with reduced peripheral and central sensitivity of alpha2 adrenergic receptors (Lake *et al.* l980), that correlate with data showing elevated noradrenaline levels in CSF in some schizophrenic patients (Lake *et al.* 1980). Decreased DBH activity is induced by drug therapy or by the presence of organic damage in the CNS.

There are certain specific features for the diagnostic categories of depressive disorders and schizophrenia common to adults and children. In the case of child depression, the common features are: prominent somatic symptoms, no weight changes, little change in mood (i.e. depressive mood) over 24 hours, absence of late insomnia, prominent psychomotor inhibition, frequent comorbidities in most cases, anxiety symptoms in many cases, and ineffectiveness of tricyclic antidepressants.

Schizophrenia in children and adolescents is often characterized by catatonic, hebephrenic, phobic, obsessive, hypochondriac, depressive and anxious syndromes (Paclt, 1993). These findings highlight the fact that diagnoses of schizophrenia and depressive disorder in children were rarely or inaccurate diagnosed in children. There are not many investigations of biochemical markers in children and adolescents with schizophrenia or depressive disorders (Eberhard *et al.* 1989; Queiroz *et al.* 1991).

In ADHD and in non-socialized conduct disorder reduced DBH level in serum and urine have been reported (Bowden *et al.* 1988; Rogeness *et al.* 1989a; Rogeness *et al.* 1989b; Paclt *et al.* 1990; Gabel *et al.* 1993b; Galvin *et al.* 1995; Galvin *et al.* 1997; Paclt *et al.* 1998). Low DBH levels correlate indirectly with the severity of hyperkinetic syndrome in children (Galvin *et al.* 1995; Galvin *et al.* 1997).

We hypothesized that in child depression and in hyperkinetic disorder DBH activity will decrease because noradrenergic activity is decreased in depression and in ADHD. We also expected that in child schizophrenia without comorbidities DBH activity will not differ from controls.

MATERIAL AND METHODS

Participants

Healthy controls: A check-up sampling of healthy subjects was performed during periodic preventive investigations by general practitioners for children and adolescents. A total of 42 healthy children aged between 7 and 14 years were investigated (male-female ratio was 1:1).

Patients: These patients were examined the first day after admission to a psychiatric ward.

Patients were diagnosed by two independent graduated child psychiatrists using the DSM-IV and the ICD-10, included some scales and structured examinations. Fish's scale CPRS (Children Psychiatric Rating Scale 1985 is structure psychiatric examination for children up to 15 years) – Czech version (Paclt *et al.* 1998a), Kovacs'scale, CDI (CDI, Children Depression Inventory – Kovacs 1985 – is 27 items self report questionnaire with high reliability, internal consistence – 0, 82, validity $p<0.0001$) – Czech version (Paclt *et al.* 1998a), and Conners – CPQ (questionnaire for parents about children with hyperactivity and conduct disorders, Conners 1985) – Czech version (Paclt *et al.* 1998a) . Only children and adolescents, who did not take any psychotropic drugs for ADHD during the first episode of schizophrenia or during the first episode of depression, were included in this study. On the first day of hospitalization children had a clinical examination and a biochemical DBH test.

Patients with a diagnosis of depressive disorder in remission (CDI < 45) were re-examined clinically and tested for DBH activity after 4–8 weeks of therapy by antidepressant, when CDI < 45, after clinical recovery. We examined 15 children (6 boys and 9 girls) with acute schizophrenia aged 7–14 years, using Fish´s scale (CPRS) > 64. We also examined 15 children (8 boys and 7 girls) with depressive disorder aged 7–14 years, using Kovac´s scale (CDI) > 65. A group of 30 children (all boys) with ADHD were examined using the Conner´s scale (CPQ) > 30.

Parents as well as children above 7 years gave informed consent in written form.

Assessment of dopamine beta hydroxylase activity

Samples of human blood were collected and investigated according to the method described by Nagatsu *et al.* (1972, 1974), what is used in all previous papers with this topic.

Statistical processing

For statistical processing Kruska 22-Wallis, Variance Analysis, Bonferroni testing and t-tests were used.

Tab. 1. Dopamin beta hydroxylase activity in children: controls, depressive disorder – acute and remission, acute schizophrenia, and ADHD.

Diagnoses, disorder's course patients	Number	DBH act.	Standard deviation
Controls (children: age: 7–14 years)	N=42	48.0	11.10
Depressive disorder (Children: acute depressive symptoms 7–14 years)	N=15	15.9	5.10
Children, depressive* disorder–remission, 7–14 years	N=15	55.5	5.40
Children: schizophrenia, acute symptoms 7–14 years	N=15	50.5	10.40
Children, ADHD, 7–11 years	N=30	22.0	3.50

*) Therapy by antidepressants (SSRI, clomipramine)

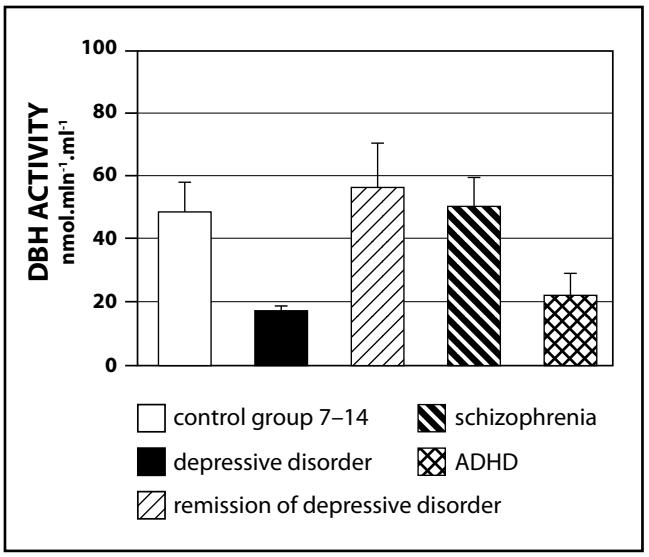

Fig. 1. DBH activity.

