

7-oxygenated Derivatives of Dehydroepiandrosterone and Obesity

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Abstract: 7-hydroxy/oxo derivatives of dehydroepiandrosterone are potential regulators of the local cortisol activity due to their competition in the cortisol-cortisone balance mediated by 11 β -hydroxysteroid dehydrogenase. 7-hydroxy-dehydroepiandrosterone is marketed as anti-obesity medication, though no clinical study aimed at the benefit of administering 7-oxygenated derivatives of dehydroepiandrosterone has appeared until now. We tried to show whether there exist differences in levels of circulating 7-hydroxy/oxo-dehydroepiandrosterone derivatives between lean and obese boys and girls. From a cohort of adolescents investigated within the frame of anti-obesity programme 10 obese boys and 10 obese girls were compared with age-matched lean boys and girls in their anthropometric data, and concentrations of both epimers of 7-hydroxy-dehydroepiandrosterone and 7-oxo-dehydroepiandrosterone were determined by the RIA method. The basal levels of 7 α -hydroxy-dehydroepiandrosterone were significantly higher in obese boys than in lean boys but not in girls. The association was found for anthropometric parameters and 7 α -hydroxy-dehydroepiandrosterone, however again only in boys and not in girls. Higher levels of 7 α -hydroxy-dehydroepiandrosterone its positive association with anthropometric data in obese boys may serve as a sign that, at least in boys, 7-oxygenated 5-ene-steroids may take part in regulating the hormonal signal for fat formation or distribution.

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Introduction

7 α -hydroxy-dehydroepiandrosterone (7 α -OH-DHEA) was first isolated and identified by Okada et al. (1959) in the urine of a patient with adrenal carcinoma and, soon thereafter (Stárka, 1961; Stárka et al., 1962), in the urine of normal men and women. 7-hydroxylation in rat liver homogenate microsomes was characterized (Stárka and Kutová, 1962) and the 7-hydroxylation of dehydroepiandrosterone was discovered in various tissues, including of the brain (Akwa et al., 1992, 1993; Doostzadeh and Morfin, 1996; Doostzadeh et al., 1997; Rose et al., 1997). Numerous authors paid attention to the presence and role of 7-oxygenated dehydroepiandrosterone derivatives in the brain (Morfin and Stárka, 2001).

For a long time, 7-oxygenated derivatives of dehydroepiandrosterone were considered as degradation metabolites without any metabolic function. However, later on it has been established that at the cellular level, irreversible 7 α -hydroxylation of 3 β -hydroxy-5-ene steroids produces derivatives, which are believed to be responsible for at least some immunity-promoting and antiglucocorticoid effects (Morfin and Courchay, 1994; Hampl et al., 2000; Morfin et al., 2000; Morfin, 2002; Auci et al., 2009). As “neuroprotective steroids” and immunity promoters in the brain, 7 α -hydroxy-steroids could contribute to the panels of cellular protection and defense (Morfin and Stárka, 2001; Dušková et al., 2011).

One of the potential ways by which 7-oxygenated dehydroepiandrosterone derivatives exert their protective effects was proposed by several authors (Muller et al., 2006; Hennebert et al., 2007a, b, 2009; Nashev et al., 2007). They documented that these metabolites are substrates for 11 β -hydroxysteroid dehydrogenase type 1 and that they can compete with the transformation of cortisol to cortisone and vice versa. 7-hydroxy-dehydroepiandrosterone has been recently introduced to the market with supplements as an anti-obesity drug (www.dietspotlight.com/lean-xtreme-review/). The idea is based on use of 7-hydroxy-derivatives of DHEA as cortisol regulators and is near to the concept of their function as ergosteroids (Lardy et al., 1995). However, there are only few studies confirming anti-obesitogenic effects of these supplements in humans and only one study, which only marginally deals with effect of transdermally administered 7-oxo-dehydroepiandrosterone (7-oxo-DHEA) on lipid metabolism (Šulcová et al., 2000).

Here we try to show, how the circulating concentrations of dehydroepiandrosterone 7-hydroxy/oxo-derivatives correlate with anthropometric parameters and body composition in teenagers.

