# Adipocytokines delay pubertal maturation of human Sertoli cells

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**Background:** Obesity is one of the most important health challenges worldwide and is becoming more prevalent in adolescents and children. Metabolic syndrome related co-morbidities are increasingly recognized in children, predisposing them to early cardiovascular disease. Reproduction is an important target of obesity complications, including adverse effects on spermatogenesis and steroidogenesis. Adipocytokines secreted from adipose tissue are key factors in various complications of obesity. The aim of the present work was to study the potential of selected adipocytokines to affect Sertoli cell function and possibly link these findings to the observed attenuation of spermatogenesis in obese males.

**Material and Methods:** Testicular biopsies were obtained from healthy middle-aged donors during elective surgery (e.g. hydroceles, hernia repair). Highly purified adult human Sertoli cells (HSCs) were isolated by fluorescence-activated cell sorting (FACS) using CD90 as a sorting marker. Cells were cultured and exposed to various concentrations (10-1000ng/ml) of 10 different adipocytokines, including Adiponektin, Leptin, AFABP, TNFα, Nampt, Resistin, Progranulin, Irisin, Chemerin and Omentin for 2 to 7 days. Gene expression of the following Sertoli cell genes: GDNF, FSHR, BMP-4, CYP26A1, LIF and FGF-2 was quantified with qPCR.

## Results:

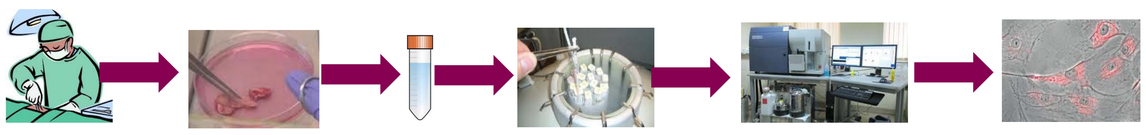

*Figure 1*

Testicular biopsies were obtained from healthy middle-aged donors during elective surgeries. The tissue was digested and samples were frozen. Highly purified adult human Sertoli cells (HSCs) were isolated by fluorescence-activated cell sorting (FACS) using CD90 as a sorting marker and seeded and treated with different concentrations of adipocytokines.

### Adipocytokine stimulation with physiological concentrations for 48 hours

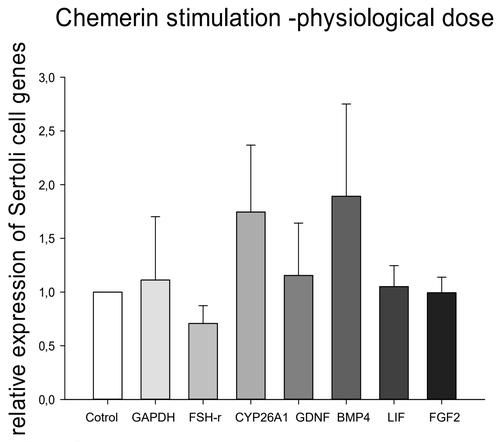


*Figure 2*

Exposure to physiological concentrations of adipocytokines (10-100ng/ml), as found in lean children and adults, for 48 hours did not significantly affect the expression of Sertoli cell-specific genes.

### Adipocytokine stimulation with supraphysiological concentrations for 48 h

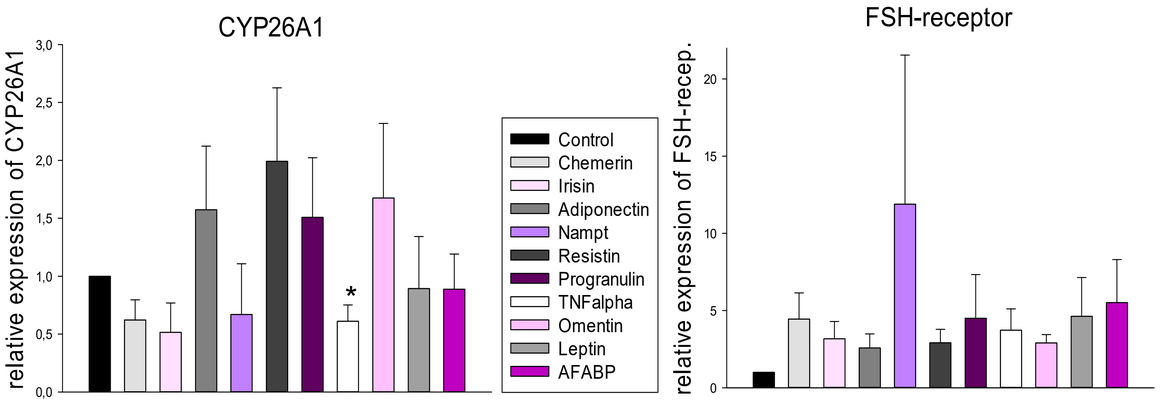


*Figure 3*

In contrast, exposure to higher doses of Chemerin, Progranulin, Irisin, Nampt, AFABP, Adiponectin, TNFalpha and Leptin for 48h, as found in obesity, showed a tendency to an increased FSH-receptor expression. CYP26A1 expression in HSCs was slightly downregulated after exposure to Irisin, Nampt and significantly after TNFalpha.

