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11β–Hydroxysteroid Dehydrogenase Type 1 Activity in Short Small-For-GA Children and in Response to GH Therapy

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ABSTRACT: Small for GA (SGA) children are at risk for developing the metabolic syndrome. Those who do not catch up, and remain short (SSGA), may benefit from GH therapy. 11β Hydroxysteroid dehydrogenase type 1 (11β-HSD-1) is expressed in visceral fat and is implicated in metabolic morbidity. We hypothesized that SSGA children will have increased basal and glucocorticoid (GC)-stimulated 11β-HSD-1 activity. Twenty SSGA children, aged 7.1 ± 1 y (mean ± SD), were studied before and while on GH therapy and compared with 12 normal age-matched controls. 11β-HSD-1 activity was evaluated by gas chromatography mass spectrometry (GCMS) of urinary steroid product/substrate ratios. GC-stimulated 11β-HSD-1 activity was assessed after overnight dexamethazone (DEX), by oral cortisone conversion to cortisol. In SSGA children, 11β-HSD-1 activity was lower ($p < 0.05$) and GC-stimulated activity enhanced. SSGA children had maximal cortisol generation of 883 ± 108 compared with 690 ± 63 nmol/L in controls ($p < 0.04$). GH treatment suppressed 11β-HSD-1 activity. GC-stimulated enzyme activity correlated negatively with GA ($r = -0.53$, $p < 0.01$) and birth weight ($r = -0.55$, $p < 0.01$). SSGA is associated with enhanced GC-stimulated 11β-HSD-1 activity. This may be programmed *in utero*, as it is not a function of body composition or secondary metabolic derangement. GH therapy normalizes GC-stimulated 11β-HSD-1 activity. **(*Pediatr Res* 70: 208–212, 2011)**

By definition, 5–10% of all neonates are born small for GA (SGA). Some of these children do not catch up (1,2) and remain short. They may benefit from GH therapy (3–5). This subgroup is designated in this article as short SGA (SSGA). Regardless of their later growth pattern, SGA children are at risk for developing the metabolic syndrome later in life (6–10). This increased risk for future morbidity has been documented more in SGA individuals who had catch up growth (11–13), than in those who did not (14–16).

Fetal programming might be coupled with several endocrine pathways (17), including the hypothalamic-pituitary-adrenal (HPA) axis (18–20). Indeed, elevated cortisol levels have been reported for adults born SGA (21) and in SSGA children (22–24). Elevated cortisol levels may also be involved in pre- and postnatal growth, as demonstrated by the inverse correlation between cortisol levels in cord blood and embryo length gained during the first trimester in intrauterine growth retarded (IUGR) children (25).

Prereceptor modulation of cortisol by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) converts cortisone to cortisol for intracrine action (26). Among other regulatory mechanisms of enzyme activity (27), GH inhibits 11β-HSD-1 activity and gene expression, while GH deficiency is associated with enhanced enzyme activity (28–31).

The working hypotheses of this study were that SSGA children will have increased basal and GC-stimulated 11β-HSD-1 activity and that these will be inhibited by GH treatment. Toward these hypotheses, we studied *in vivo* 11β-HSD-1 activity, as measured by the ratios of urinary cortisol/cortisone metabolites and cortisone-generated cortisol, and their response to GC in prepubertal SSGA children at baseline and while on human GH (hGH) therapy.

PATIENTS AND METHODS

Patients. Between November 2004 and May 2005, 32 prepubertal nonobese children enrolled in this study: 20 SSGA and 12 normal controls, who were appropriate for GA (AGA) siblings of the SSGA group. For SSGA children, pretreatment height was shorter by −2.5 Standard Deviation Score (SDS), and birth weight or length smaller by −2 SDS for GA. SSGA children did not receive glucocorticoids (GCs) during the perinatal period; they were healthy, with no anomalies or perinatal morbidity and had normal GH response to provocative stimulation. Inclusion criteria for controls were good health, prepubertal, normal birth weight, and normal current weight and height for age (Table 1). The Helsinki Committee of the Rambam Medical Center approved the protocol. Parents of all participants signed informed consent after receiving explanations of the study.

