



Monoamines and Kynurenine Involvement in Pathogenetic Mechanisms of Attention Deficit Hyperactivity Disorder or Hyperkinetic Syndrome



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Abstract

Background: Pathogenetic mechanisms of attention deficit hyperactivity disorder (ADHD) or hyperkinetic syndrome (HKS) are not clear. The aim was to identify possible clinical and biochemical (monoaminergic) correlates of ADHD/HKS.

Methods: The levels of monoamines, their metabolites and kynurenine metabolite in urine samples were estimated using fluorometric and chromatographic methods.

Results: It was found that ADHD/HKS is followed by activation of dopaminergic and inhibition of noradrenergic systems. 3 weeks of psychostimulant - sydnocarb treatment had improved children's clinical status that was followed by decrease of dopaminergic and serotonergic system activities. Sydnocarb therapy has revealed reciprocal relationship between serotonergic and kynurenine systems.

Conclusion: Symptom improvement in ADHD/HKS children is followed by an activation of the kynurenine system. We propose a hypothesis that the kynurenine system plays significant role in the pathogenetic mechanisms of ADHD/HKS. We want to draw attention that these results were received using sample size of 42 patients. Thus, it is necessary to perform such kind investigations on the more representative and larger samples.

Keywords: Attention deficit hyperactivity disorder; Hyperkinetic syndrome; Children; Dopamine; Serotonin; kynurenine; Psychostimulant sydnocarb

Introduction

From the 1970s, a considerable number of investigations have been undertaken in which the authors have tried to reveal the pathogenetic mechanisms of ADHD, according to Diagnostic and Statistical Manual, fifth edition (DSM-5) [1] or hyperkinetic syndrome (HKS), according to International Classifications of Diseases, tenth edition, clinical modification (ICD-10-CM) [2].

The aetiology of ADHD/HKS is not known and pathogenesis is not clear. It has been shown that changes in the central monoaminergic systems play important role in ADHD/HKS [3,4]. Campbell M and Spenser E.K [5] wrote that "It remains to be shown where discrete biochemically - based subgroups show a different response to drugs: to psychostimulants, imipramine or neuroleptics" (p. 273). In spite that it was written 30 years ago the problem still remains urgent.

We decided to identify possible clinical-biochemical correlates of ADHD/HKS using a number of urinary biochemical indices that reflect catecholamine and serotonin neurotransmitter metabolism. Of particular interest is the detection of specific features of monoamine metabolism correlating with ADHD/HKS severity. It is supposed that such kind of approach may be

useful both in the understanding of the pathogenetic mechanisms of ADHD/HKS and in selecting pathophysiologically reasoned psychopharmacological tactics of the therapy of ADHD/HKS patients with different severity of condition.

Subjects and Methods

As a whole there were examined 42 children with ADHD/HKS. In compliance with the degree of motor hyperactivity and inattention, two groups of children with HKS were selected. Children of group 1 (mild HKS, mHKS) consisted of 6 patients with mild motor hyperactivity and inattention in which the emotional disturbances mainly took the form of emotional lability. Group 2 included 6 patients with severe form of HKS (sHKS). Children of this group were characterized by excessive motor activity, pronounced inattention and affective disorders; insignificant environmental stimuli caused affective outbursts with aggression and a tendency to destructions [6]. Both these groups consisted of patients with borderline intellectual disability (BID) (according to DSM-5). Group 3 (control) consisted of 8 patients without any features of HKS (in all groups the patients were 7-11 years old children). Clinical delineation of different ADHD/HKS forms was carried out as described in [7].

We consider that the most spare and convenient approach in our study is urine investigation. Methods for the determination of monoamines, their metabolites and N-methylnicotinamide (one of the main metabolites of kynurenine pathway of tryptophan metabolism) in urine samples were described elsewhere [6].

Results and Discussion

It was shown that mHKS in comparison with the controls was characterized by significant increase of dopamine (DA) excretion by 165% ($p < 0.001$) and a decrease of noradrenaline (NA) excretion by 46% ($p < 0.001$). In sHKS children DA and L-dopa excretion were significantly increased by 432% and 124% (both $p < 0.001$), respectively, whereas excretion of NA did not change in comparison with control group. It was found that there are significant differences between severe and mild form of HKS. We can conclude that HKS is followed - within limits - by activation of dopaminergic system and inhibition of noradrenergic system. It has to take into the account that this conclusion is based only on the sample of 42 children. Further investigations are necessary on the larger sample sizes.

