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Blunted Catecholamine Responses after Glucose Ingestion in Children with Attention Deficit Disorder

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ABSTRACT

Eating simple sugars has been suggested as having adverse behavioral and cognitive effects in children with attention deficit disorder (ADD). but a physiologic mechanism has not been established. To address this issue, metabolic, hormonal, and cognitive responses to a standard oral glucose load (1.75 g/kg) were compared in 17 children with ADD and 11 control children. Baseline and oral glucose-stimulated plasma glucose and insulin levels were similar in both groups, including the nadir glucose level 3–5 h after oral glucose (3.5 ± 0.2 mmol/L in ADD and 3.3 ± 0.2 mmol/L in control children). The late glucose fall stimulated a rise in plasma epinephrine that was nearly 50% lower in ADD than in control children (1212 ± 202 pmol/L *versus* 2228 ± 436 pmol/L, $p < 0.02$). Plasma norepinephrine levels were also lower in ADD than in control children, whereas growth hormone and glucagon concentrations did not differ between the groups. Matching test scores were lower and reaction times faster in ADD than in control children before and after oral glucose, and both groups showed a deterioration on the continuous performance test in association with the late fall in glucose and rise in epinephrine. These data suggest that children with ADD have a general impairment of sympathetic activation involving adrenomedullary as well as well as central catecholamine regulation. (***Pediatr Res* 38: 539–542, 1995**)

Abbreviations

ADD, attention deficit disorder
YCI, Yale Children's Inventory
ANOVA, analysis of variance

The influence of diet and especially dietary sugar on behavioral problems in children with ADD remains controversial. Parents of children with ADD believe that sugar can exacerbate symptoms in ADD as reflected in a recent survey (1). Eighty percent of parents had attempted to implement a diet low in refined carbohydrates and 35% of the families believed that there was sufficient improvement in their child's behavior to continue this dietary restriction (1). On the other hand, results of sugar challenge tests have varied widely: some studies failed to demonstrate any effects (2–4), whereas other found improvements (5, 6), exacerbations (7, 8), or mixed behavioral effects (9). These disparate results may be explained, in part, by differences in age, the diagnostic criteria used to define the study populations and in the timing and composition of the challenge meals. Moreover, a biologic basis for enhanced sensitivity to dietary sugar in ADD children has not been demonstrated.

Recent studies from our laboratory indicate that in healthy normal children even modest reductions in plasma glucose, as observed in the late postprandial period 3–5 h after oral glucose, are able to evoke a sharp increase in circulating epinephrine levels and symptoms related to this epinephrine response (10). We hypothesized that children with ADD might be particularly vulnerable to such vigorous postprandial adrenergic surges with respect to alterations in behavior and cognitive performance. Consequently, in the present study, we compared metabolic, hormonal, and cognitive responses to glucose ingestion in normal and ADD children. The two groups were characterized using objective diagnostic criteria and the responses in each subject were determined during a standard 5-h oral glucose tolerance test.

METHODS

Subjects. Twenty-eight subjects (11 control and 17 ADD children) ranging in age from 7 to 14 y were studied. The subjects in the ADD group were recruited from youngsters referred to the Yale Center for Learning and Attention Disor-

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ders. They were eligible for inclusion if their risk status for ADD was rated as moderate or high on the YCI (11). Because the study was performed during summer vacation, only three of the children were taking stimulants. They were instructed to discontinue the medication for 5 d before the study. Normal controls were children of University staff or healthy siblings of patients attending the Yale Pediatric Endocrinology Clinic. They were in good health, had no known psychosocial problems, and were taking no medications. YCI scores for the normal controls confirmed that they did not satisfy criteria for ADD. None of the controls or patients had a history of diabetes, known brain injury, seizure disorder, obesity, or impaired intelligence. There were no significant differences between the two groups with respect to age, gender distribution or anthropometric characteristics (Table 1). Informed written consent was obtained from all of the subjects (and their parents) before enrollment in the study.

Procedures. All of the children fasted after midnight except for water and the study was begun on the following morning at 0800 h. An i.v. catheter was inserted in a vein of the nondominant hand or forearm for blood sampling. That hand was kept in a heated box (60–65°C) to arterialize venous blood samples (12).