Design. Fasting second morning urine samples were collected on d 1 for steroid analysis by gas chromatography mass spectrometry (GCMS) (32). At 2300 h of d 1, subjects received 1 mg/m^2 dexamethazone(DEX) to suppress endogenous cortisol production and to evaluate the effect of GC on 11β-HSD-1 activity. The next morning, a clinical test of *in vivo* cortisol generation from cortisone (33) was performed to evaluate 11β-HSD-1 activity under the influence of a GC. At 0800 h the following day, serum cortisol was measured and subjects received enterally 25 mg/m^2 cortisone acetate (Rekah, Israel) as a substrate for 11β-HSD-1. The enzymatic product cortisol was measured after 2 and 4 h. Cortisol generation was defined as the increased level over the DEX-suppressed baseline. SSGA children repeated the urine analysis and the GC-stimulated cortisol generation test after 3 mo of GH treatment (Norditropin Simplexx, Novonordisk, Denmark; 0.03 mg/kg/d).

Medical surveillance at baseline and after 3 mo of hGH treatment included auxology; IGF-1 levels; complete blood count; electrolytes; fasting plasma

Abbreviations: a-C/b-C, α cortol/β cortol; **a-CL/b-CL,** α cortolone/β cortolone; **allo THF,** 5 α tetrahydrocortisol; **DEX,** dexamethazone; **GC,** glucocorticoids; **GCMS,** gas chromatography mass spectrometry; **hGH,** human GH; **11β-HSD-1,** 11-beta hydroxysteroid dehydrogenase type 1; **SDS,** Standard Deviation Score; **SGA,** small for GA; **SSGA,** short small for GA; **THE,** tetrahydrocortisone; **THF,** tetrahydrocortisol

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Table 1. *Anthropometric data of SSGA and control subjects*

	SSGA	Controls
n	20	12
Sex (female/male)	9/11	4/8
GA (wk)	37.2 ± 2.5	40.3 ± 2.1
Age range (y)	5–9	4.6–11
Age average (y)	7.1 ± 1	8.2 ± 1.9
Birth weight (g)	2070 ± 390*	3250 ± 340
Birth weight (SDS)	−2.46 ± 1.1*	−0.4 ± 0.1
Current height (cm)	107.5 ± 6.5*	125.9 ± 13.2
Current height (SDS)	−2.86 ± 0.45*	−0.4 ± 0.7
Current weight (kg)	17.2 ± 3.1*	26.5 ± 8.4
BMI (SDS)	−0.8 ± 0.7*	−0.1 ± 1.2

Mean ± SD.
* $p < 0.0001$.

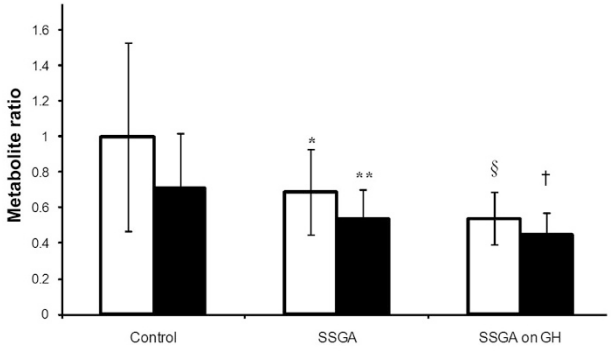

Figure 1. Basal urinary 11β-HSD-1 activity in SSGA and control children, as calculated from the product/substrate ratios (THF + allo THF)/THE (□) and (THF + allo THF + a-C+b-C)/(THE+ a-CL+b-CL) (■). Mean ± SD, control *vs* SSGA, *$p = 0.034$, **$p = 0.044$. Basal *vs*. hGH-treated calculated urinary 11β-HSD-1 activity in SSGA. Mean ± SD, §$p = 0.008$, †$p = 0.014$.

glucose; serum insulin and lipid levels; and a safety panel of liver, renal, and thyroid functions.

Methods. GCMS was performed to evaluate urinary metabolites of cortisol and cortisone as previously described, using gas chromatography equipped with an Agilent 7683 Autoinjector interfaced to an Agilent 5972 mass-selective detector (32).

11β-HSD-1 activity was calculated by the ratios (THF + allo THF)/THE and (THF + allo THF + a-C + b-C)/(THE + a-CL + b-CL) where THF denotes tetrahydrocortisol; allo THF, 5 α tetrahydrocortisol; THE, tetrahydrocortisone; a-C, α cortol; b-C, β cortol; a-CL, α cortolone; and b-CL, β cortolone.

