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Catecholamine Response to Exercise in Children with Attention Deficit Hyperactivity Disorder

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ABSTRACT

The objective of this study was to examine differences in catecholamine (CA) response to exercise between children who had received a diagnosis of attention-deficit/hyperactivity disorder (ADHD) and age- and gender-matched controls. On the basis of the notion of a CA dysfunction in ADHD, we reasoned that the normal robust increase in circulating CA seen in response to exercise would be blunted in children with ADHD. To test this, we recruited 10 treatment-naïve children with newly diagnosed ADHD and 8 age-matched controls (all male) and measured CA response to an exercise test in which the work was scaled to each subject's physical capability. After exercise, epinephrine and norepinephrine increased in both control and ADHD subjects ($p = 0.006$ and $p = 0.002$, respectively), but the responses were substantially blunted in the ADHD group ($p = 0.018$) even though the work performed did not differ from controls. Circulating dopamine increased significantly in the control subjects ($p < 0.016$), but no increase was noted in the subjects with ADHD.

Finally, a significant attenuation in the lactate response to exercise was found in ADHD (between groups, $p < 0.005$). Our data suggest that CA excretion after exercise challenges in children with ADHD is deficient. This deficiency can be detected using a minimally invasive, nonpharmacologic challenge. (*Pediatr Res* 53: 756–761, 2003)

Abbreviations

ADHD, attention-deficit/hyperactivity disorder
CA, catecholamine
NE, norepinephrine
EPI, epinephrine
DA, dopamine
HPA, hypothalamic-pituitary-adrenal
BMI, body mass index
VO₂, oxygen consumption
CV, coefficients of variation

A leading pathophysiologic hypothesis of attention-deficit/hyperactivity disorder (ADHD) is based on the notion of a catecholamine [CA; norepinephrine (NE), epinephrine (EPI), and dopamine (DA)] dysfunction (1, 2). This hypothesis suggests that the CA response to environmental stimuli is attenuated in ADHD and is derived primarily from observations that drugs such as methylphenidate and amphetamine—considered to be CA agonists—are effective in treating the symptoms of ADHD (1). Despite this compelling evidence, a definitive role of CA responsiveness in ADHD remains controversial (3).

Testing CA responsiveness in children with ADHD has proved to be complex. Protocols that elicit psychological stress using cognitive challenges—the bulk of research that has been done in children with ADHD—can yield measurable CA responses, but the stimulus is difficult to quantify or standardize (4, 5). Pharmacologic interventions that stimulate stress through, for example, rapid alterations in glycemia, are nonphysiologic, require extensive monitoring, and may not be acceptable or feasible for studies in children (6).

In the present study, we examined the possibility that exercise testing might be useful in differentiating CA responses to stress between subjects who have a diagnosis of ADHD and age- and gender-matched controls. Physical activity is widely known to be a powerful stimulus of the hypothalamic-pituitary-adrenal (HPA) and noradrenergic systems (7). Physical and mental stress each elicits physiologic responses that are mediated through the autonomic nervous system and endocrine system (8). In contrast to other types of stress-inducing protocols, exercise is a naturally occurring and physiologic stimulus of stress hormones, and the magnitude of the input (*i.e.* the

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work rate and duration) can be measured precisely and scaled to the capability of the subject. To our knowledge, testing the CA response using exercise has never been reported in children with ADHD.

We reasoned that the normal robust increase in circulating CA in response to exercise would be blunted in children with ADHD. To test this, we recruited treatment naïve children with newly diagnosed ADHD and measured CA response to an exercise test in which the work was scaled to each subject's physical capability.

METHODS

The study was approved by the Institutional Review Board of the University of California, Irvine. Informed assent and consent were obtained from each subject and his or her parent or legally authorized representative, respectively, before the implementation of any study-related procedures. Standard, calibrated scales and stadiometers were used to determine height, weight, body mass index (BMI; wt/ht^2), and BMI-for-age percentile (9).

