

Adipose tissue - a source of hyperandrogenism in obese females?

I.V. Wagner^{1,2,3}, L. Sahlin¹, I. Savchuk¹, K. Svechnikov¹, O. Söder¹

¹: Karolinska Institutet, Department of Women's and Children's Health, Pediatric Endocrinology Unit, Stockholm, Sweden

²: Integrated Research and Treatment Center (IFB Adiposity Diseases), University of Leipzig, Leipzig, Germany

³: ESPE Research Fellow 2014-2016, Karolinska Institutet, Stockholm

Background:

Obesity in females is often associated with metabolic complications and hyperandrogenism. However, the source of androgens is not entirely clear.



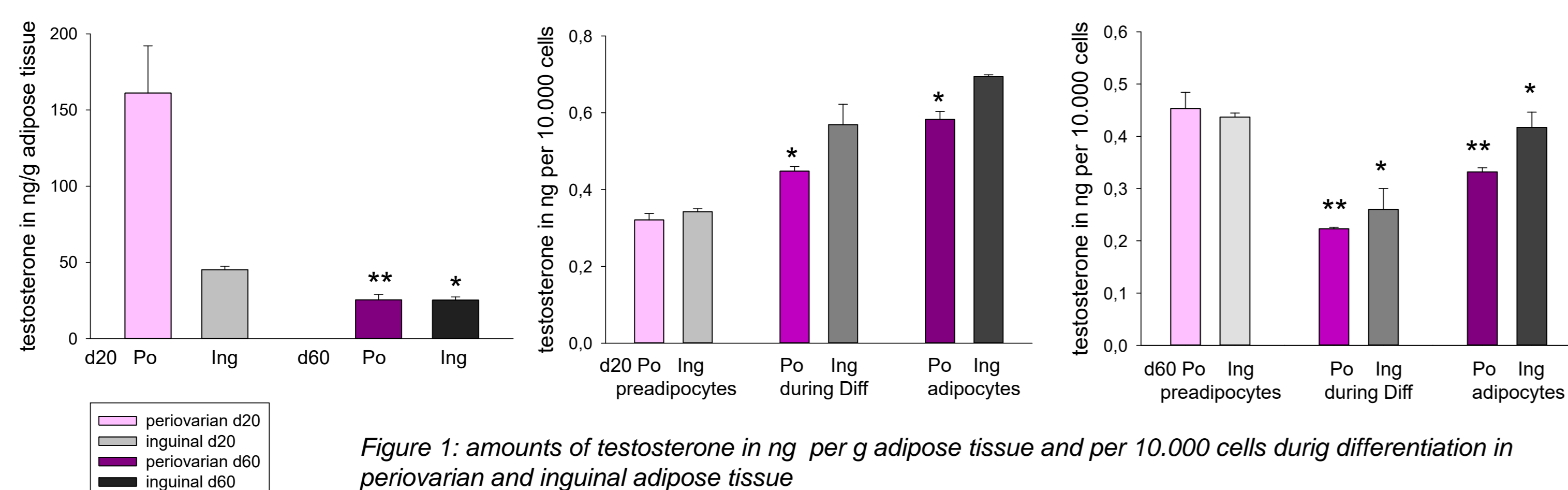
Our objective was to find out if adipose tissue (AT) is a site of steroid production during childhood and adolescence, and if this source could add to hyperandrogenism in obese females. We employed a female rat model for our study.

Material and Methods:

Periovarian and inguinal AT was collected and cells were isolated and cultured from young (day 20) and adult (day 60), lean female rats for gene expression analysis of steroidogenic enzymes and determination of testosterone in AT and in the supernatant of cultured cells. Thin layer chromatography (TLC) was performed on preadipocytes and adipocytes to evaluate the conversion of pregnenolone to other steroids. Steroidogenic gene expression was analyzed at the transcriptional level by qPCR from AT of lean and obese rats.