11β-HSD-2 activity was calculated by the ratios THE/(THF + allo THF) and (a-CL + b-CL)/(a-C + b-C). 5α reductase activity was calculated by An/Et, 11-OH-An/11-OH-Et, allo THB/THB, and allo THF/THF where An denotes androsterone; Et, etiocholanalone; 11-OH-An, 11-hydroxy-androsterone; 11-OH-Et, 11-hydroxy etiocholanalone; and allo THB, 5 α tetrahydrocorticosterone) (34,35).

Cortisol generation test is based on:

$$\text{Cortisone} \xrightarrow{11\beta\text{-HSD-1}} \text{Total cortisol}$$

11β-HSD-1-generated cortisol = Total cortisol [−] DEX-suppressedcortisol

Serum cortisol was assayed on Immulite 2000 systems (Siemens, Los Angeles, CA, USA). Interassay CV% 5.2%–7.4% and Intrassay CV% 6.2%–9.4%.

Statistical analysis. A separate variance *t* test was performed to validate differences between SSGA and control children. After verification of normal distribution by D'Agostino's K-squared test ($p = 0.04$), paired *t* test was performed to estimate the impact of GH treatment. Correlations were calculated to assess interrelation between variables.

Sample size was determined by the number of available patients to this protocol.

Appropriate statistical techniques and methodic caution were used to ensure statistical significant results in this sample size.

RESULTS

Patients' surveillance, including complete blood count; electrolytes; fasting plasma glucose; serum insulin and lipid levels; and a safety panel of liver, renal, and thyroid functions, and IGF-1 levels, was normal in all subjects.

The mean basal 11β-HSD-1 activity, calculated from urinary (THF+ allo THF)/THE and (THF + allo THF + a-C+b-C)/(THE+ a-CL+b-CL) ratios, was lower in the SSGA group (0.69 ± 0.24 and 0.53 ± 0.16, respectively, mean ± SD) than in the control group (1.00 ± 0.53, $p = 0.034$ and 0.71 ± 0.31, $p = 0.044$, respectively, Fig. 1).

Mean basal urinary 11β-HSD-2 and 5α reductase activities were comparable in the two groups and on hGH therapy (Table 2).

Overnight DEX suppressed 0800 h endogenous cortisol to mean values of 28 ± 20 and 23 ± 17 nmol/L in SSGA and control groups, respectively. Cortisol levels after subtracting baseline cortisol are presented in Figure 2. GC-stimulated 11β-HSD-1 activity, as reflected by cortisone-generated cortisol, was enhanced in SSGA children *versus* controls; SSGA children had maximal cortisol generation of 883 ± 108 compared with 690 ± 63 nmol/L in controls ($p > 0.040$).

Three-month treatment with hGH in SSGA children resulted in height velocity SDS of 3.8 ± 1.7, and increased IGF-1 levels from 105 ± 71 to 150 ± 82 ng/mL ($p < 0.02$). hGH treatment of SSGA children resulted in a reduction of calculated urinary 11β-HSD-1 activity, expressed as (THF+ allo THF)/THE ratio, from 0.69 ± 0.24 to 0.54 ± 0.15 ($p > 0.008$); and (THF + allo THF + a-C+b-C)/(THE+ a-CL+b-CL) from 0.53 ± 0.16 to 0.45 ± 0.12 ($p > 0.014$, Fig. 1). hGH therapy inhibited GC-stimulated 11β-HSD-1 activity in SSGA and normalized it to 750 ± 63 nmol/L ($p < 0.05$), levels that are not statistically different from normal controls (Fig. 2).

In SSGA, but not in control children, GC-stimulated 11β-HSD-1 activity correlated negatively with both GA ($r = -0.53$, $p < 0.01$) and birth weight ($r = -0.55$, $p < 0.01$, Fig. 3); activity was higher in children with shorter gestation and lower birth weight. GC-stimulated 11β-HSD-1 activity did not correlate with age, height SDS, weight SDS, BMI SDS, or Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and there was no sexual dimorphism. GC-stimulated 11β-HSD-1 activities did not correlate with the growth response to GH therapy, and urinary calculated 11β-HSD-1 activity did not correlate with any anthropometric or metabolic parameter. Due to lack of statistical evidence of a relation between body size and 11β-HSD-1 activity, no adjustment was made for body size in calculations relating to SSGA children.