Diagnosis of ADHD. Families were recruited by a screening study for evaluation of children with ADHD at the University of California, Irvine, Child Development Center. Children between the ages of 7 and 12 y were eligible. For inclusion in the ADHD group, a diagnosis of ADHD-combined hyperactive/impulsive subtypes was required. This was confirmed in a psychiatric interview of the parent about the child, by endorsement of at least six of the nine symptoms of inattention and six of the nine symptoms of hyperactivity/impulsivity on the Diagnostic Interview Schedule for Children. Children with a current history of depression, anxiety, epilepsy, or other medical conditions were excluded. All children who entered the study were naïve with respect to the use of stimulant medications to treat ADHD. Gender- and age-matched children who were healthy and had no history of ADHD were recruited as a control group.

Exercise protocols. We used an exercise that has been found to be effective in scaling the exercise input to the capabilities of healthy children as well as children with physiologic impairments (10). Each subject underwent two separate exercise testing sessions performed on different days within a week. First, we used a ramp-type progressive exercise test on an electronically braked cycle ergometer used extensively in children and adolescents (11). The second session consisted of a series of 10, 2-min bouts of constant-work rate cycle ergometry with 1-min resting intervals between each exercise bout. The work rate was individualized for each subject by finding the work rate corresponding to 50% of the difference between the anaerobic or lactate threshold of each subject (determined noninvasively from the ramp test) and the peak oxygen consumption (VO_2) (12, 13). This approach was used, in contrast to the prolonged exercise testing, because although young children enjoy prolonged periods of physical activity, they find it hard to sustain constant exercise for more than several minutes at a time. In fact, typical bouts of exercise in children last only 25–30 s (14). The total duration of the second exercise

protocol was 30 min (20 min of cycle ergometer exercise interspersed with 10 min of rest).

We calculated total external work performed by each subject [*i.e.* power \times duration (kilojoules)] and normalized the total work performed to body mass. Finally, we measured the peak and end-exercise heart rate of each subject during the second exercise session.

Blood sampling. An indwelling venous catheter was inserted in the antecubital area. Blood samples were collected at pre-exercise (after 30 min of rest), during the last (tenth) 2-min exercise bout, 30 and 60 min after exercise.

EPI, NE, and DA. EPI, NE, and DA were measured by a radioenzymatic technique based on the conversion of the CA to radiolabeled metanephrine and normetanephrine. This CA assay uses an extraction technique that eliminates substances that may inhibit the radioenzymatic assay. It also concentrates the CA to provide a more sensitive assay. One milliliter of plasma samples was extracted and then concentrated into a 0.1-mL volume before conversion into their radiolabeled metabolites. The assay has an extraction efficiency of 78%. The sensitivity of the assay is 10 and 6 pg/mL for NE and EPI. The intra-assay coefficients of variation (CV) are 4 and 13% for samples containing low levels of CA; variation is less for samples with high levels of CA. The inter-assay CV are 10% and 16%, respectively, for NE and EPI, so the assay is consistent over time. This technique is approximately 10 times more sensitive than the more commonly used assays and thus can reveal changes in venous CA levels that often go undetected (15).

Lactate. Lactate was measured with the use of YSI lactate analyzer (YSI 1500, Yellow Springs, OH, U.S.A.). The intra-assay CV was 2.8%, the interassay CV was 3.5%, and the sensitivity was 0.2 mg/dL.

Statistical analysis. Two-sample *t* tests were used to determine baseline differences in anthropometric variables, fitness variables, and circulating CA between control subjects and subjects with ADHD before the exercise protocol. Repeated measures ANOVA was used to test differences in response to the exercise bout between ADHD and control tests groups. For detecting possible differences in the pattern of response to exercise over time, the primary test of interest was the interaction of the between-subjects factor (group: ADHD *versus* control) and the within-subject factor (time: before, peak, 30 min after, and 60 min after). A post hoc single degree of freedom contrast to compare the baseline to peak change by group was tested to characterize whether the magnitude of response differed between the groups. Data are presented as mean \pm SEM.