The subjects rested for at least 20 min after catheter insertion before baseline blood samples were obtained for measurement of plasma glucose, catecholamines, insulin, growth hormone, and glucagon. Oral glucose was then ingested at the standard dose of 1.75 g/kg body weight. Blood samples for plasma glucose determinations were obtained every 30 min for the first 2 h and every 10 min for the remaining 3 h to precisely determine nadir glucose levels. Insulin, glucagon catecholamines, and growth hormone were measured at least every 30 min for 5 h. Representative plasma glucose, insulin and epinephrine responses in a normal control subject are shown in the Figure 1.

All of the ADD children and seven of the control children participated in hourly tests of attention before and during the glucose tolerance test. Three different tests were used: the continuous performance, visual search, and matching tests. They were explained, and practice sessions were completed before baseline assessments to minimize learning effects during the study. The same battery of tests was repeated at baseline and at each hour for 5 h after glucose ingestion.

Biochemical measurements. Plasma glucose levels were determined on glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma levels of catecholamines were measured by radioenzymatic assay (Amersham Corp., Arlington Heights,

Table 1. *Characteristics of two study groups**

	ADD children	Control children
n	17	11
M/F	13/4	8/3
Age (y)	11 ± 1	11 ± 1
Height (cm)	152 ± 4	147 ± 4
Weight (kg)	43 ± 3	38 ± 3
BMI (kg/m^2)	18 ± 1	17 ± 1

* Data presented as means ± SE. BMI, body mass index.

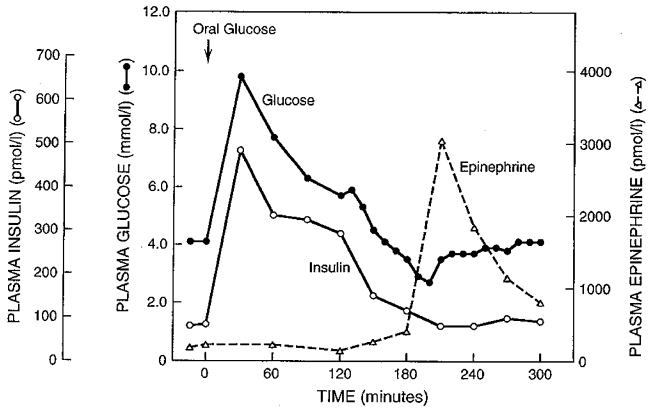

Figure 1. Plasma glucose (*closed circles*), insulin (*open circles*), and epinephrine (*open triangles*) before and after oral glucose ingestion in a representative control subject.

IL) and insulin, growth hormone and glucagon (ICN Biomedicals, Carson, CA) were determined by RIA.

Tests of attention. Three different measures of attention were used. For the continuous performance test, children were asked to respond to the letter X only when preceded by the letter A. There were 30 true instances and 30 "false targets," that is, X without A before it. The stimulus presentation rate was initially set at 200 ms with a 500-ms interstimulus interval. These times were adapted to the subjects' own error rate on a trial by trial basis. Up to three hundred letters were presented. Subjects were graded for false positives (*i.e.* hitting the key when there was an X but no A before it) and for missing an AX sequence.

For the visual search test, the screen was filled with rows of the letter I and divided into quadrants. There was one letter B on each screen. Subjects viewed the screen for 1 s and then were asked to identify the quadrant containing the letter B. Subjects were graded for number of correct responses.

In the matching task, subjects were given pairs of stimuli and asked to make same/different judgments based on a stimulus feature such as size, shape and color. Subjects were rated on reaction times and number of correct matches.

Analyses. Comparisons of plasma glucose, hormones, and computer test performance were analyzed for changes over time and between groups using two-way ANOVA variance with repeated measures using the SAS^R program. Between and within groups differences in basal and nadir plasma glucose levels and basal and maximal hormone responses were also analyzed by two-way ANOVA. To avoid confounding effects of spontaneous growth hormone peaks, the mean of growth hormone levels between 60–120 min after oral glucose (hyperglycemic phase of the glucose tolerance test) were used to define basal values. Within and between group differences in computer task performance were also examined at the plasma glucose nadir and plasma epinephrine maximum using ANOVA. When the time of the epinephrine peak did not coincide with the computer testing, the battery of tests given immediately after the peak response was used. The testing session before or after the glucose nadir (whichever was closest) was used for this comparison. All data are presented as

means ± SE, and p values <0.05 were considered statistically significant.