DISCUSSION

The pathophysiology of the increased risk for metabolic syndrome in SGA individuals is poorly understood. Nevertheless, this risk has been clinically documented. Several theories

Table 2. *Urinary 11β-HSD-2 and 5 α reductase activities of controls* vs *SSGA before and on GH (mean ± SD)*

	SSGA	Controls	*p*	SSGA on GH	*p*
5α-reductase activity					
An/Et	0.9 ± 0.4	1.1 ± 0.6	0.12	0.9 ± 0.5	0.32
11-OH-An/11-OH-Et	2.6 ± 3.3	1.1 ± 0.3	0.12	1.9 ± 1.4	0.99
allo THB/THB	2.7 ± 1.9	3.7 ± 2.1	0.87	3.0 ± 2.0	0.91
allo THF /THF	0.8 ± 0.3	0.9 ± 0.4	0.53	0.7 ± 0.3	0.85
11ß-HSD-2 activity					
THE/(THF + allo THF)	1.58 ± 0.53	1.36 ± 0.62	0.31	1.9 ± 0.6	0.1
(a-CL + b-CL)/(a-C + b-C)	4.6 ± 1.7	5.5 ± 2.58	0.23	5.8 ± 3.6	0.26

An, androsterone; Et, etiocholanalone; 11-OH-An, 11-hydroxy-androsterone; 11-OH-Et, 11-hydroxyl-etiocholanalone; allo THB, 5 a tetrahydrocorticosterone.

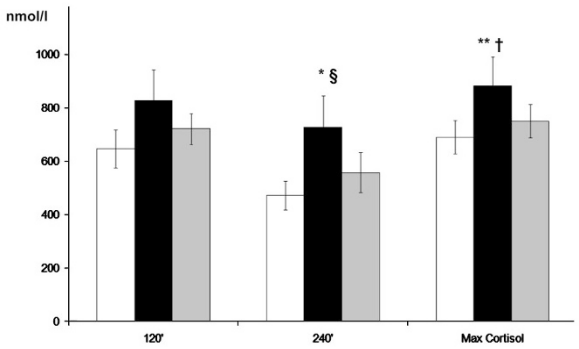

Figure 2. GC-stimulated cortisol generation in SSGA (■) and control children (□). Mean ± SEM, control *vs* SSGA, $*p$ **< 0.012 (at 240′),** $**p < 0.04$ **(maximum cortisol).** GH effect on GC-stimulated 11β-HSD-1 activity in SSGA (▣) compared with SSGA before treatment (■). Mean ± SEM, $\S p < 0.04$ (at 240′)**,** $\dagger p < 0.05$ (maximum cortisol). Baseline cortisol was subtracted from each data point.

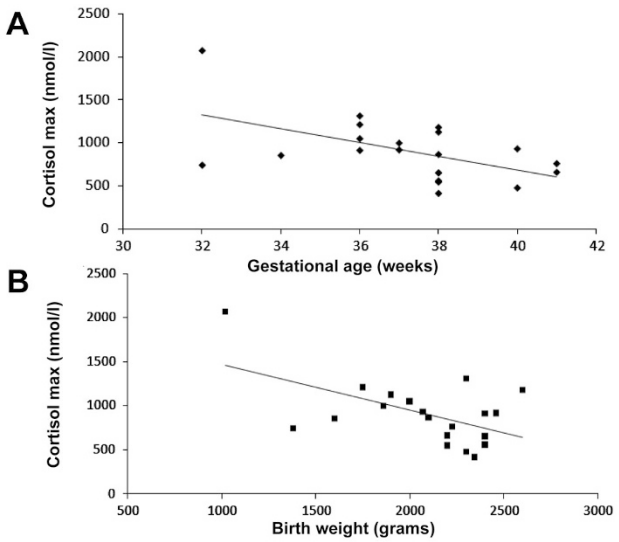

Figure 3. (*A*) GC-stimulated 11β-HSD-1 activity as a function of GA. $r = -0.53$, $p = 0.01$. (*B*) GC-stimulated 11β-HSD-1 activity as a function of birth weight. $r = -0.55$, $p = 0.01$.

have been proposed to explain the connection between fetal growth and metabolic morbidity (36–38). One theory suggests that increased fetal exposure to cortisol might program the fetus for later hypertension and metabolic disease (39,40). In pregnant rats, dietary restriction has been shown to induce hypomethylation of GC receptor genes in the liver of the offspring (41).