RESULTS

Baseline Demographic Data

Ten newly diagnosed untreated male subjects (eight Caucasian, two Hispanic) with ADHD and eight healthy age-matched male controls (seven Caucasian, one Hispanic) volunteered for the study and met the screening criteria. Subject characteristics are presented in Table 1. No significant differences in age, height, weight, or BMI were found between control and ADHD groups.

Effect of Brief Exercise

Peak VO_2 , work rate, and heart rate. No significant differences were found in peak VO_2 , peak VO_2 corrected for body weight, peak work rate, and lactate threshold between control subjects and subjects with ADHD (Table 1). The work rate performed per kilogram of body weight (kJ/kg) was almost identical in the ADHD and control groups. The control group reached a higher heart rate by end-exercise compared with the subjects with ADHD, but this difference was not significant (189.4 ± 3.1 versus 178.1 ± 5.1 respectively; Fig. 1).

Plasma lactate and CA. Plasma lactate increased significantly during exercise in both control and ADHD groups ($p < 0.001$). There was a significant between-group difference in the lactate response to exercise, with a more prominent change in the control group ($p < 0.005$; Fig. 2).

Baseline levels of NE and EPI were within the normal range for both children with ADHD and controls, suggesting that the blood drawing technique/timing was not stressful. Baseline plasma NE were significantly lower in the ADHD children ($p = 0.004$). In response to exercise, mean NE levels rose in both groups; however, the rise in plasma NE was significantly greater in the control children compared with children with ADHD, reaching levels that were more than 2-fold higher in the control group ($p < 0.0005$; Fig. 3).

No difference was found for baseline plasma EPI. EPI levels increased in both ADHD ($p = 0.002$) and controls ($p = 0.006$) after exercise. A statistically significant higher level of EPI at peak exercise was found in the control group ($p = 0.018$). Baseline plasma levels of DA tended to be higher in the ADHD group, but this difference was not significant. After exercise, DA levels in the ADHD group did not change, whereas a significant increase was noted in the control group ($p = 0.016$).

DISCUSSION

This study demonstrates for the first time abnormal responses of circulating EPI, NE, and DA accompanying cycle ergometer exercise in treatment-naïve children with newly diagnosed ADHD. EPI and NE did increase in both control subjects and subjects with ADHD, but the responses were substantially blunted in the ADHD group even though the work performed did not differ from controls. Circulating DA increased significantly in the control subjects, but no increase was noted in the subjects with ADHD. Finally, a significant

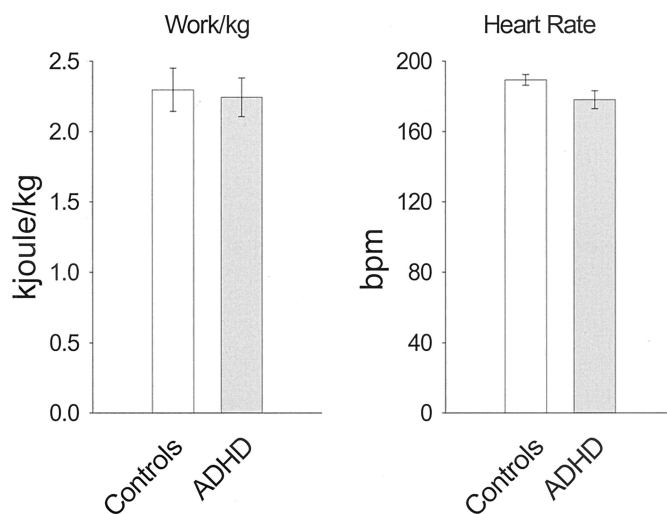


Figure 1. Comparison among total work per body weight and peak heart rate in control subjects and subjects with ADHD. Both ADHD and control groups performed the same total work per body weight. Peak heart rate was higher in the control group but not significantly so.

