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Cortisol reactivity and weight gain among adolescents who vary in prenatal drug exposure

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Abstract

Objective—Low inhibitory control is linked with weight gain among youth. Inhibitory problems are associated with disruption to the Hypothalamic-Pituitary-Adrenal axis (HPA) cortisol response. Increased cortisol predicts appetite and weight gain (though may be gender specific). This study hypothesized that cortisol reactivity explains the association between inhibition and weight gain while considering the moderating factors of early stressors to the HPA axis (e.g. prenatal-drug exposure; PDE) and gender.

Methods—Adolescents with PDE (n = 76) and non-exposed comparison adolescents (NE; n = 61) completed the Conner's Continuous Performance Test (CPT) and provided salivary cortisol samples. BMI z-score were measured at the initial and 12-month follow-up evaluations. A bootstrapped moderated-mediation analysis was conducted to test for conditional indirect effects of cortisol reactivity.

Results—Lower inhibition was associated with increased cortisol reactivity among youth who were NE, and increased cortisol reactivity was associated with weight gain among girls. Cortisol reactivity mediated the relation between inhibition and BMI z-score change for the girls in the group who was NE.

Conclusion—Increased cortisol reactivity may play a mechanistic role in predicting weight gain among non-prenatally drug exposed girls. Cortisol reactivity may be a biomarker for targeted interventions to improve biological regulation and ultimately health risk among girls.

Keywords

Cortisol; Inhibition; BMI; Prenatal Drug Exposure; Gender

In the United States, the prevalence of overweight/obesity is high, particularly among African-American adolescents.¹ Excess weight gain during childhood is a major determinant

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of young adult obesity. Increases in *rate* of weight gain has the potential to increase subsequent obesity-related health risks in young adults.²

Impaired self-regulation has been implicated in excess weight gain among children.^{3,4} Inhibition, an aspect of self-control, refers to the ability to control an impulse or behavior.⁵ Although studies support an association between inhibitory control and weight gain,^{5–7} most studies are cross-sectional.^{7,8} Limited longitudinal evidence suggests that low inhibitory control during childhood increases the likelihood of overweight by adolescence, for girls only.^{3,4,9} In addition, little is known about how and why they are connected.⁷ Research on this topic has often focused on behavioral mediators with limited attention to neurocognitive functioning and obesity.^{7,10}

Cortisol, a glucocorticoid hormone produced by the Hypothalamic-Pituitary-Adrenal axis (HPA), serves as a major indicator of physiological states in response to stress.^{7,10} Under normal, low stress conditions, the HPA axis follows a diurnal pattern and releases. Cortisol in high concentrations in the morning, decreases sharply toward midday, and slowly decreases throughout the rest of the day.¹¹ With an acute stressor, the hypothalamus releases corticotrophin releasing hormone (CRH), thereby activating the HPA axis to secrete cortisol, which mobilizes fats and prevents nutrient uptake. Although CRH increases alertness and causes appetite suppression, it is cleared quickly. However, under conditions of chronic stress, the HPA axis may become dysregulated by prolonged, repeated glucocorticoid elevations, resulting in down-regulation of the HPA axis response and prevention of an expected stress response. Upon activation of the stress response, the HPA axis coordinates responses with the hippocampus, amygdala, and prefrontal cortex. These brain areas are integral to cognition and inhibition because they aid in interpreting whether events are stressful.¹² Inhibition problems are typically associated with disruptions to the HPA axis, or cortisol response.¹¹

Cortisol regulates glucose metabolism. Chronically elevated cortisol may result in appetite stimulation, particularly for fatty, sugary, and starchy foods, resulting in weight gain with increased visceral and truncal fat deposition.¹³ However, findings regarding cortisol *reactivity* and weight gain are mixed. Cortisol reactivity is the difference between baseline cortisol and cortisol response to stress. Several studies report that *increased* cortisol reactivity is positively associated with higher body mass in adolescents and older children,¹⁴ others have reported associations between *less* cortisol reactivity and higher body mass¹⁵ or found no association.¹⁶ Most studies of the cortisol–adiposity association have not considered moderating influences, such as chronic stress exposure and gender.^{14,16}

