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Increased Plasma Catecholamines as Markers for Hyperkinesis

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ABSTRACT: Increased Conners scores were found in 13 of 14 hyperkinetic children with significantly raised plasma dopamine and/or epinephrine levels. One child with normal circulating catecholamines was identified as false hyperkinetic, his behaviour being determined by an abnormal family interaction. The biochemical interpretation and the diagnostic significance of these results in children with attention deficit disorder and hyperactivity are discussed.

Introduction

Intracerebrally applied dopamine is known to induce hyperactivity in animals (1, 2). Hyperactive children are frequently treated with methylphenidate, a drug which acts via central dopaminergic mechanisms (3). Plasma methylphenidate concentration in children correlates with the percentage of improvement (3) in the abbreviated Conners rating scale (4, 5), suggesting a relationship between dopamine concentration and clinical response. In this study we raise the question as to whether or not direct measurements of plasma catecholamine levels, including dopamine, would be of value in the diagnosis of hyperactivity in children and if the Conners score correlates with circulating catecholamine levels. Previous investigations showed no changes, (6, 7) or lowered levels (8) of 3-methoxy-4-hydroxyphenylglycol (MHPG), the urinary metabolites of norepinephrine, or homovanillic acid (HVA), the urinary metabolite of dopamine in hyperkinetic children. In this respect, most studies have found no signif-

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icant differences between attention deficit disorder in children and normal control subjects (9).

To our knowledge this is the first report describing significant changes of plasma catecholamine levels in children with attention deficit disorder and hyperactivity.

Patients and Methods

Fifteen hyperkinetic children (age range 7-15 years) fulfilling the diagnostic criteria of DSM-III for attention deficit disorder (10) were referred to us by various pediatricians. Most of the children were also examined by psychiatrists. The patients, as well as eleven healthy controls (age range 6-14 years), with no sign of hyperactivity or attention deficit disorder, were included in this outpatient study, in which informed consent was obtained from each of the parents. All patients avoided any medical treatment for at least 6 weeks prior to the study. For ethical reasons we were unable to withhold medication for a longer period of time in order to perform repeated venipunctures to obtain sequential plasma catecholamine studies. The degree of hyperactivity was assessed by means of the abbreviated Conners rating scale (4, 5) parent form, whereby scores above 18 were considered abnormal. Venous blood samples were taken in tubes containing disodium EDTA, with the children in the supine position at 9 a.m. using an indwelling catheter and after 10 minutes of rest in order to avoid unnecessary stress from use of a needle. The concentrations of plasma catecholamines were determined by reverse phase HPLC with electrochemical detection, a reproducible and highly sensitive method (11, 12). The radioenzymatic method has been shown to result in lower dopamine values (13). The detection limit was 0.8 pg/ml for norepinephrine, 1.0 pg/ml for epinephrine and 3.0 pg/ml for dopamine. Chromatographic separation was carried out on a C-18 plasma catecholamine column (5x150 mm, spherical particle size: 5 μm) after $Al_2 O_3$ extraction. Results are expressed in pg/ml and the standard error of 2 determinations was less than 15 per cent. The statistical significance of the results was estimated by means of the Student t-test.

Results and Discussion

Plasma catecholamine levels and the corresponding Conners scores in the 15 hyperkinetic children are depicted in Table 1. Thirteen of 15

TABLE 1

Plasma Catecholamine Levels and Conners Score in Hyperkinetics

Patient Nr.	(Age)	Epinephrine pg/ml	Norepinephrine pg/ml	Dopamine pg/ml	Conners Score
156	(14)	110	194	40	22
560	(11)	159	189	26	20
576	(7)	366	406	88	20
576a*	4 months later	218	498	90	19
583	(11)	142	156	88	23
588	(9)	125	268	91	24
588a*	3 months later	101	208	71	23
591	(9)	43	200	40	21
748	(15)	47	217	60	21
795	(15)	31	196	10	21
803	(11)	110	340	50	22
810	(13)	64	228	71	15
832	(15)	97	226	91	23
832a*	after 2 weeks Sulpirid	120	178	103	22
1116	(11)	167	352	86	22
1446	(8)	120	247	55	21
1476	(10)	127	238	64	22
1515	(13)	86	250	56	20
Patient group n = 15	Mean ± SD	120 ± 80	248 ± 69	61 ± 25	21.1 ± 2.1
Control group n = 11	Mean ± SD	43 ± 22	184 ± 66	17 ± 14	10.9 ± 2.6
Significance Student t-test		$p<0.01$	NS	$p<0.0001$	$p<0.0001$