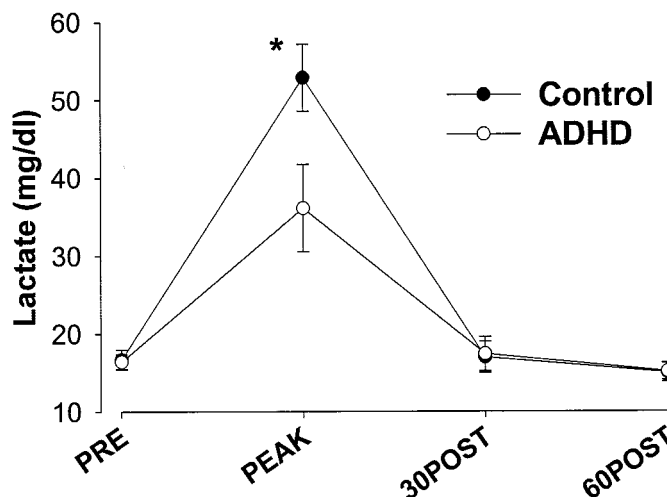


Figure 2. The effect of exercise on lactate levels. Both control subjects and subjects with ADHD had an increase in lactate level after exercise. Control subjects had a statistically significant higher lactate response to exercise compared with subjects with ADHD (* $p < 0.005$).

lower lactate response to exercise was found in ADHD, an observation consistent with a blunted CA response to exercise.

Table 1. Anthropometric, peak VO_2 , and peak work rate in subjects with ADHD and control subjects

	ADHD (n = 10)	Control (n = 8)
Age (years)	8.4 ± 0.4 (range 7–10)	8.6 ± 0.5 (range 7–11)
Height (cm)	135 ± 3 (range 117–145)	138 ± 3 (range 127–154)
Weight (kg)	33.8 ± 2.8 (range 22.3–52.7)	34.4 ± 2.8 (range 25.0–48.6)
BMI (kg/m ²)	18.2 ± 1.1 (range 14.4–25.1)	17.8 ± 0.7 (range 15.3–20.5)
Peak VO_2 (L/min)-ramp test	1.01 ± 0.07 (range 0.47–1.34)	1.11 ± 0.09 (range 0.83–1.48)
Peak VO_2 (mL · min ⁻¹ · kg ⁻¹)-ramp test	30.2 ± 1.7 (range 21.2–37.2)	32.8 ± 2.0 (range 24.4–41.6)
Lactate threshold (L/min)	0.78 ± 0.06 (range 0.48–1.03)	0.79 ± 0.05 (range 0.62–1.09)
Work rate for constant work rate protocol (watts)	66.0 ± 4.7 (range 45.0–85.0)	64.0 ± 5.0 (range 50.0–87.0)
Peak work rate (watts)-ramp test	85.7 ± 5.7 (range 45–105)	98.7 ± 7.1 (range 80.0–130.0)
Heart rate during constant work rate protocol (beats/min)	152.1 ± 4.6 (range 124–172)	159.9 ± 7.1 (range 136–189)

Data are presented as mean ± SEM.