Activation of the HPA axis and cortisol release are central components in coping with daily stressors.¹⁷ However, repeated or chronic stress exposure has been linked with disrupted HPA axis functioning, particularly during early brain development.¹¹ Stressors, such as prenatal drug exposure (PDE; cocaine/heroin) may impact fetal brain development and dysregulate the HPA axis and the cortisol response to stress.^{11,17} Several studies and a recent review have demonstrated the likelihood of down-regulation, or blunting, in the cortisol response system among adolescents with PDE.¹⁸ It is plausible that repeated activation of cortisol secretion leading to disruption of the neuroendocrine system in response to stressors,

such as PDE, may have detrimental effects on metabolic processes related to appetite and weight gain.¹³

In sum, low inhibitory control has been linked with weight gain in children⁴ and cortisol production.¹¹ Increased cortisol secretion is predictive of increased appetite and weight gain (though this association may be gender specific).¹⁰ It is plausible that increased cortisol reactivity may explain the association between inhibitory control and weight gain. If HPA axis functioning is disrupted (as with PDE), failure to find this link among this population may provide additional evidence that cortisol serves as a mechanism in weight gain.

We tested three hypotheses. 1) The relation between low inhibition and cortisol reactivity varies by PDE status with low inhibition related to increased cortisol reactivity among those were non-exposed (NE), rather than the youth with PDE. No association is expected in the group with PDE. 2) The association between cortisol reactivity and BMI z-score change varies by gender, with increased cortisol reactivity predictive of greater BMI z-score change (over 1 year) for girls, not boys. 3) There is a conditional indirect effect of cortisol reactivity on the association between inhibition and BMI z-score change. Specifically, increased cortisol reactivity mediates the relation between low inhibition and weight gain for girls in the group who was NE.

Method

Participants

Participants were 137 adolescents (M=14.12 years, SD=1.16), 55% in the group with PDE (76/137). More than half (54%) of the group with PDE was exposed to both cocaine and heroin. The total sample was 50% male and predominantly (99%) African American (Table 1). Adolescents had been enrolled in a home-based trial for substance-abusing women and infants.^{18,19} Eligibility requirements included gestational age >32 weeks, birth weight >1,750g, and no birth complications/admission to the neonatal intensive care unit.¹⁹ Infant prenatal cocaine and/or heroin exposure were validated by positive maternal or infant urine toxicology or maternal self-report of use. Toxicology screens were conducted routinely during all deliveries during that time period.¹⁹

Children non-exposed to cocaine or heroin were recruited at age 5 (n=70)¹⁹ and in early adolescence (n=24).¹⁸ The group that was NE served as a community comparison for the PDE group. Recruitment of the group that was NE occurred at a primary care clinic serving the same University Hospital where the participants with PDE were recruited. Inclusion criteria, based on medical record review, included birth in the University Hospital between 1991 and 1993, negative toxicology screens, no evidence of maternal substance use, in the custody of their biological mother, and group matched by socioeconomic status, maternal age at first pregnancy, child age, gender, and race with the group with PDE.^{18,19}

Procedures

This study was approved by the Institutional Review Board of a major university. All participants provided written consent (caregivers) or assent (adolescents). Youth participated in a laboratory-based assessment (Time 1) and one year follow-up (Time 2).

At Time 1, adolescents completed several neuropsychological assessments and provided saliva samples collected over a 4.5–6 hour period, later assayed for cortisol. Participants were instructed to fast for three hours prior to assessment because cortisol can be affected by glucose. The first saliva sample was collected pre-task ($M=9:41\text{am}$, $SD=.85\text{ hrs}$)¹⁸ after which adolescents completed the computer-based mild stressors. Approximately 30 minutes after the mild stressors, a second cortisol sample was collected (post-task; $M=10:42\text{ am}$, $SD=.86\text{ hrs}$); 99% of pre and 97% of post task saliva collections were completed before noon.¹⁸ At Time 2, only anthropometry was conducted, all other measures were collected at Time 1.

Measures

Body mass index—Anthropometry was conducted at Time 1 and Time 2 (approximately 12 months apart). Body mass was measured twice using a Tanita scale, and the average was retained. Following a standard protocol, height was measured twice to the nearest 0.10 cm using a SECA stadiometer, and the average was retained. BMI was calculated by dividing weight in kg by height in meters squared. BMI-for-age z-score were calculated based on 2000 Center for Disease Control Growth Charts. BMI z-score change was calculated as the difference between Time 1 and Time 2 BMI z-scores.