Material and Methods

Groups

Study participants (20 girls and 20 boys) were recruited from the COPAT project (Childhood Obesity Prevalence and Treatment), which had focused on epidemiological (stratified random selection) and intervention (overweight/obesity group) study in Czech adolescents. Age-matched groups of lean (BMI-SDS < -0.64

or BMI < 25th percentile) and obese (BMI-SDS > 3.0 or BMI > 99th percentile) subjects of both sexes in the age of 13.0–17.9 years were studied. Their general anthropometric characterization is shown in Table 1. In the female group 14 girls had regular menstrual cycle, 4 irregular cycle and 2 girls did not report about their menses. Only one girl used hormonal contraception. Two girls and 4 boys fulfilled the requirements of the criteria of metabolic syndrome according to The International Diabetes Federation (IDF). This difference was not significant. Only two obese girls had glycemia over 5.6 mmol/l in the range of disturbed glucose tolerance. The values of analytes important for glucose control as glycemia (mean 5.04 vs. 5.025 mmol/l), insulin (15.49 vs. 10.15 mIU/l), C-peptide (0.90 vs. 0.68 µg/l) and HOMA-index (3.29 vs. 2.11) for girls and boys did not differ significantly.

The current study was approved by the Ethics Committee of the Institute of Endocrinology and was performed in accordance with the Helsinki Declaration. All participants and their parent(s) provided written informed consent with the original COPAT project. Only those subjects who had agreed that data and blood samples could be used and analysed in subsequent research projects of the Institute of Endocrinology were included in the current pilot study.

Anthropometric characterisation

Body height was measured with a stadiometer (precision 0.1 cm), body weight was measured by Tanita BC-418 MA (precision 0.1 kg). The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. The percentage of total fat was measured by bioelectric impedance – Tanita BC-418 MA, the percentage of trunk fat (TF) and the degree of visceral fat enlargement (VF) by the Tanita AB-140 ViScan (both Tanita Corporation, Tokyo, Japan). Body circumferences were measured with a tape measure (precision 0.1 cm) in a horizontal level; waist circumference midway between the upper iliac crest and the lower rib, abdominal circumference at the level of umbilicus and hip circumference over the maximum buttocks diameter. Sagittal abdominal diameter (SAD) was measured with a pelvimeter at the level L4/5 in a horizontal level. Skinfolds (biceps, triceps, subscapular, suprailiac) were measured with Best calliper.

Steroid analysis

Peripheral blood samples were taken from the cubital vein after 12 hours of fasting between 7.00–9.00 a.m. BD Vacutainer® Plus plastic serum tubes with the silicone coated (Becton Dickinson Vacutainer Systems, UK) were used. Code-identified plasma samples were immediately put in deep frozen boxes (minus 80 degrees Celsius) after blood withdrawal or laboratory analyses to prevent degradation of this biological material. 7 α - and 7 β -OH-DHEA were measured in plasma by radioimmunoassays using polyclonal rabbit antisera against 7-OH-DHEA-19-(O-carboxymethyl)oxime conjugates, with bovine serum albumin and radioiodinated homologous derivatives with tyrosine methyl ester as tracers (Lapčik et al., 1998,