The therapy of ADHD/HKS is a complex problem. For several decades the psychostimulants (primarily, methylphenidate and amphetamine) are the most frequently used ADHD treatments [8,9]. In the 1970s, the psychostimulant Sydnocarb [3-(β -phenylisopropyl)-N-phenyl-carbamoyl-sydnominine] was synthesized and introduced in clinical practice in the Soviet Union as an effective treatment of child HKS [7,10]. It was shown by Krasov [7] that treatment mHKS children with sydnocarb was effective in 94% of cases whereas such kind of treatment of sHKS children was effective only in 24% of cases.

We have investigated the state of monoaminergic systems in children with mild HKS form under sydnocarb treatment. Patients were divided in 2 groups: mHKS with normal intellect (18 boys) and mHKS with BID (12 boys). Patients received 5-15 mg sydnocarb (daily during 1-1.5 months) (for ethical reasons sHKS children were not included in the study). There were similar changes in the level of daily excretion of monoamine metabolites in both groups. Thus, after psychostimulant medication, homovanillic acid (HVA) excretion decreased by 55% ($p < 0.001$) and 29%. Our results show that the improved clinical status of HKS children under psychostimulant sydnocarb treatment at least partially coincided with a decrease of dopaminergic activity.

The data about the involvement of serotonin in pathogenetic mechanism of ADHD/HKS are controversial [11]. We have shown that there were no significant changes in 5-hydroxyindoleacetic acid (5-HIAA) excretion in children with mild and severe HKS forms in comparison to controls [6]. However, 3 weeks after sydnocarb medication, we found a significant decrease in 5-HIAA excretion in both groups, by 61% ($p < 0.001$) and 39% ($p < 0.01$), respectively. This indirectly points to a potential decrease of serotonin levels in the brain. Thus sydnocarb treatment has revealed serotonin involvement in pathogenesis of ADHD/HKS.

This is supported by data that the paradoxical calming effect of psychostimulant treatment on the increased locomotor activity in the animal model was dependent on serotonergic activity [12].

It has been shown [13] that the kynurenine pathway of the metabolism of tryptophan, the precursor molecule in both the serotonin and the kynurenine metabolic pathways, is the main one found in mammals: about 90-95% of tryptophan molecules are metabolized via this pathway and only about 5-10% of these molecules are used for serotonin synthesis. We have examined the possible involvement of kynurenine pathway in the HKS pathogenetic mechanisms. It was found that HKS children under sydnocarb treatment were characterized by an increase of N-MNA excretion by 34% and 28% ($p < 0.05$ both groups), respectively. The N-MNA/5-HIAA ratio under sydnocarb medication increased 2.0-3.5 times. These data indicate that under sydnocarb treatment, the kynurenine pathway of tryptophan metabolism begins to prevail to an even greater extent over serotonin pathway of tryptophan metabolism. This could lead to the observed decrease of serotonergic activity following medication, and this was followed by the improvement of clinical status of HKS children. There are data that some kynurenine metabolites (L-kynurenine, 3-hydroxykynurenine, picolinic acid) formed along the kynurenine pathway possess the ability to inhibit locomotor activity in animals [13]. Their views are in part supported by results of Gainetdinov et al. [12]. We can hypothesize that increased urine excretion of kynurenine metabolite - N-MDA as well as N-MNA/5-HIAA ratio can serve as predictors of the efficacy of psychostimulant medication.

In conclusion, we propose a hypothesis that the kynurenine system plays significant role in the pathogenetic mechanisms of ADHD/HKS. Accordingly, ADHD/HKS might be characterized by an activation of serotonergic and an inhibition of kynurenine systems. Symptom improvement in ADHD/HKS children is followed by an activation of the kynurenine system. Our investigation indicates that ADHD/HKS is characterized by profound disturbances and dysregulation of monoamine metabolism.

Limitations

There are some limitations of the study.

- i. It is necessary to have larger sample size.
- ii. It will be useful to examine some other parameters of kynurenine pathway.
- iii. For more precise understanding the mechanisms of serotonin involvement in pathogenesis of ADHD/HKS it will be useful the direct measurements of serotonin in the platelets.

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