

# **Actions of androgens and estrogens in experimental models of cardiovascular disease**

## **Akademisk avhandling**

Som för avläggande av medicine doktorexamen vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg.  
Fredagen den 19 november 2010, kl. 9.00

**av Johan Bourghardt**

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Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffield

Avhandlingen baseras på följande arbeten:

- I. Androgen Receptor-Dependent and -Independent Atheroprotection by Testosterone in Male Mice**  
Bourghardt J, Wilhelmson ASK, Alexanderson C, De Gendt K, Verhoeven G, Krettek A, Ohlsson C, Tivesten Å.  
*Endocrinology* 2010, *in press*
- II. Accelerated Atherosclerosis Associated with Features of the Metabolic Syndrome in Female Mice Lacking the Androgen Receptor**  
Bourghardt J, Wilhelmson ASK, Alexanderson C, De Gendt K, Verhoeven G, Holmäng A, Krettek A, Ohlsson C, Tivesten Å.  
*Manuscript*
- III. Protection Against the Development of Abdominal Aortic Aneurysms in Male Androgen Receptor Deficient Mice**  
Bourghardt J\*, Alexanderson C\*, Wilhelmson ASK, Alexanderson C, De Gendt K, Verhoeven G, Tivesten Å.  
*Manuscript*  
\*These authors contributed equally
- IV. The Endogenous Estradiol Metabolite 2-Methoxyestradiol Reduces Atherosclerotic Lesion Formation in Female Apolipoprotein E-Deficient Mice**  
Bourghardt J, Bergström G, Krettek A, Sjöberg S, Borén J, Tivesten Å.  
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**GÖTEBORGS UNIVERSITET**

# **Actions of androgens and estrogens in experimental models of cardiovascular disease**

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## **Abstract**

Men are at higher risk of developing both atherosclerotic cardiovascular disease and abdominal aortic aneurysm (AAA). Actions of sex steroids are hypothesized to underlie these gender differences. Testosterone, the major androgen, reduces atherosclerosis in male animal models but is suggested to promote AAA formation. However, the role of the androgen receptor (AR) in mediating these effects of androgens is unknown. Further, the physiological metabolic actions of androgens in females are unclear. Estradiol, the major estrogen in females, reduces atherosclerosis in female animal models and can be metabolized to 2-methoxyestradiol, a biologically active metabolite, in the vascular wall.

This thesis aimed 1) to determine the role of the AR in the atheroprotection by testosterone in male mice, and 2) to investigate the physiological, AR-dependent actions of androgens in the development of atherosclerosis in female mice, and 3) to investigate the role of the AR in the development of AAA in male mice, and 4) to examine whether 2-methoxyestradiol affects the development of atherosclerosis in female mice.

Male and female AR-deficient mice (AR<sup>-</sup> and AR<sup>-/-</sup>) on apolipoprotein E-deficient background were generated using Cre/loxP technology. Male AR<sup>-</sup> mice fed a high-fat diet displayed accelerated atherosclerosis and reduced atheroprotection by testosterone. Female AR<sup>-/-</sup> mice fed a high-fat diet displayed accelerated atherosclerosis associated with several features of the metabolic syndrome including obesity, insulin resistance and dyslipidemia. In an angiotensin II-induced model of AAA formation, male AR<sup>-</sup> mice were protected from the development of AAA while displaying increased atherosclerosis, and testosterone increased AAA formation in controls, but not in AR<sup>-</sup> mice. In addition, 2-methoxyestradiol treatment reduced atherosclerotic lesion formation in female apolipoprotein E-deficient mice.

In conclusion, AR-mediated actions of androgens play important roles in both male and female mice. In males, AR-mediated actions of testosterone reduce atherosclerosis and promote AAA formation. In females, AR-mediated effects of androgens are important for metabolism and protects against atherosclerosis. Further, the estradiol metabolite 2-methoxyestradiol may hold promise as an atheroprotective drug.

**Keywords:** AR, atherosclerosis, AAA, androgens, testosterone, 2-methoxyestradiol