RESULTS

Metabolic and hormonal responses. Basal plasma glucose (Table 2) and plasma insulin (96 ± 7 pmol/L in ADD and 88 ± 14 pmol/L in control children) were similar in both groups, as were plasma glucose and insulin profiles after glucose ingestion (data not shown). Even more important, as shown in Table 2, the mean peak and nadir plasma glucose levels determined from glucose profile of each subject were virtually identical in both groups (p = not significant). The plasma glucose nadir occurred at a mean time of 224 min in ADD children (range 180–270 min) and at 224 min in controls (range 150–300 min) (p = not significant).

Counterregulatory hormone levels before and after oral glucose are shown in Table 2. Baseline plasma epinephrine levels were similar and mean epinephrine concentrations rose in both groups in response to the late postprandial fall in plasma glucose. However, the rise in plasma epinephrine was significantly greater in control children than in ADD children, reaching values that were nearly 2-fold higher in the control than the ADD group ($p < 0.02$). Basal norepinephrine levels were slightly, but not significantly lower in ADD than control children. Moreover, norepinephrine concentrations tended to fall after oral glucose in the ADD, but not the control group; between group differences that were statistically significant ($p < 0.02$). In contrast, basal and peak growth hormone and glucagon levels were similar in both groups during the study.

Measures of attention (Table 3). Scores on the matching test were slightly but significantly lower for the ADD group at baseline. Matching scores did not change significantly in either group over time; nor were there changes associated with the glucose nadir or after the peak in epinephrine. Reaction time on the matching test also differed significantly between groups at baseline and throughout the study with the ADD group having a faster reaction time relative to controls ($p = 0.02$).

Table 2. *Mean basal, peak, and nadir plasma glucose and counterregulatory hormone levels*

	ADD (n = 17)	Controls (n = 11)
Glucose (mmol/L)		
Basal	4.5 ± 0.1	4.4 ± 0.1
Peak	7.5 ± 0.2	7.5 ± 0.4
Nadir	3.5 ± 0.2	3.3 ± 0.2
Epinephrine (pmol/L)		
Basal	229 ± 27	223 ± 33
Peak	1212 ± 202*	2228 ± 436
Norepinephrine (nmol/L)		
Basal	1.55 ± 0.15	1.79 ± 0.19
At 240–300 min	1.25 ± .10*	1.71 ± 0.15
Glucagon (ng/L)		
Basal	113 ± 11	119 ± 11
Peak	217 ± 27	229 ± 26
Growth hormone (μg/L)		
Basal	3 ± 1	3 ± 1
Peak	19 ± 2	21 ± 3

* Significantly different from values in controls, $p < 0.02$.

Table 3. *Scores on tests of attention in the two study groups at baseline, glucose nadir, and epinephrine peak*

Test	Baseline	Glucose nadir	Epinephrine peak
Matching score (number correct)			
ADD	26.9 ± 0.7*	26.7 ± 1.1*	27.1 ± 0.8*
Control	28.4 ± 0.6	29.1 ± 0.4	29.1 ± 0.4
Reaction time (ms)			
ADD	687 ± 53*	556 ± 42*	509 ± 40*
Control	745 ± 124	689 ± 102	675 ± 106
Visual search (number correct)			
ADD	37.2 ± 0.8	36.5 ± 0.6	35.6 ± 1.5
Control	35.1 ± 1.8	36.4 ± 0.9	36.0 ± 1.0
Continuous performance—false positives (number)			
ADD	2.6 ± 0.6	6.9 ± 2.0†	6.8 ± 2.1†
Control	1.0 ± 0.4	6.0 ± 2.3†	5.7 ± 2.4†
Omissions (number)			
ADD	5.4 ± 0.8	8.3 ± 1.4†	8.0 ± 1.3†
Control	4.7 ± 1.6	8.4 ± 2.1†	8.0 ± 2.2†

* Significantly different from controls, $p < 0.02$.
† Significantly different from baseline, $p < 0.05$.

There were no between group differences on the visual search task at baseline, at any time point, at glucose nadir or after the epinephrine peak. There were no significant changes over time in either group.

