

Metabolic and ovarian consequences of perinatal sex steroid programming

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

- I Postnatal testosterone exposure results in insulin resistance, enlarged mesenteric adipocytes, and an atherogenic lipid profile in adult female rats: comparisons with estradiol and dihydrotestosterone.**
Alexanderson C, Eriksson E, Stener-Victorin E, Lystig T, Gabrielsson B, Lönn M, Holmäng A.
Endocrinology. 2007 Nov; 148(11):5369-76.
- II One single early postnatal oestradiol injection results in profound effects on ovary and parametrial adipose tissue in adult female rats.**
Alexanderson C, Stener-Victorin E, Lönn L, Kullberg J, Levin M, Cajander S, Lönn M, Holmäng A.
Submitted.
- III Early postnatal estradiol exposure causes insulin resistance and signs of inflammation in circulation and skeletal muscle.**
Alexanderson C, Eriksson E, Stener-Victorin E, Lönn M, Holmäng A.
Submitted.
- IV Having a male twin is associated with body mass index and metabolism in middle-aged and old women**
Alexanderson C, Henningson S, Lichtenstein P, Holmäng A, Eriksson E.
Submitted.



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Metabolic and ovarian consequences of perinatal sex steroid programming

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ABSTRACT

Endocrine and metabolic disturbances in adulthood may stem from insults such as nutritional and hormonal alterations that occur at critical periods in pre- or postnatal life – a process known as programming. This means that suboptimal conditions *in utero* and early life may contribute to adult reproductive and metabolic impairments such as type 2 diabetes, insulin resistance, and dyslipidemia. The aims of this thesis were 1) to identify the potential metabolic and ovarian programming effects of early postnatal sex steroid exposure in adult female rats, and 2) to utilize data collected by the Swedish Twin Registry to investigate, in a large cohort of dizygotic twins, the potential effects of prenatal androgen exposure on metabolism and anthropometry in adult women with a male twin.

The main findings of this thesis were:

A single early postnatal dose of testosterone or estradiol caused insulin resistance and an increase in mesenteric adipocyte size in adult female rats. Testosterone exposure also resulted in dyslipidemia and estradiol exposure in elevated triglyceride levels. Rats exposed to estradiol displayed more pronounced insulin resistance than rats exposed to testosterone or dihydrotestosterone. Testosterone-injected rats exhibited increased mesenteric adipose tissue. Dihydrotestosterone-injected rats exhibited reduced insulin sensitivity only. Estradiol administration directly after birth altered ovarian morphology and expression of genes involved in follicle development. Estradiol exposure also decreased the weight of parametrial adipose tissue, increased parametrial adipose tissue lipoprotein lipase activity, and altered parametrial adipose tissue expression of genes involved in adipose tissue metabolism. In addition, reduced insulin sensitivity in postnatal estradiol-exposed rats was accompanied by an increase in the serum levels of inflammatory markers, and skeletal muscle alterations in the expression of immune-related genes and genes involved in the regulation of glucose and lipid metabolism. Adult women with a twin brother exhibited increased weight and BMI, and a higher risk of being overweight compared to women from same-sex twin pairs. The differences in BMI and weight between the groups were observed in women of 60 years and older, but not in those below 60 years of age. Dyslipidemia, but not type 2 diabetes mellitus, was more common in women with a male twin.

In summary, perinatal exposure to sex steroids affected the developing organism, predisposing to reproductive and endocrine abnormalities and features of the metabolic syndrome at adult age. Changes in insulin sensitivity, lipid profile, adipose tissue distribution, cellularity and metabolism, as well as in ovarian morphology, are factors that can be programmed perinatally with health consequences in adulthood. Our observations of dyslipidemia and increased BMI and body weight in opposite-sex female twins are consistent with the results of animal experiments, indicating that the programming effects of early androgen exposure are of relevance also for humans.

Keywords: programming, sex steroids, insulin resistance, skeletal muscle, adipose tissue, ovary