Table 1 – Essential characteristics of the investigated cohort

| | Obese boys (n=10) | | Thin boys (n=10) | | p | Obese girls (n=10) | | Thin girls (n=10) | | p |
|--|---|--|---|--|--------------|---|--|---|--|--------------|
| | median (lower quartile; upper quartile) | | median (lower quartile; upper quartile) | | | median (lower quartile; upper quartile) | | median (lower quartile; upper quartile) | | |
| Age (years) | 16.5 (15.0; 16.7) | | 16.4 (15.2; 16.8) | | 0.902 | 15.6 (14.3; 16.6) | | 15.0 (14.1; 16.5) | | 0.776 |
| Body height (cm) | 174.8 (172.6; 181.8) | | 176.3 (171.8; 180.8) | | 0.976 | 165.9 (155.8; 169.2) | | 164.4 (159.4; 169.8) | | 0.816 |
| Body height (z-score) | -0.2 (-0.7; 0.7) | | -0.5 (-0.8; -0.5) | | 0.762 | 0.02 (-0.7; 0.5) | | -0.1 (-0.7; 0.7) | | 0.806 |
| Body weight (kg) | 110.8 (106.4; 117.4) | | 51.4 (47.9; 56.1) | | 0.000 | 96.8 (84.9; 98.5) | | 45.0 (36.2; 47.7) | | 0.000 |
| Body weight (z-score) | 4.4 (3.7; 5.2) | | -1.6 (-1.9; -1.2) | | 0.000 | 4.3 (3.3; 5.1) | | -1.4 (-1.9; -1.0) | | 0.000 |
| BMI (kg/m ²) | 35.1 (34.0; 37.3) | | 16.5 (15.5; 17.6) | | 0.000 | 33.0 (32.1; 35.3) | | 16.3 (15.1; 16.3) | | 0.000 |
| BMI (z-score) | 5.1 (4.6; 6.1) | | -1.6 (-1.9; -1.3) | | 0.000 | 4.7 (4.5; 5.6) | | -1.6 (-2.1; -1.4) | | 0.000 |
| Waist circumference (cm) | 105.5 (101.0; 114.6) | | 65.8 (61.9; 68.1) | | 0.000 | 90.3 (89.1; 100.0) | | 61.3 (58.5; 62.6) | | 0.000 |
| Abdominal circumference (cm) | 114.5 (108.5; 123) | | 70.5 (65.5; 73.5) | | 0.000 | 105.8 (101.9; 111.9) | | 68.5 (64.0; 70.1) | | 0.000 |
| SAD (cm) | 27.5 (27; 31.3) | | 16 (14.8; 17.5) | | 0.000 | 26 (24; 27.8) | | 14.8 (13.9; 16.5) | | 0.000 |
| Hip circumference (cm) | 118 (114.8; 122.8) | | 85.9 (83.0; 90.3) | | 0.000 | 118.4 (113.1; 122.3) | | 84 (79.8; 87) | | 0.000 |
| Sum of four skinfolds (mm) | 96.5 (78.5; 117.5) | | 17.8 (11.2; 22.4) | | 0.000 | 89 (75; 112) | | 25.5 (21.6; 42) | | 0.000 |
| Total fat (%) | 32.4 (30.3; 38.3) | | 11.0 (9.9; 14.1) | | 0.000 | 41.4 (35.3; 44.2) | | 18.7 (14.0; 20.0) | | 0.000 |
| ViScan – TF (%) | 41.8 (37.9; 51.8) | | 13 (12.5; 13.5) | | 0.000 | 45.2 (43.9; 47.4) | | 19.7 (15.2; 24) | | 0.000 |
| ViScan – VF (degree of visceral fat enlargement) | 24 (19.8; 33) | | 2.8 (2; 4) | | 0.000 | 11.5 (10; 13) | | 2.5 (1.5; 3) | | 0.000 |

BMI – Body Mass Index; SAD – Sagittal Abdominal Diameter; ViScan – TF – Bioimpedance – Trunk Fat; ViScan – VF – Bioimpedance – Visceral Fat Level. Significance was tested by Mann-Whitney test, p-value <0.05 was considered significant (in bold text)

1999). 7-oxo-DHEA was determined by the RIA method according to Kazihnitková et al. (2007). Intra- and interassay coefficients of variation were 6.7% and 10.0% for 7 α -OH-DHEA, and 7.1% and 10.6% for 7 β -OH-DHEA, respectively; the detection limits were 1.06 and 0.95 pg/tube. The cross-reactivity of the antisera with chemically related steroids present in the material analyzed was as follows. For 7 β -OH-DHEA antibody: 7 α -OH-DHEA (the opposite epimer), 0.28%; DHEA, 0.18%; androstenedione, 0.096%; testosterone, 0.013%; cross-reactivity with other hormonal steroids such as cortisol, estradiol, progesterone and dihydrotestosterone was negligible. For 7 α -OH-DHEA antibody: 7 β -OH-DHEA, 1.16%; DHEA, 1.95%; androstenedione, 0.38%; pregnenolone and dihydrotestosterone, 0.04% each; and testosterone, 0.01%. The cross-reactivity with other hormonal steroids such as cortisol, estradiol, and progesterone was negligible.

Statistical analysis

Due to non-Gaussian data distribution, the median, lower and upper quartiles were used to describe data. Differences between investigated groups were determined by Mann-Whitney test. The relationships between compared methods were evaluated using non-parametric correlation analysis (the Spearman rank correlation coefficient). The data analysis was performed using the statistical software Statgraphics Plus 5.0 from Statpoint, Inc. (Warrenton, Virginia, USA) and NCSS 2007 (Kaysville, Utah, USA).

Results

Table 2 shows the principal anthropometric data and serum concentrations of 7-oxygenated DHEA derivatives. Besides anthropometric data a significant difference between obese and lean group was found only for 7 α -OH-DHEA and only in boys. The basal levels of 7 α -OH-DHEA were significantly higher in obese boys than in lean boys.