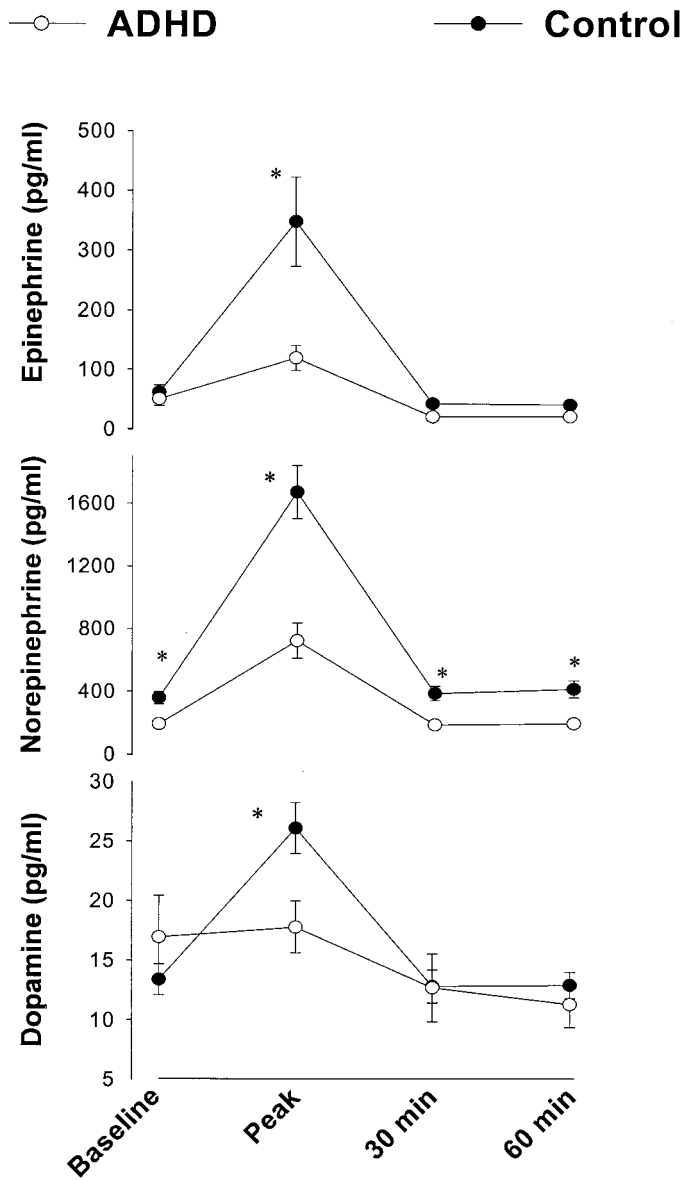


Figure 3. The effect of exercise on CA levels. Significant differences in EPI, NE, and DA responses to exercise were found between the control subjects and subjects with ADHD (* $p < 0.05$).

We selected a relatively high-intensity exercise protocol for this study because the CA response for work performed above the lactate threshold is known to be substantial (16). CA are increased with heavy exercise, in part because of CNS mechanisms. Activation of the HPA axis and sympathetic-adrenal-medullary activation leads to EPI release from the adrenal medulla and NE and, to a lesser degree, DA release, from nerve endings into the circulation (17, 18). Thus, exercise shares with other stresses (e.g. psychosocial) some common pathways that lead to increased CA output. In addition, the CA response to heavy exercise is further stimulated by systemic changes in acid-base balance and reduced oxygen availability to the working tissues (19).

Remarkably, the increase in circulating DA in response to exercise found in healthy children was absent in the subjects with ADHD (Fig. 3). Previous studies have demonstrated an

increase in circulating DA in response to cycle ergometer (20) and resistance exercise (21) in adults, but this is the first documentation of the increase in circulating DA in healthy children. Whether the lack of a DA response in the periphery in ADHD is related, as some investigators propose, to a systemic “dopamine deficit” (22, 23) or, alternatively, simply to less stimulation of the adrenals in response to exercise has yet to be determined.

The present data provide indirect support for the connection between exercise and stimulation of HPA and noradrenergic systems in children with ADHD. This is in agreement with previous studies, for example, Hanna and *et al.* (24), Pliszka *et al.* (25), and Anderson *et al.* (4) who found substantially lower rates of EPI excretion in urine during cognitive testing in subjects with ADHD. These observations are consistent with earlier studies correlating academic performance and EPI excretion (26).

Most consistent with our observation of a blunted CA response to a physiologic stress in ADHD is the study of Girardi *et al.* (6). These investigators gave subjects an oral glucose load that led to an initial hyperglycemia followed by a rapid lowering of blood glucose and an accompanying CA burst. As in our study, Girardi *et al.* noted a blunted CA response in children who had a diagnosis of ADHD.