Conners' Continuous Performance Test II—The Conner's Continuous Performance Test (CPT) assesses sustained visual attention or the ability to discriminate between target and non-target stimuli presented at variable intervals.²⁰ Single letters appear on the computer screen for 250 ms. Participants are asked to press the spacebar when any letter except "X" appears. Commission errors occur when subjects press the spacebar on trials when the letter "X" is presented. Commission errors served as a measure of inhibitory control, with high scores interpreted as low inhibitory control. In validation studies with healthy children, split-half reliability for all CPT-dependent variables ranged between 0.73–0.95, and test-retest reliabilities for a 3-month interval ranged from 0.55–0.84.

Cortisol reactivity—Whole saliva samples were collected through passive drool. Samples were frozen at -20°C , and transported to Salimetrics Laboratories via dry ice and overnight delivery State College, PA.²¹ Samples were assayed in duplicate using a commercially available immunoassay. Test volume was 25 μL and sensitivity ranged 0.007–3.0 $\mu\text{g/dL}$. On average, intra-assay coefficients of variation were less than 5%, and inter-assay coefficients of variation were less than 15%. Salivary cortisol values were skewed and kurtotic and subjected to $\ln$ transformation. Using procedures previously reported, a continuous change reactivity score was calculated.¹⁸

Mild stressors—Mild stress was elicited via two computer-administered tasks, the Balloon Analogue Risk Task-Youth (BART-Y) and the Behavioral Indicator of Resiliency to Distress (BIRD). The BART-Y measures risk-taking propensity from a cognitive decision-making perspective.²² Participants are asked to inflate a computerized balloon over multiple trials for an accumulation of points leading to prizes. The larger the balloon, the larger the prize; the balloon can explode at any time, making a loud popping sound. If the balloon explodes, accumulated points are lost. The BIRD was designed to mimic the adult

computerized distress tolerance task.²³ Participants are asked to click on the numbered box below the green dot before it moves to another box. The goal is to free a computerized bird from a cage. The computerized bird emits a shrill chirping sound each time it is freed. The green dot sometimes moves very slowly and sometimes extremely quickly between the boxes. Cortisol samples were deemed 'reactive' to the stressor if they had a 10% difference between pre and post task cortisol levels and an absolute difference of at least 0.02 µg/dL between pre task and post task cortisol collections.¹⁸ Overall, 19% of the sample demonstrated a measurable reaction to the mild stressors, consistent with current literature.²¹

Data Analytic Plan

Data were analyzed using IBM SPSS 22 Statistics Developer Version 22. Outliers were identified using visual inspection and boxplots. Cases with more than ± 3 standard deviations from the mean were assigned to the value of the closest non-extreme value, thereby minimizing the effect of extreme values while maintaining the rank order of the distribution.²⁴ Data missing completely at random (equipment error) were imputed using hot deck procedures.²⁵

Bivariate Pearson correlations were conducted among variables of interest (PDE status, cortisol reactivity, gender, BMI z-score, inhibition) and theoretically relevant variables (prenatal tobacco exposure, prenatal alcohol exposure, time of cortisol collection and child age). Categorical variables (child gender, PDE status, prenatal tobacco exposure, prenatal alcohol exposure) were dummy coded (footnote in Table 1). One way ANOVAs were conducted to examine the impact of intervention status on variables of interest. Mediation analyses were conducted using the SPSS macro PROCESS²⁶ (Model 28).

Moderation analyses were conducted to examine if 1) PDE status moderated the relation between inhibition and cortisol reactivity and 2) child gender moderated the relation between cortisol reactivity and BMI z-score change. To examine whether the interactions conformed to the hypothesized pattern, simple slopes analyses were conducted (PDE v. NE and girls v. boys).²⁶

To test for conditional indirect effects, a moderated mediation analysis was conducted using bootstrapping (5000 samples). Bootstrapping involves drawing repeated samples from the data with replacement to gain multiple estimates of the indirect effect.²⁶ This statistical approach to test mediation offers three advantages over prior approaches. It does not make the erroneous assumption of normality for direct effects, multiple mediators and moderators can be tested simultaneously, and Type II errors are reduced because fewer inferential tests are required²⁶. Bootstrapping bases significant results upon finding that the 95% Confidence Interval (CI) does not contain zero.