Baseline scores on the continuous performance tests were not significantly different between the two groups. In both groups, false positive and omissions tended to increase over time ($p < 0.05$) and significant increases were observed in association with the fall in glucose and with the epinephrine surge ($p < 0.05$ *versus* baseline in both groups). However, the ADD children did not differ significantly from controls.

DISCUSSION

The question whether children with ADD have exaggerated sensitivity to dietary sugar has been the subject of considerable study and continuing controversy. Critical reviews of the literature in this area (13, 14) indicate that most of the studies are beset by a variety of methodologic problems that we have attempted to limit in this investigation by including only subjects and controls who were within a narrow age range and who were diagnosed as ADD using scales from the YCI (11). The potential confounding effects of variations in the timing and composition of test meals were avoided by using a standard 5-h glucose tolerance test, and this was combined with comprehensive metabolic, hormonal, and neuropsychologic assessments. Sufficient numbers of patients and controls were recruited to reveal small to moderate differences between the groups and within each group over time. Oral glucose rather than sucrose was used because of extensive experience with this standard method of assessing glucose tolerance. It should be noted, however, that the response to sucrose (common table sugar) might be different.

In general, results of this study failed to indicate important differences between ADD and healthy control children in most of the metabolic, hormonal, and functional responses that followed oral glucose ingestion. Both groups of children effectively disposed of the glucose load (preventing hyperglyce-

mia) and both showed a mild fall in plasma glucose in the late postprandial period; insulin, growth hormone and glucagon responses were also virtually identical. On neuropsychologic testing, the groups differed slightly but significantly with respect to matching scores and reaction times. These differences were in the expected directions; that is, ADD children made more mistakes on matching and had more rapid, impulsive response times. However, the differences in neuropsychologic performance were observed at baseline and were not exaggerated by the fall in plasma glucose or the late rise in counterregulatory hormones. The late metabolic and hormonal changes were associated with an impairment of scores on the continuous performance task that was similar in both groups. This finding is consistent with recent observations that even mild reductions in plasma glucose and associated increases in plasma epinephrine have adverse effects on cortical functioning in healthy children, as assessed by auditory cortical evoked potentials (15). Nevertheless, we were unable to demonstrate differences in neuropsychologic test scores between ADD and control children that could be attributed to an effect of sugar ingestion *per se*. On the other hand, the changes in plasma catecholamine levels that followed oral glucose were strikingly different between ADD and control children.

Responsive increases in epinephrine secretion provide an important hormonal defense mechanism against an acute fall in plasma glucose (16). Recent studies from our laboratory (10) indicate that the plasma glucose level that triggers an epinephrine response is considerably higher in healthy children than healthy adults (approximately 3.7 *versus* 3.0 mmol/L, respectively). As demonstrated by both groups of children in this study, plasma glucose levels regularly fell below 3.7 mmol/L several hours after ingesting rapidly absorbed carbohydrate, resulting in a prompt increase in circulating epinephrine concentrations. One of the aims of the present study was to examine whether the putative hypersensitivity to dietary sugar in ADD children *versus* normal children might be related to a greater fall in plasma glucose or an exaggerated rise in plasma epinephrine or both in the late postprandial period. The observation that responsive increases in epinephrine were markedly blunted in ADD *versus* control children despite similar falls in plasma glucose was surprising.

Several studies that examined alterations in norepinephrine metabolism suggest that central sympathetic activity is reduced in children with ADD, resulting in hypoarousal and in inability to inhibit impulsivity (17). In comparison to control children, children with ADD have been reported to excrete less urinary 3-methoxy-4-hydroxyphenolglycerol (MHPG), and other breakdown products of norepinephrine metabolism (18–21). The lower plasma norepinephrine levels in the ADD group in this study is consistent with reduced central sympathetic activity in these subjects. On the other hand, the effect of ADD on plasma epinephrine responses to physiologic stimuli has not been established. Thus, our findings of abnormally low epinephrine responses to hypoglycemia in ADD children is particularly noteworthy. These data suggest that ADD children have a more generalized impairment of sympathetic activation than previously suspected, involving adrenomedullary as well as central catecholamine regulation. It is intriguing to speculate that both of these reductions in sympathetic activity are related to regional alterations in brain glucose metabolism as has been reported in adults with childhood-onset ADD (22).

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