RESULTS

DBH activity is statistically significantly decreased in non-treated depressive disorder in children ($p<0.01$) and ADHD in children ($p<0.05$). DBH activity is normalised during antidepressant therapy in child depression. Child schizophrenia patients present with normal DBH activity (Table 1; Figure 1).

DISCUSSION

Our results show unchanged levels of DBH in children with schizophrenia. Wei *et al.* (1992) investigated DBH activity in serum in adult schizophrenic patients as well as in first-degree relatives and normal people. They found that DBH activity is higher in untreated patients compared with those treated with neuroleptics. They

also observed that DBH activity was inversely proportional to homovanillic acid concentration. Markianos *et al.* (1990) found significantly lower plasma level of DBH in patients with a positive family history and a diagnosis of paranoid schizophrenia than in those with a negative family history or in healthy people. In schizophrenics with signs of brain atrophy, as measured by computer tomography, DBH values in CSF were as low as in other CNS atrophic processes (Kammen *et al.* 1983).

Our results also show a correlation between decreased DBH activity and depressive disorder in children. This finding has been previously reported for adult depression and for adult melancholic depression (Puzynski *et al.* 1983a; Puzynski *et al.* 1983b; Schatzberg *et al.* 1992).

Studies dedicated to biochemical aspects of schizophrenia and depressive disorder in childhood and adolescence are rare. Young *et al.* (1980) do not deal with the same diagnostic group like we were studying. Eberhardt *et al.* (1989) performed a long-term investigation of 23 sibling pairs for whom schizophrenia occurred simultaneously in both siblings and found normal DBH activity and no correlation between DBH activity and psychotic or prodromal symptoms. Belmaker *et al.* (1978) found increased DBH activity in functional psychoses in childhood and adolescence. When comparing these data with the data in the introduction section, our study was conceptualised based on the hypothesis that DBH activity changes during childhood and adolescence observed in schizophrenic patients are probably similar to the changes observed during adulthood. DBH activity in adult schizophrenic patients, also in those untreated, is known to show some variability with a tendency to elevated DBH activity (Meltzer *et al.* 1976; Belmaker *et al.* 1978; Markianos *et al.* 1976; Baron *et al.* 1980; Wei *et al.* 1992). This variability is further influenced by the clinical condition and possibly by antipsychotic treatment.

These results differ from those of other studies dealing with autism in children and adults. These authors found lower DBH activity in autistic children and adults. Decreased DBH activity was identified also in relatives of patients with infantile autismus. (Lake *et al.* 1977).

There is only one study dealing with biochemical aspects of depressive disorders in childhood. Queiroz *et al.* (1991) examined levels of plasmatic cortisol and catecholamine metabolites in urine (VMA, HMA and 5-HIAA) in a group of 46 children of both sexes. They found an increased level of cathecholamine metabolites in urine and a lower peak of cortisol only in boys. The values did not reach statistical significance in girls. Querioz *et al.* (1991) did not find a correlation between clinical symptoms and syndromes, as measured by the relevant scales, and biochemical parameters' values.

Our results coincide with those reported by Queiroz *et al.* (1991). Decreased DBH levels were found by most authors in the case of adult patients. More specifically, other authors have found decreased DBH activity values in connection with severe depressive symptoms as well as recovery of those values along with improvement of the clinical condition.

One innovate contribution of the present study lies in demonstrating that DBH activity is decreased in ADHD patients aged 6 to 11 years. Galwin *et al.* (1995) found low DBH activity in children with emotional deprivation, which had occurred in the first 72 months of life. This finding might indicate that noradrenergic activity can be influenced by severe psychogenetic factors during this developmentally sensitive period.

In our previous paper (Kopečková *et al.* 2008) we studied all polymorphisms in the DBH gene and their potencial association with ADHD in children of same age. We found an association between ADHD and the G444A polymorphism in the recessive model. ADHD risk was also significantly higher in carriers of two simultaneous polymorphism alleles, namely DBH +444A and DBH +1603T (O.R. = 15). Our results are in agreement with other studies on the variability in DBH genes and with other in vivo and in vitro studies (Barkley *et al.* 2006; Carrasco *et al.* 2006; Kim *et al.* 2006). We are currently investigating the potential correlation between homozygotes DBH +l603 and DBH +444 A, severe hyperactivity and impulsivity, and low DBH plasma level (Galvin *et al.* l995; Galvin *et al.* 1997; Barkley *et al.* 2006) in children with ADHD. Our results need the replication; not-treated patients with the diagnose of the child schizophrenia and depression are very rare.

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