Results

The mean Time 1 BMI z-score was 0.97 (SD=0.84); 18% of youth were classified as overweight (BMI between the 85th and 95th percentile for age and gender), and 27% had obesity (BMI above the 95th percentile for age and gender). McNemar tests showed that the group that was NE was significantly less likely than the group with PDE to have been

prenatally exposed to alcohol ($p=.001$) but not tobacco ($p=.71$). There were no group differences in Time 1 BMI z-score $t(135)=-0.14$, $p=.88$, or Time 2 BMI z-score $t(103)=.13$, $p=.26$. One-way ANOVAs revealed no intervention group differences on any outcome variables ($p<.05$). Bivariate correlations and descriptive data are shown on Table 1. Age was correlated with cortisol reactivity and was included as a covariate. Cortisol collection time was not associated with any endogenous model variables, but was included as a covariate to account for theoretical confounds. Unstandardized coefficients for the complete model are presented in Figure 1.

Moderation Predicting Cortisol Reactivity

The moderating effect of the group with PDE on the path between the independent variable (inhibition) and the putative mediator (cortisol reactivity) was examined. The interaction coefficient, (inhibition*PDE) was a significant predictor of the mediator cortisol reactivity (Figure 1). Specifically, lower inhibition was predictive of greater cortisol reactivity for the group that was NE (Figure S2).

Moderation Predicting BMI z-score Change

The moderating effect of child gender on the path between the putative mediating variable (cortisol reactivity) and the dependent variable (BMI z-score change) was examined. The interaction coefficient (child gender*cortisol reactivity) was a significant predictor of the dependent variable, BMI z-score change (Figure 1) such that higher cortisol reactivity was predictive of increases in BMI z-score among girls (Figure S3).

Moderated Mediation Predicting BMI z-score

The complete moderated mediation model estimated the indirect (meditational) effects of inhibition on child BMI z-score change through cortisol reactivity at varying levels of the moderators (PDE exposure and child gender). Bootstrapped CIs obtained²⁶ showed that cortisol reactivity significantly mediated the relation between inhibition and BMI z-score change for girls in the NE group (Table 2). Examination of the index of moderated mediation showed that the indirect effects were significantly different for girls in the group that was NE (95% CI: $-.0136$ to $-.0005$).

Discussion

Our goal was to examine cortisol as a mechanism to explain the association between inhibition and weight gain among adolescents who vary in PDE status. The study had three main findings: 1) lower inhibition was associated with increased cortisol reactivity among youth who were NE, with no association for youth with PDE, 2) increased cortisol reactivity was associated with increased weight gain among girls, but not boys, and 3) cortisol appears to mediate the association between inhibition and weight gain for girls who were NE. These results support the hypothesis that increased cortisol reactivity plays a mechanistic role in predicting weight gain among girls. This study fills a gap in the literature by examining the mediators and moderators of relations between neurocognitive functioning and weight gain.⁷

PDE Status Moderates the Association between Inhibition and Cortisol Reactivity

Impulsivity was significantly associated with cortisol reactivity, only for the group that was NE. This finding is consistent with previous literature that describes blunted cortisol reactivity following early life adversity (such as PDE).²⁷ The research regarding low inhibitory control and blunted stress responsivity has focused primarily on drug use and sexual behavior.²⁷ This study extends existing research related to HPA axis functioning by examining how weight gain relates to low inhibition and *high* cortisol stress response, while considering the impact of gender.¹⁴

Gender Moderates the Association between Cortisol Reactivity and Weight Gain

The finding that cortisol reactivity was associated with weight gain only for girls is consistent with gender differences identified in previous studies.^{10,14,21} Physiological mechanisms may underlie gender differences. Chronic cortisol elevations in girls may change the HPA axis and estrogen production. Estrogen is of particular interest because it has been associated with fat deposition in girls.¹⁰ Also, there may be gender differences in patterns of glucocorticoid receptor expression or within dopaminergic systems.¹⁰ Gender differences have been documented regarding food choices,²⁸ and brain function related to food.²⁹ Our results suggest that some of the mixed research regarding cortisol reactivity and weight may be attributed to moderating factors, such as gender. Future research should examine gender specific responses in cortisol reactivity and their relation to weight gain.