The association was found for anthropometric parameters (body weight, BMI, body circumferences, SAD, sum of four skinfolds, total fat percentage, TF and VF) and for 7 α -hydroxydehydroepiandrosterone, however again only in boys and not in girls. In girls there is a significant correlation between body composition (hip circumference, TF, VF) and 7-oxo-DHEA concentration (Table 3).

Discussion

There are many different theories about the underlying cause of obesity and fat retention and dozens of different ways to try to correct it. Some cortisol regulators based on 7-oxygenated DHEA derivatives are currently marketed as anti-obesity medication.

Dehydroepiandrosterone (DHEA) is hydroxylated to position 7 α by the cytochrome P450 7B1 (CYP7B1) in the human brain and liver. This produces 7 α -OH-DHEA that is a substrate for 11 β -hydroxysteroid dehydrogenase type 1

Table 2 – Age (years), body mass index (kg/m²) (BMI) and 7-oxygenated derivatives of dehydroepiandrosterone (nmol/l) in lean and obese boys and girls

| | Obese boys (n=10) | Thin boys (n=10) | p | Obese girls (n=10) | Thin girls (n=10) | p |
|--------------------------|---|---|--------------|---|---|--------------|
| | median (lower quartile; upper quartile) | median (lower quartile; upper quartile) | | median (lower quartile; upper quartile) | median (lower quartile; upper quartile) | |
| Age (years) | 16.5 (15.0; 16.7) | 16.4 (15.2; 16.8) | 0.902 | 15.6 (14.3; 16.6) | 15.0 (14.1; 16.5) | 0.776 |
| BMI (kg/m ²) | 35.1 (34.0; 37.3) | 16.5 (15.5; 17.6) | 0.000 | 33.0 (32.1; 35.3) | 16.3 (15.1; 16.3) | 0.000 |
| 7 α -OH-DHEA | 1.8 (1.3; 2.6) | 1.1 (0.9; 1.3) | 0.017 | 1.5 (1.2; 2.2) | 1.5 (1.0; 1.8) | 0.856 |
| 7 β -OH-DHEA | 1.1 (0.7; 1.3) | 0.7 (0.4; 1.2) | 0.122 | 1.2 (0.9; 1.4) | 1.0 (0.8; 1.3) | 0.397 |
| 7-oxo-DHEA | 0.8 (0.6; 1.5) | 0.7 (0.4; 1.0) | 0.096 | 0.6 (0.6; 0.7) | 0.4 (0.3; 0.6) | 0.156 |

BMI – Body Mass Index; 7 α -OH-DHEA – 7 α -hydroxy-dehydroepiandrosterone; 7 β -OH-DHEA – 7 β -hydroxy-dehydroepiandrosterone; 7-oxo-DHEA – 7-oxo-dehydroepiandrosterone. Significance was tested by Mann-Whitney test, p-value <0.05 was considered significant (in bold text)

(11 β -HSD1), which exists in the same tissues and carries out the inter-conversion of 7 α - and 7 β -OH-DHEA through a 7-oxo-intermediary. Since the role of 11 β -HSD1 is to transform the inactive cortisone into active cortisol, its competitive inhibition by 7 α -OH-DHEA may support the paradigm of native anti-glucocorticoid arising from DHEA (Hampl et al., 2000; Morfin et al., 2000; Morfin, 2002; Hennebert et al., 2007a, b). The metabolic abnormalities found associated with high blood glucocorticoid levels include insulin-resistance, visceral obesity, hypertension, dyslipidaemia and an increased risk of cardiovascular diseases (Anagnostis et al., 2009; Morton, 2010). Therefore, our objective was to investigate whether the concentration of 7-oxo/oxy derivatives of DHEA are associated with anthropometric and metabolic parameters, which are known to be dependent at least partially on glucocorticoid activity (as adiposity and fat distribution, lipid spectrum, or insulin resistance). These findings may support the previously proposed native anti-glucocorticoid paradigm and suggest that 7 α -OH-DHEA production is a key for the fine tuning of glucocorticoid levels in tissues.