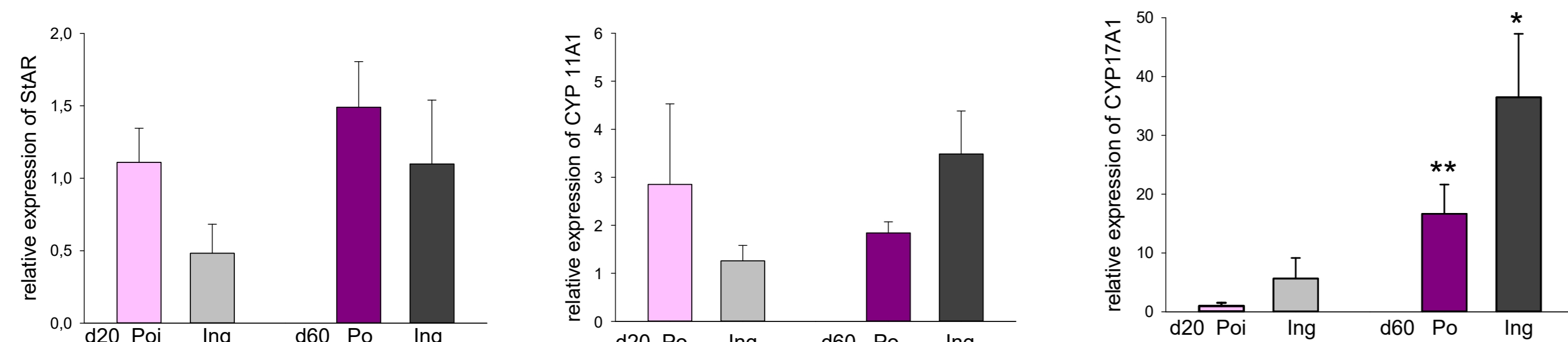
Results:

Testosterone is stored in periovarian and inguinal adipose tissue and isolated preadipocytes and adipocytes of young and old female rats