Conditional Indirect Effects of Cortisol Reactivity

This study extends prior research by examining both the mediating effect of cortisol reactivity, and the moderating impact of gender and early stress exposure on weight gain. Consistent with prior work,¹⁴ both stress exposure and gender differences were observed in regard to HPA axis activity and weight gain. The current study builds upon prior research¹⁴ by examining HPA axis activity as a potential mechanism linking inhibitory control to adolescent weight gain, while incorporating the impact of gender and stress exposure to explain associations between inhibitory control and weight gain.⁶⁻⁸

Strengths and limitations

Findings should be considered in the context of the limitations and strengths. Small sample size precluded our ability to examine more complex models that may have accounted for additional factors effecting cortisol reactivity. Information on use of medications was not available and the homogeneous nature of our sample limits generalizability. However, the findings from a high risk sample with many adolescents with overweight and obesity contribute to understanding mechanisms that contribute to weight gain.

This study has numerous strengths. The longitudinal design and systematic assessment of prenatal drug exposure provides clarity regarding mechanisms influencing weight gain. The study employed objective measures of BMI, inhibition and biological indicators, avoiding problems associated with self-report.⁷

Clinical Implications

Almost half (45%) of the adolescents in this study had a classification of overweight/obese, consistent with the national average among African-American adolescents.¹ BMI *trajectories* during childhood are strongly associated with cardiovascular risks, above and beyond BMI at any given point in time in childhood.² The mid-teen years may “represent a ‘tipping point’ after which the vascular system no longer adapts to childhood adiposity and readily measurable vascular damage begins to occur.”² Adolescence is characterized by relative immaturity of the frontally mediated cognitive control system which is vital to the inhibition of impulsive responses and to decision making based on environmental stimuli.⁷ Underdeveloped inhibitory skills combined with greater autonomy over food choices in adolescence¹⁰ pose a risk for weight gain during this critical time. Results of the current study highlight the role of biological underpinnings in the relation between inhibition and weight gain. Results show that physiological processes likely play a mechanistic role. Interventions that target self-regulation skills have produced improvements in executive functioning and weight regulation,³⁰ and cortisol reactivity may be a biomarker for targeted interventions to improve biological regulation and ultimately health risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Armstrong and Dr. Buckingham-Howes conceptualized and designed the study, drafted the original manuscript, and reviewed and revised the manuscript. Dr. Armstrong carried out the analyses. Dr. Black obtained grant funding for the parent study, contributed to the conceptualization of the current study and critically reviewed the manuscript.

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Figure 1.

Conditional indirect effects model examine the mediating role of cortisol reactivity on the relation between inhibition and BMI z-score change.

Model controls for child age, and time of day cortisol sample was collected.

Unstandardized B weights and (standard errors) are presented along each path.

* $p = .05$ ** $p < .01$ non-significant paths are noted by the dotted line.

Index of moderated mediation = $-.006$ (CI: $-.0136$ to $-.0005$)

Table 1

Correlations between key study variables and key demographic variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Child Age	1								
2. Child Sex ^a	.092	1							
3. PDE Status ^b	.088	.000	1						
4. Alcohol exposure ^b	.007	.000	.372**	1					
5. Tobacco Exposure ^b	-.124	-.015	.578**	.404**	1				
6. Cortisol Collection Time	-.025	.054	.249**	.153	.302**	1			
7. Cortisol Reactivity	-.227**	-.124	-.119	-.156	-.124	.006	1		
8. BMI z-score change	-.109	-.088	.198*	.119	.114	.120	.080	1	
9. CPT commission T-score	-.095	.016	-.066	-.124	.008	-.020	.107	-.028	1
Mean (SD) or %	11.92 (.16)	50%	45%	62%	47%	9:37 (51)	-.059 (.16)	.001 (.35)	52.8 (9.42)

^aCoded in reference to boys^bCoded in reference to non-exposed*
p < .05,**
p < .01

Conditional indirect effects of inhibition on BMI z-score change through cortisol reactivity by gender and PDE status

Table 2

Outcome	Girls		Boys	
	Estimate	Bootstrapped CI	Estimate	Bootstrapped CI
Prenatally drug exposed	-.0011	-.0047 .0005	-.0014	-.0056 .0003
Non-prenatally drug exposed	.0023*	.0001 .0066	.0007	-.0004 .0032

* Significance is based on the bootstrapped confidence interval (CI) not containing zero