### Adipocytokine stimulation with supraphysiological concentrations for 7d

Long term treatment for 7 days of HSCs with higher doses of adipocytokines, as found in obesity (100-1000ng/ml), suppressed FSH-receptor expression by (79, 83, 30, 64, 71 and 26%, respectively) as found in the prepubertal state.

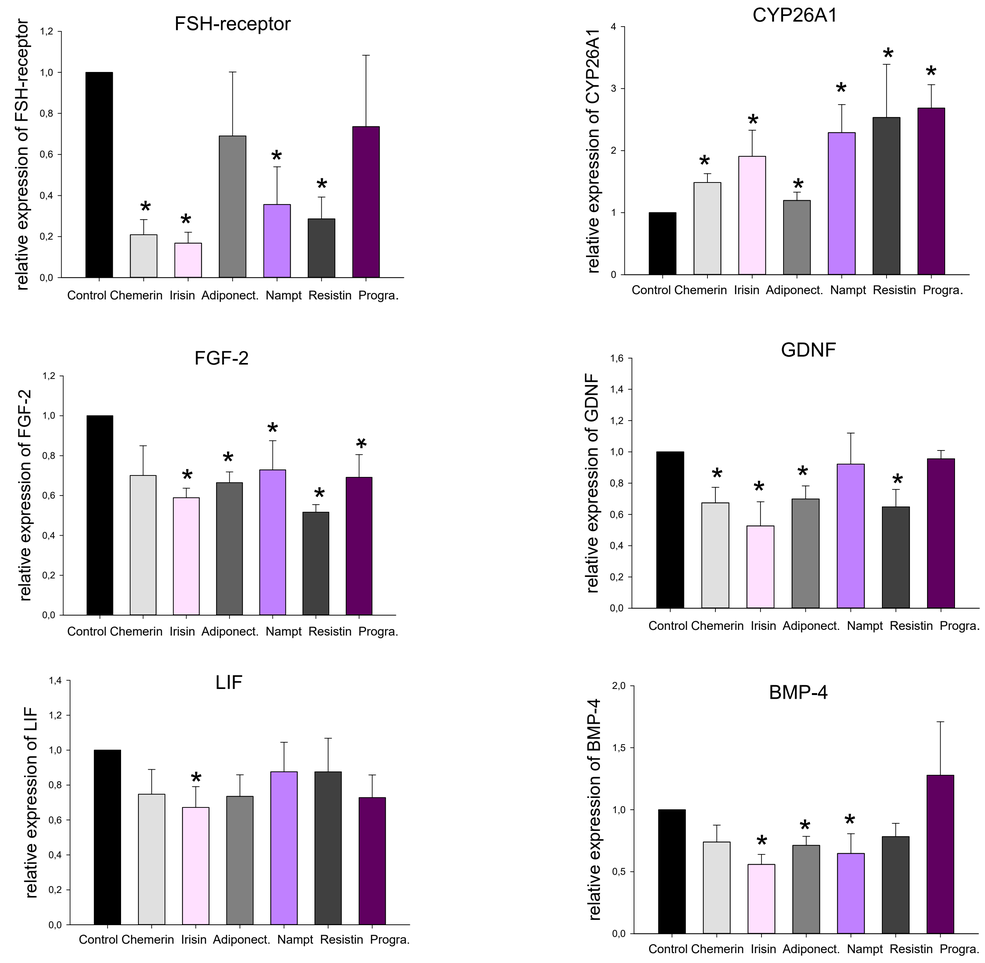


*Figure 4*

Further, those adipocytokines significantly attenuated the expression of BMP-4, GDNF, LIFand FGF-2 by HSCs. In contrast, Nampt, Irisin, Chemerin, Resistin and Progranulin significantly upregulated CYP26A1 expression (by 126, 90, 48, 126 and 153%, respectively) and reset Sertoli cells to the prepubertal phase.

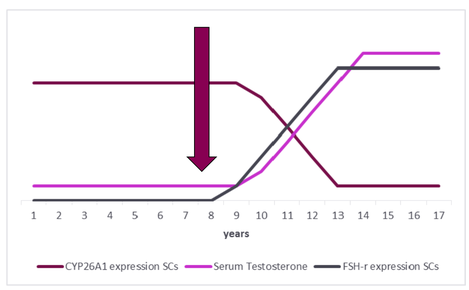


*Figure 5*

Model of how supraphysiological concentrations, as found in obese children, could influence Sertoli cell function. Maturation could be stopped or delayed with negative impacts on spermatogenesis and adult fertility.

**Conclusion:**
We propose that adipocytokines at high concentrations, which are often observed in obese children and adults, negatively affect adult Sertoli cell function. Adipocytokines might lead to a maturation stop of Sertoli cells during the important phase of puberty and keep Sertoli cells in a prepubertal quiescent phase. This could negatively affect spermatogenesis and may lead to severe fertility problems during adulthood.

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