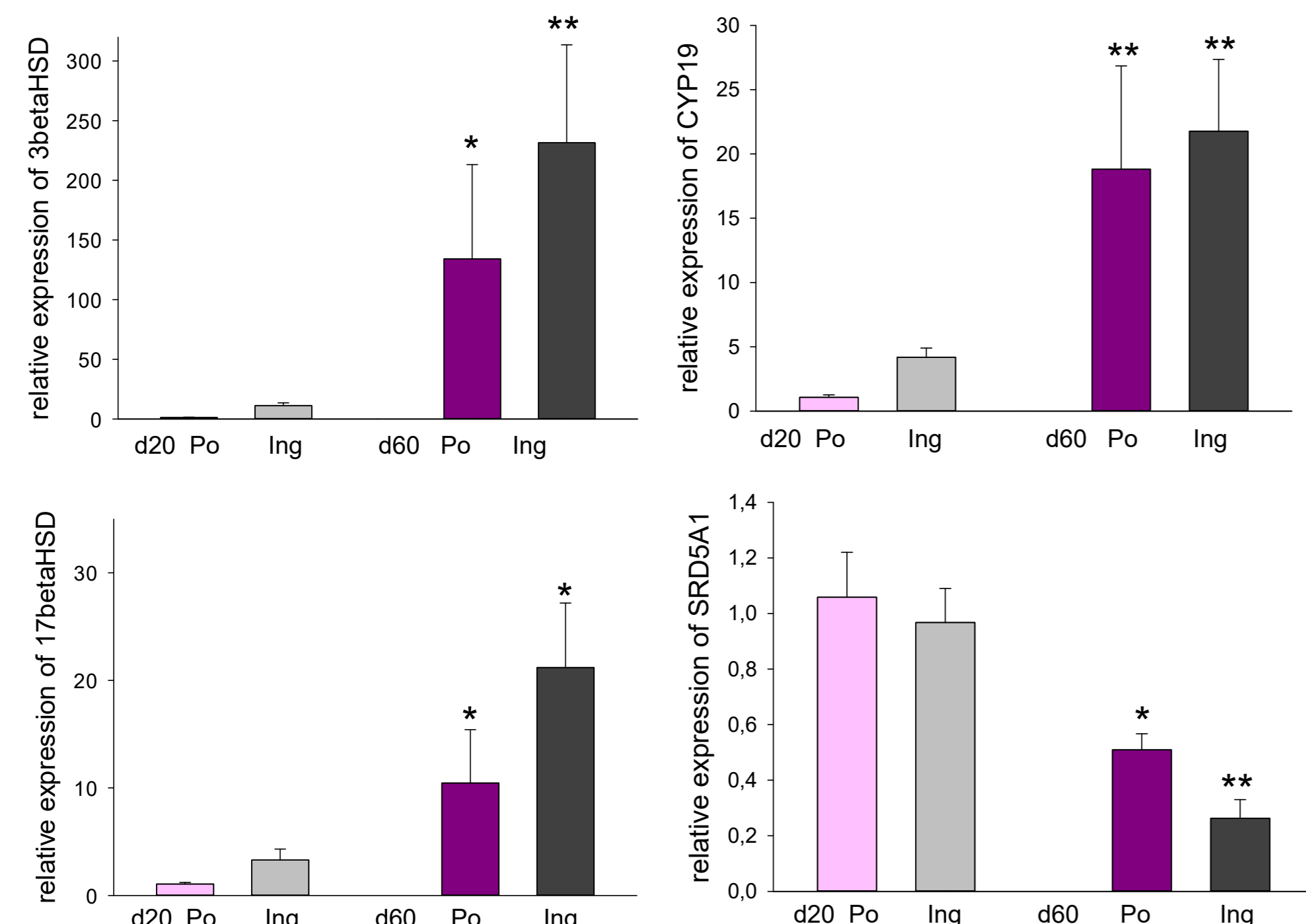


We found significant amounts of testosterone in adipose tissue from both depots (periovarian and inguinal) in young animals and adult rats (25ng to 153ng/g adipose tissue) and in the supernatants of preadipocytes and adipocytes (0.33-0.69ng/10000cells) with the highest values in mature adipocytes of young rats.

Steroidogenic enzymes are expressed in adipose tissue and isolated cells



Steroidogenic enzymes, including *StAR*, *Cyp11a1*, *Cyp17a1*, *CYP19*, *Hsd3b2*, *Hsd17b3* and *SRD5A1* were expressed in AT and isolated cells in culture, from both depots and ages, with higher expression levels in mature adipocytes.



Interestingly, high expression levels of *CYP17A1*, *Hsd3bs*, *Hsd17b3* and *CYP19* were found in periovarian and even higher levels in inguinal adipose tissue of 60 day old female rats. *SRD5A1* was the lowest in inguinal adipose tissue of adult rats.

Steroidogenic gene expression in isolated preadipocytes and adipocytes during differentiation

Gene	Periovarian d20	Gene	Inguinal d20	Gene	Periovarian d60	Gene	Inguinal d60
<i>StAR</i>	608.49	<i>StAR</i>	304.39	<i>StAR</i>	70.12	<i>StAR</i>	164.83
<i>Cyp11A1</i>	441.38	<i>Cyp11A1</i>	207.83	<i>Cyp11A1</i>	137.92	<i>Cyp11A1</i>	2.31
<i>CYP17A1</i>	362.82	<i>Cyp17</i>	80.91	<i>Cyp17</i>	70.12	<i>Cyp17</i>	85.35
<i>Hsd3bs</i>	267.64	<i>Hsd3bs</i>	54.40	<i>Hsd3bs</i>	54.79	<i>Hsd3bs</i>	1.89
<i>Hsd17b3</i>	34.85	<i>Hsd17b3</i>	24.77	<i>Hsd17b3</i>	43.86	<i>Hsd17b3</i>	1.12
<i>CYP19</i>	31.13	<i>CYP19</i>	23.25	<i>CYP19</i>	44.06	<i>CYP19</i>	1.93
<i>SRD5A1</i>	131.60	<i>SRD5A1</i>	164.02	<i>SRD5A1</i>	77.83	<i>SRD5A1</i>	157.56