Results of this study show basal activity of 11β-HSD-1 to be lower in SSGA children than in controls, while GC-stimulated activity, measured as cortisol generation from cortisone, was higher. In SSGA children, 3 mo of GH treatment down-regulated and normalized 11β-HSD-1 activity. This difference may be due to GC induction of 11β-HSD1 at the transcriptional level (42).

There are several limitations, which were unavoidable in the design of this study. DEX, which is known to up-regulate 11β-HSD-1 (43), is an essential component in the *in vivo* cortisol generation test and is required to suppress endogenous cortisol production. On the other hand, DEX suppression is not required for enzyme activity assessment by urinary metabolites. We therefore present the two aspects separately, showing GCMS-based calculation of enzyme activity in the basal state and GC-stimulated cortisol generation.

The urinary metabolite ratios (Fm/Em–Cortisol metabolites/Cortisone metabolites) reflect the combined activity of 11β-HSD-1, 11β-HSD2, and the relative activity of the A-ring reductase. Urinary 11β-HSD-2 and 5α reductase activities were comparable in SSGA and controls, and therefore we used urine metabolite ratio as a measure of global 11β-HSD-1 activity.

The contribution of the HPA axis to growth and morbidity in SGA has been addressed extensively in the literature (21–24,44,45). For one, SSGA children have demonstrated less suppression by DEX, a finding that might be related to reports of their having a higher 0800 h cortisol level (21,45).

This study concurs with data suggesting dysregulation of GCs in SGA (19), a phenomenon that may contribute to the pathogenesis of metabolic morbidity (46) and that has been demonstrated even in the absence of overt obesity (47,48). In obese subjects, the intra-adipose *in vitro* 11β-HSD-1 was found to be increased (49). Its *in vivo* activity has been reported to be increased (50,51), decreased (33,52), or unchanged (53).

A recent study demonstrates that basal *in vivo* 11β-HSD-1 activity in adipose tissue of young adults born SGA was comparable with controls, while stimulated activity was decreased (54). 11β-HSD-1 gene expression was associated with body fat but not with birth weight. We studied Fm/Em urinary ratio that reflects global activity of the 11β-HSD-1, while the liver contributes most of this activity, and it was found to be decreased in SSGA.

As expected, the mean BMI of SSGA children was lower than that of age-matched control subjects. This lower BMI

may explain the lower basal 11β-HSD-1 activity, but not the higher GC-stimulated activity. Enhanced generation of cortisol from cortisone after GC stimulation may explain the enhanced reactivity to stress in SGA individuals and may contribute to their metabolic morbidity in adult life (20,55).

We found GC-stimulated 11β-HSD-1 activity to correlate inversely with birth weight (the degree of SGA) and GA (prematurity). Enhanced GC-stimulated 11β-HSD-1 activity in children with shorter gestation and lower birth weight SDS is in agreement with previous reports of cortisol levels in SGA (21,22,56). However, this finding did not correlate with age, indicating that the process is not progressive, but rather programmed from birth. Neither did it correlate with height SDS, indicating that it is not a function of children's short stature. No correlation was found with weight SDS or BMI SDS, indicating that GC-stimulated enzyme activity is not a response to thin body composition. Of note is that correlation to BMI is only in the low to normal range, because no obese children were included in our study. GC-stimulated 11β-HSD-1 activity did not correlate with HOMA-IR, indicating that it is not secondary to the known insulin resistance of SGA children.

This is in agreement with the GH-suppressing effect on 11β-HSD-1, which has been documented *in vitro* and *in vivo* (28–31). We are not able to assess whether this enzyme modulation has any effect on the growth response to GH therapy. Nevertheless, there was no correlation between basal or GC-stimulated 11β-HSD-1 activity and the child's response to GH. Our study was designed for a 3-mo period, and as such evaluates only short-term metabolic effects of GH, and no conclusion can be drawn on whether GH effect is sustained.

In conclusion, we demonstrated that SSGA programs a biphasic 11β-HSD-1 response. We speculate that enhanced GC-stimulated 11β-HSD-1 activity may be a contributing factor in SSGA metabolic morbidity and suggest another indication for GH therapy in SSGA: normalization of 11β-HSD-1 activity.

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