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Roles of Androgens in Cardiovascular Physiology and Pathophysiology

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, den 17 mars 2023, klockan 09.00.

av

Elin Svedlund Eriksson

Fakultetsopponent:
Professor Antonio Cittadini
University of Naples Federico II, Italy

Avhandlingen baseras på följande delarbeten

I. Wilhelmson AS, Lantero Rodriguez M, Svedlund Eriksson E, Johansson I, Fogelstrand P, Stubelius A, Lindgren S, Fagman JB, Hansson GK, Carlsten H, Karlsson MCI, Ekwall O, Tivesten Å.
Testosterone Protects Against Atherosclerosis in Male Mice by Targeting Thymic Epithelial Cells-Brief Report. Arterioscler Thromb Vasc Biol. 2018 Jul;38(7):1519-1527.

II. Svedlund Eriksson E, Lantero Rodriguez M, Johansson I, Mårtensson AKF, Wilhelmson AS, Karlsson MCI, Hagberg Thulin M, Redfors B, Borén J, Omerovic E, Levin MC, Chagin AS, Tivesten Å.
Protection from post-myocardial infarction complications by androgen receptor depletion in bone. In manuscript.

III. Svedlund Eriksson E, Johansson I, Mårtensson AKF, Lantero Rodriguez M, Schilperoort M, Kroon J, Kooijman S, Omerovic E, Andersson L, Levin MC, Rensen PCN, Tivesten Å**.**
Castration of Male Mice Induces Metabolic Remodeling of the Heart. J Endocr Soc. 2022 Sep 1;6(11):bvac132.

IV. Svedlund Eriksson E, Johansson I, Poutanen M, Landin A, Norlén AK, Ryberg H, Levin MC, Ohlsson C, Tivesten Å.
Sex steroids in the heart of male mice. In manuscript.

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Roles of Androgens in Cardiovascular Physiology and Pathophysiology

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ABSTRACT

Atherosclerosis is the major underlying cause of cardiovascular disease, such as myocardial infarction (MI) and stroke, and these conditions are the leading causes of death both in Sweden and globally. The immune system is involved in the pathogenesis of atherosclerosis as well as post-MI cardiac injury. Men develop cardiovascular disease approximately ten years earlier than women and the incidence of MI is higher in men throughout life. It has been suggested that the female sex hormones, estrogens, have cardioprotective properties while the roles of androgens, often described as male sex hormones, in cardiovascular physiology and pathophysiology are less understood. The underlying mechanisms and target cells for the cardiovascular effects of androgens are poorly described and to a large extent unknown. The aim of this thesis was to define roles and underlying mechanisms of androgens in cardiac physiology, atherosclerosis and MI and to identify target cells that mediate these actions in male mice.

The main findings of this thesis were that:

1) atherosclerosis induced by testosterone deficiency in male mice is thymus- and T cell dependent and that the thymic epithelial cell is likely the target cell for the anti-atherogenic actions of testosterone.
2) depletion of the androgen receptor (AR) in bone marrow stromal cells in male mice reduced post-MI neutrophil infiltration, mortality and adverse cardiac remodelling. Hence, we have identified the target cells for these androgenic effects. Further, we demonstrate that androgens promote neutrophil egress from the bone marrow by regulating leukocyte retention factors in bone cells.
3) androgen deficiency in male mice induces metabolic remodelling and expression of the fetal gene program in the heart.
4) concentrations of sex steroids in the heart do not merely reflect serum levels in male mice. We show that progesterone levels are much higher in the heart than in skeletal muscle and that the cardiac levels are reduced during the acute phase post MI.

This thesis demonstrates important effects of androgens on both the cardiovascular and immune systems. Our results provide potential explanations to sex differences in cardiovascular disease and how androgens can exert beneficial effects in some conditions (atherosclerosis) while detrimental in others (post-MI myocardial injury). Our data may pave the way for the development of selective AR modulators for safer treatment of prostate cancer. Further, our data raise new questions, including whether the AR in bone cells may be explored as a treatment target in acute MI and if drugs that reduce androgen levels, which are used in large patient groups, may positively affect the outcome of an MI.

Keywords: androgens, androgen receptor, atherosclerosis, myocardial infarction, immune system, SARMs, male mice

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