In studies that use exercise as an input to stimulate hormonal responses, a major potential confounding factor is whether the exercise input is comparable in the control and target groups. For example, if a protocol used a single work rate to compare hormonal response to exercise in two groups of subjects with high and low relative fitness, then the results might be confounded by the fact that the magnitude of the exercise input relative to the capability of each subject was different in the two groups (*i.e.* relatively higher in the unfit sample population). We achieved the goal of appropriately normalizing the work rates in the two populations by measuring fitness in each subject and adjusting the work rate input to the individual’s capabilities. As seen in Figure 1, we found no difference in the magnitude of the work rate input (either in absolute watts or when normalized to body mass) between the two groups. Thus, it is unlikely that the observed difference in the CA response was due to a lower relative work rate input in the ADHD group; rather, the data suggest abnormal CA regulation in the subjects with ADHD.

It is noteworthy that the peak VO_2 values observed in our study tended to be in the lower range of normal values that are typically reported for cycle ergometer exercise in children. Although a strict matched-control design was not used, we sought the control group for this study from a general population and did not target children actively engaged in physical activity, as is often the case, for “normal” values in studies of exercise in children. It may well be and would not be surprising that in a large population comparison between healthy control children and children with ADHD that the latter would prove to have significantly lower levels of fitness.

A number of studies have been performed in normal subjects in which centrally acting pharmacologic agents were used to alter the CA response to exercise. Collomp *et al.* (27) and Stratton *et al.* (28) showed that benzodiaz-

epines, which stimulate γ -aminobutyric acid receptors in the brain and blunt the CA response to a variety of stressors, markedly attenuated the EPI, NE, and DA response to exercise in the circulation. Interestingly, these investigators found that benzodiazepines attenuated the lactate response to exercise, similar to the observation we made in the children with ADHD (Fig. 2), and the blunted lactate response is likely explained by the reduced effect of peripheral CA on glucose metabolism.

Although the lactate levels in response to exercise were lower, the lactate threshold (the inflection point above which lactate concentrations in the circulation markedly increase) was not affected in the Stratton study. Similarly, we found no difference in the lactate threshold, determined noninvasively, between the subjects with ADHD and control subjects. These data showing that CNS suppression can lead to blunted peripheral CA responses supports the idea that there may exist a CNS dysregulation of CA in children with ADHD.

In addition to the exercise response, we found decreased baseline NE in the patients with ADHD. Surprising, little is known about circulating levels of CA in ADHD as the majority of the studies have focused on urine CA levels (2, 4). The lower NE that we found is consistent with some (29–31) but not all (32) previous studies. In the past, some investigators have questioned the relevance of peripheral (*i.e.* circulating) levels of CA in that they may not reflect CNS activity. However, it has become clear that activity of the peripheral nervous system does correlate with activity in the brain (33). Indeed, administering CA into the peripheral circulation (*n.b.*, CA reportedly do not cross the blood-brain barrier) induce cognitive changes strongly suggestive of CNS effects (34).

Both physical exercise (35) and traditional pharmacologic treatment for ADHD with low doses of methylphenidate or amphetamine (36) increase executive function of the brain. Shepard *et al.* (37) demonstrated that long-term increases in physical activity were associated with improved academic performance in public school students. Despite the compelling physiologic role that exercise could play in the management of ADHD, to our knowledge, there have been no controlled studies designed to examine potential therapeutic benefits of exercise in ADHD. Our data pose some intriguing questions. First, does the blunted CA response to exercise also reflect a reduced exercise effect on executive function? Does repeated exercise (*i.e.* training) lead to an enhanced CA response to exercise or to other stresses in ADHD? Finally, does the CA response to exercise become normalized in the presence of traditional pharmacologic treatments with stimulant medications?

CONCLUSION

In summary, we found that the CA response to exercise was markedly reduced in children with ADHD. The agreement across studies examining the adrenomedullary and sympathetic responses in ADHD using various provocations, whether pharmacologic, cognitive, or physiologic, is remarkable. Our data suggest that CA excretion after a minimally invasive, nonpharmacologic exercise challenge in children with ADHD is defi-

cient compared with healthy control children. These preliminary data are consistent with previous studies indicating that children with ADHD have lower CA responses to pharmacologic, physiologic, and cognitive challenges.

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