Table 1: steroidogenic gene expression in isolated preadipocytes and adipocytes during differentiation, up- (pink) and downregulation (grey) compared to preadipocytes in percent

Preadipocytes and adipocytes can convert pregnenolone to testosterone

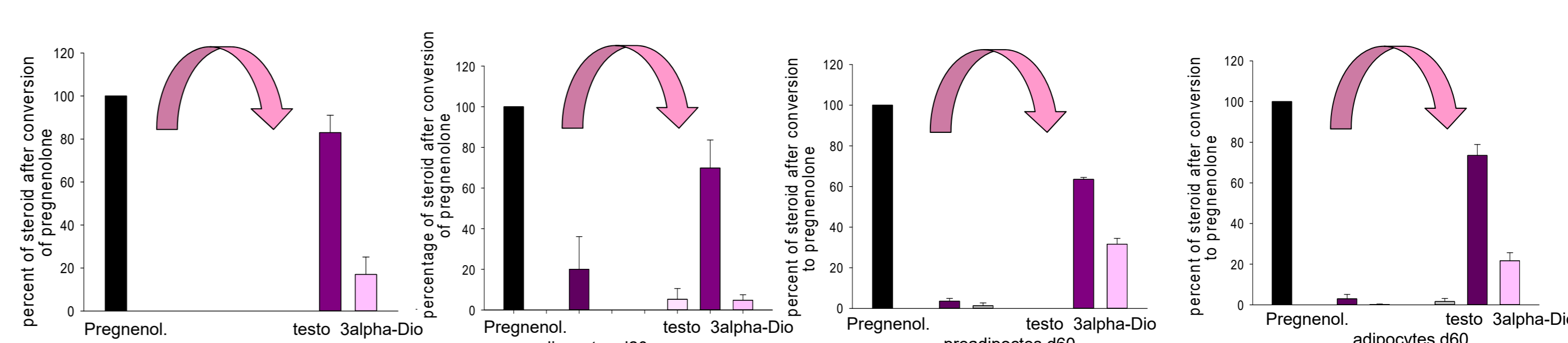
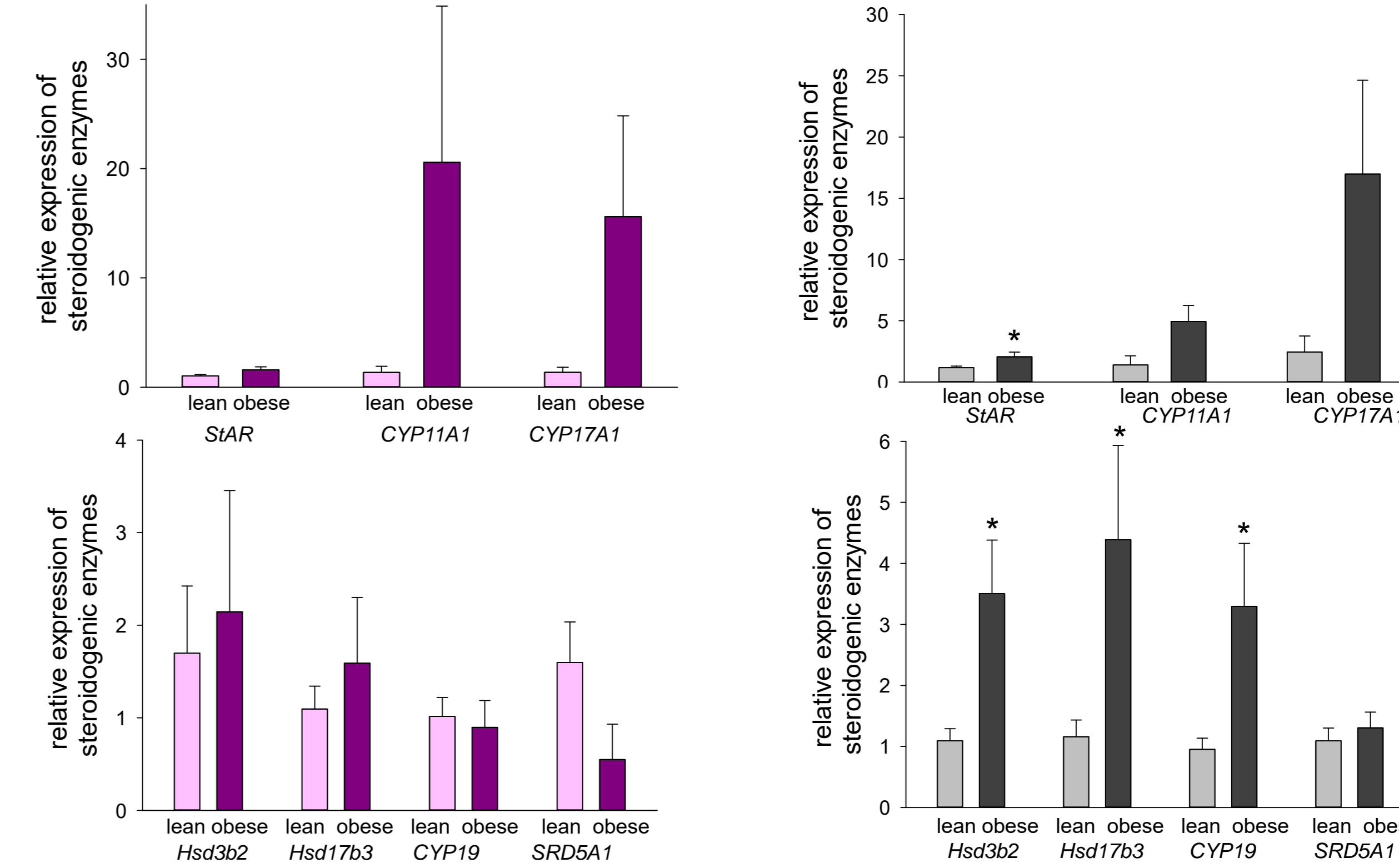