*The repeated determinations were not used for calculation of the mean values.

patients showed dopamine levels higher than 31 pg/ml; 12 of 15 showed epinephrine levels higher than 55 pg/ml; 11 of 15 had both dopamine and epinephrine increased, but only 4 of 15 exhibited norepinephrine concentrations above 250 pg/ml. By contrast, none of the control children showed increased plasma catecholamine concentrations and Conners scores above 14 (Table 1).

The difference was highly significant for dopamine ($p < 0.0001$) and significant for epinephrine ($p < 0.001$). On the other hand, there

was no significant difference in the norepinephrine levels between the two groups, a finding already reported by others (14, 15). A repeated investigation in two patients (No. 576a and 588a) revealed similar values 3 and 4 months later, respectively (Table 1). Daily sampling was impossible because of the behaviour of the patients after discontinuing medical treatment. In another case (No. 832a) a two week trial of sulpiride, a dopamine receptor antagonist (1, 2) brought no significant changes in the circulating catecholamine levels, although there was slight improvement in behaviour.

Our preliminary results of plasma catecholamine concentrations in hyperkinetic children receiving methylphenidate, and those after 6 weeks following drug discontinuation, showed clearcut changes.

Plasma dopamine-β-hydroxylase (DBH) was normal in our patients (unpublished observations) and therefore probably not responsible for the increased dopamine levels. A similar finding was previously reported by us in atopic eczema patients showing significantly increased plasma norepinephrine but normal dopamine and epinephrine concentrations (16). Normal DBH activities were already found in hyperkinetic children (17). We therefore speculate that an impaired catecholamine catabolic pathway involving decreased catechol-O-methyl-transferase and/or phenylethanolamine-N-methyltransferase activities may be responsible for the increased circulatory levels of the mediators. Nevertheless, an impaired control of catecholamine release and/or uptake in our patients is also possible. Catecholamine degradation by monoamine oxidase should also be considered and research on this topic is in progress in our laboratory. MHPG

Plasma catecholamine concentrations relate to activity of the peripheral sympathetic nervous system (PNS) and not the central nervous system (CNS) since catecholamines do not pass the blood brain barrier. Analyses of the metabolites HVA and HMPG in urine reflect catecholamine catabolism from both CNS and PNS. Raised plasma catecholamine concentrations relate to the hyperactivity in the sick children but these values have nothing to do with what is happening in the CNS of these children. Plasma catecholamine levels agreed well with most of the diagnostic criteria of DSM III and may therefore be helpful in deciding whether or not to start drug therapy using methylphenidate or other medication.

Fourteen of fifteen patients with increased catecholamine levels showed elevated Conners scores but no direct relation could be established between the dopamine and/or epinephrine concentrations and the degree of hyperactivity according to the abbreviated rating scale.

We recorded a normal Conners score in only one child (No. 810) who had increased plasma catecholamine values. Another case (No. 795) with normal catecholamine levels had a Conners score of 21. However a more careful examination revealed a permanent mother-child conflict in the family, but normal behaviour of the child in school and outside the family. This finding suggests that high Conners scores with normal catecholamine levels may be helpful in finding children who are hyperactive as a result primarily of impaired psychosocial relationships rather than a true biochemical disorder.

On the other hand the abbreviated Conners rating scale does not really reflect the diagnostic criteria of DSM III and this may be the reason why we failed to show a direct correlation between plasma dopamine and/or epinephrine concentration and the severity of the hyperkinetic disorder, as measured by the Conners rating scale. One should keep in mind that our children were selected by the diagnostic criteria of DSM III and most of them were evaluated by psychiatrists.

Our data indicate that increased circulatory levels of dopamine and/or epinephrine may be good markers for attention deficit disorder with hyperactivity in children, in addition to the DSM III criteria.

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