Our pilot study with limited number of individuals under investigation shows some association of higher 7 α -OH-DHEA levels with anthropometric data in obese

Table 3 – Spearman’s correlations between circulating 7-oxygenated derivatives of DHEA and anthropometric parameters and body composition

| | | 7 α -OH-DHEA | | 7 β -OH-DHEA | | 7-oxo-DHEA | |
|------------------------------|---|---------------------|--------|--------------------|--------|------------|--------------|
| | | boys | girls | boys | girls | boys | girls |
| Height (cm) | r | -0.184 | -0.020 | -0.470 | 0.039 | -0.055 | 0.126 |
| | p | 0.451 | 0.935 | 0.042 | 0.875 | 0.823 | 0.607 |
| Body weight (kg) | r | 0.675 | 0.090 | 0.212 | 0.154 | 0.233 | 0.369 |
| | p | 0.002 | 0.175 | 0.383 | 0.528 | 0.337 | 0.120 |
| BMI (kg/m ²) | r | 0.696 | 0.206 | 0.326 | 0.272 | 0.222 | 0.385 |
| | p | 0.000 | 0.397 | 0.173 | 0.260 | 0.359 | 0.103 |
| Waist circumference (cm) | r | 0.603 | 0.107 | 0.146 | 0.119 | 0.321 | 0.277 |
| | p | 0.006 | 0.663 | 0.551 | 0.628 | 0.180 | 0.251 |
| Abdominal circumference (cm) | r | 0.650 | 0.225 | 0.253 | 0.313 | 0.175 | 0.366 |
| | p | 0.003 | 0.355 | 0.295 | 0.193 | 0.743 | 0.124 |
| SAD (cm) | r | 0.547 | 0.045 | 0.178 | -0.091 | 0.187 | 0.446 |
| | p | 0.019 | 0.861 | 0.480 | 0.717 | 0.456 | 0.064 |
| Hip circumference (cm) | r | 0.701 | 0.278 | 0.255 | 0.307 | 0.141 | 0.485 |
| | p | 0.000 | 0.250 | 0.292 | 0.202 | 0.565 | 0.035 |
| Subscapular skinfold (mm) | r | 0.774 | -0.051 | 0.506 | 0.045 | 0.291 | 0.189 |
| | p | 0.000 | 0.834 | 0.027 | 0.856 | 0.227 | 0.438 |
| Sum of four skinfolds (mm) | r | 0.743 | 0.183 | 0.407 | 0.248 | 0.168 | 0.391 |
| | p | 0.000 | 0.453 | 0.084 | 0.306 | 0.495 | 0.100 |
| Total fat (%) | r | 0.639 | 0.176 | 0.449 | 0.228 | 0.006 | 0.403 |
| | p | 0.004 | 0.484 | 0.062 | 0.363 | 0.827 | 0.097 |
| ViScan – TF (%) | r | 0.589 | 0.263 | 0.280 | 0.241 | 0.412 | 0.627 |
| | p | 0.016 | 0.385 | 0.294 | 0.428 | 0.112 | 0.022 |
| ViScan – VF (fat level) | r | 0.526 | 0.336 | 0.121 | 0.241 | 0.285 | 0.591 |
| | p | 0.036 | 0.261 | 0.657 | 0.428 | 0.284 | 0.033 |

BMI – Body Mass Index; SAD – Sagittal Abdominal Diameter; ViScan – TF – Bioimpedance – Trunk Fat; ViScan – VF – Bioimpedance – Visceral Fat Level; 7 α -OH-DHEA – 7 α -hydroxy-dehydroepiandrosterone; 7 β -OH-DHEA – 7 β -hydroxy-dehydroepiandrosterone; 7-oxo-DHEA – 7-oxo-dehydroepiandrosterone; r – regression coefficient; p – p-value. Data significant at $p < 0.05$ are in bold text

boys, not in girls. We have no explanation for this difference between the sexes, gender differences in DHEA metabolism or lower level of 7-oxygenated derivatives

of DHEA in girls might play some role as well as lower incidence of metabolic syndrome in girls than in boys. The increase of 7 α -OH-DHEA may be a result of the increased production and conversion of 7-oxo-DHEA as a substrate for 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) and thus decreasing the concentration of cortisol on account of cortisone. Inhibitors of 11 β -HSD1 might represent a promising therapeutic target in obesity and metabolic syndrome.

To answer the question whether endogenous competitive substrates for 11 β -HSD1 as 7-oxo-DHEA and perhaps also of pregnenolone are really involved in fat accumulation more investigations in this field are needed.

Conclusion

Higher levels of 7 α -hydroxy-dehydroepiandrosterone and its positive association with anthropometric data in obese boys may serve as a sign that, at least in boys, 7-oxo-DHEA may take part in regulating the hormonal signal for fat formation or distribution.

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