Figure 3: preadipocyte and adipocyte conversion of pregnenolone to other steroids in young and old animals (periovarian tissue)

TLC data revealed that preadipocytes and adipocytes were able to convert pregnenolone to mainly testosterone and 3-alpha-diol. Data is shown for cells from periovarian tissue but results were similar in cells from inguinal adipose tissue. Steroidogenic enzymes are expressed and the machinery is working to produce steroids and especially testosterone in preadipocytes and adipocytes.

Higher expression of steroidogenic enzymes were found in obese animals



Finally we analyzed expression levels of steroidogenic enzymes in lean and obese animals and found higher levels for all steroidogenic enzymes in obese of both depots, being significant in inguinal AT (*Star* +77.5% p=0.048, *Hsd3b2* +221% p=0.015, *Hsd17b3* +280% p=0.009; *CYP19* +246% p=0.023).

Conclusion:

Although the results need to be confirmed in human subjects, our study demonstrates that the whole tested steroidogenic machinery is expressed in adipose tissue and that it may serve as an additional significant site of steroid production. Thus, high levels of androgens in female obesity might be produced by adipose tissue and thereby add to the vicious circle of metabolic complications in obese females.

Karolinska Institutet

Dr. Isabel Wagner

Department of Women's and Children's Health
Pediatric Endocrinology Unit

Corresponding author: isabel.wagner@ki.se



Karolinska Institutet

