Abnormal Plasma Catecholamines in Hyperkinetic Children

Gruia Ionescu, Reinhold Kiehl, Livia Ona, and Frieda Wichmann-Kunz

Introduction

Dopamine is known to induce hyperactivity in animals (Costall and Naylor 1976; Jenner and Maraden 1979). Hyperactive children are frequently treated with methylphenidate, a drug acting via central dopaminergic mechanisms (Shaywitz et al. 1982). In one study, methylphenidate concentration in children correlates with the percentage of improvement (Shaywitz et al. 1982) on the abbreviated Conner's rating scale (Eichsleder 1987), suggesting a relationship between dopamine concentration and clinical response. In contrast to this conclusion, however, other results have been reported (Gualtieri et al. 1982). The question now is whether direct measurements of plasma catecholamine levels, including dopamine, would be of value in the diagnosis of hyperactivity in children and whether the Conner's score correlates with the circulating catecholamine levels. Previous investigations have shown no differences (Rapoport et al. 1974; Shetty and Chase 1976) or lowered levels (Shekim et al., 1983) in the urinary metabolites of norepinephrine, 3-methoxy-4-hydroxy-phenylglycol (MHPG), dopamine, or homovanillic acid (HVA) in hyperkinetics. In this respect, most studies have found no significant differences between attention-deficit disorder children and normal control subjects (Zametkin and Rapoport 1987). 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

Twelve hyperkinetic children (aged 7–15 years) fulfilling the diagnostic criteria of DSM-III for attention deficit disorder were assigned to us by various pediatricians; most of the children were also examined by psychiatrists. The patients as well as 11 healthy controls (aged 6–14 years) with no sign of hyperactivity or attention deficit disorder were included in this study as outpatients with informed consent of the parents. All patients avoided any medical treatment for at least 6 weeks before admission. The degree of hyperactivity was assessed according to the abbreviated Conner's rating scale (Eichsleder 1987), parent form, whereby scores above 18 were considered abnormal. Venous blood samples were taken on Na-EDTA in the supine position at 9 AM (indwelling catheter) after a 10-min bedrest. The concentration of plasma catecholamines was determined by reverse phase high-performance liquid chromatography (HPLC) with electrochemical detection (Weicker et al. 1984). 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 col-

From the Research Department, Spezialklinik Neukirchen, Neukirchen, West Germany.
Address reprint requests to Dr. Gruia Ionescu, Research Department, Spezialklinik Neukirchen, D-8497 Neukirchen, West Germany.
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umn (5 × 150 mm, spherical particle size 5 μm) after Al_2O_3 extraction. Equipment, standardized method and reagents were supplied by Waters Millipore (FRG). Results are expressed in pg/ml and the standard error of 2 determinations was less than 15%. The statistical significance of the results was estimated by means of the Student's *t*-test.

Results

Plasma catecholamine levels as well as the corresponding Conner's scores are depicted in 12 hyperkinetics (Table 1). Ten of 12 patients showed dopamine levels higher than 30 pg/ml, 8 of 12 showed epinephrine levels higher than 65 pg/ml, 7 of 12 showed increases in both dopamine and epinephrine, but only 4 of 12 exhibited norepinephrine concentrations above 230 pg/ml. The control children, however, showed neither an increase in plasma catecholamine concentrations nor scores above 14 on the Conner's scale (Table 1).

The difference was highly significant for dopamine ($p < 0.0001$) and significant for epinephrine ($p < 0.001$), which strongly suggests a close relationship between the circulatory levels of these neurotransmitters and the pathogenesis of the hyperkinetic syndrome. On the other hand, there was no significant difference in the norepinephrine levels of the two groups, a finding reported by others (Rapoport et al. 1974; Ferguson et al. 1981). Our results do not support the norepinephrine hypothesis (Zametkin and Rapoport 1987). Our 12 hyperkinetic children included only 2 girls, therefore we cannot make any determinations about gender differences. However, our controls show no such differences, and we may assume that this is also the case for our patients. A repeated investigation

Table 1. Plasma Catecholamine Levels and Conner's Score in Hyperkinetics

Patient no.	Age	Gender	Epinephrine pg/ml	Norepinephrine pg/ml	Dopamine pg/ml	Conner's score
156	14	M	110	194	40	22
560	11	M	159	189	26	20
576	7	F	366	406	88	20
576a[a]	4 months later		218	498	90	19
583	11	M	142	156	88	23
588	9	M	125	268	91	24
588a[a]	3 months later		101	208	71	23
591	9	M	43	200	40	21
748	15	M	47	217	60	21
795	15	M	31	196	10	21
803	11	F	110	340	50	22
810	13	M	64	228	71	15
832	15	M	97	226	91	23
832a[a]	after 2 weeks Sulpirid		120	178	103	22
1116	11	M	167	352	86	22
Patient group $n = 12$	Mean ± SD		122 ± 89	248 ± 78	62 ± 28	21.2 ± 2.3
Control group $n = 11$	Mean ± SD	6 M, 5 F	43 ± 22	184 ± 66	17 ± 14	10.9 ± 2.6
Significance Students' *t*-test			$p < 0.01$	NS	$p < 0.0001$	$p < 0.0001$

[a]The repeated determinations were not used for calculation of the mean values.

of 2 patients (Nos. 576a and 588a) revealed similar values 3 and 4 months later, respectively (Table 1).

In another case (No. 832a), a 2-week oral treatment with sulpiride, a dopamine receptor antagonist (Costall and Naylor 1976; Jenner and Maraden 1979) brought no significant changes in the circulating levels, but the behavioral response was slightly improved. Considering these results, it would be interesting to investigate plasma catecholamine levels before and after therapy with methylphenidate.

Ten of 11 patients with increased catecholamine levels showed elevated Conner's scores but no direct relationship could be established between the dopamine and/or epinephrine concentrations and the hyperactivity degree according to the abbreviated rating scale. In only 1 case (No. 810) did we record a normal Conner's score, although plasma catecholamine levels were increased. Another case (No. 795) with normal catecholamine levels had a Conner's score of 21. However, a closer investigation of the home situation revealed a constant mother-child conflict but normal behavior of the child in his social environment.

Discussion

Plasma dopamine-β-hydroxylase (DBH) was normal in our patients (in preparation) and therefore not responsible for the increased dopamine levels. We previously reported a similar finding in atopic eczema patients showing significantly increased plasma norepinephrine but normal dopamine and epinephrine concentrations (Ionescu and Kiehl 1988). Normal DBH activities were already found in hyperkinetic children (Mikkelson et al. 1981). We therefore suggest that an impaired catecholamine catabolic pathway involving decreased catechol-O-methyltransferase- and/or phenyletanolamine-N-methyl-transferase activities may be responsible for the increased circulatory levels of the mediator. 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.

Our data indicate that increased circulatory levels of dopamine and/or epinephrine may be a good marker for the attention deficit disorder with hyperactivity in children.

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