The effects of stress on atherosclerosis in mice

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg

Fredagen den 26 november kl 13.00

Av
Evelina Bernberg

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Dep. of Integrative Biology and Physiology, University of Minnesota, Minnesota, USA

Avhandlingen baseras på följande delarbeten:

I **Effects of social isolation and environmental enrichment on atherosclerosis in ApoE$^{-/-}$ mice**
Evelina Bernberg, Irene J Andersson, Li-ming Gan, Andrew S Naylor, Maria E Johansson, Göran Bergström
Stress **2008**. 11(5): 381–389

II **Repeated exposure to stressors do not accelerate atherosclerosis in ApoE$^{-/-}$ mice**
Evelina Bernberg, Irene J Andersson, Sofia Tidstrand, Maria E Johansson, Göran Bergström
Atherosclerosis **2009**. 204: 90–95

III **Social disruption stress increases IL-6 levels and accelerates atherosclerosis in ApoE$^{-/-}$ mice**
Evelina Bernberg, Maria E Johansson, Göran ML Bergström
In manuscript

IV **Metoprolol reduces pro-inflammatory cytokines and atherosclerosis in ApoE$^{-/-}$ mice**
Evelina Bernberg, Maria E Johansson, Göran ML Bergström
In manuscript

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The effects of stress on atherosclerosis in mice

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ABSTRACT

Psychosocial stress has been recognized as an independent risk factor for cardiovascular disease and atherosclerosis. However, little is known about the mechanisms converting this psychosocial load into physical disease. This thesis aims to find and evaluate a well controlled animal model for stress and use it to study the long term consequences of stress on atherosclerosis. We also aim to use this model to search for mechanisms causing stress to accelerate the progression of atherosclerosis.

We exposed atherosclerosis-prone $ApoE^{-/-}$ mice to social isolation, five physical stressors or social disruption stress (SDR-stress). A subgroup of SDR-mice and unstressed mice were treated with metoprolol. Atherosclerosis was assessed and blood samples were collected for analysis of corticosterone, lipids and cytokines.

We found that social isolation and SDR-stress increased atherosclerosis, while the five more physical stressors failed to be atherogenic. Metoprolol *per se* reduced atherosclerosis in unstressed mice. Plasma corticosterone levels were increased after all 5 physical stressors and SDR-stress, but not in socially isolated mice. Plasma lipid levels were increased in socially isolated mice. Serum levels of the haemotopoietic cytokine G-CSF were decreased in socially isolated mice, pro-inflammatory cytokines IL-6 and CXCL1 were increased after SDR-stress, but no effects on cytokine release was found after the five physical stressors. β-blockade with metoprolol likely reduced SDR-stress-induced increases in both IL-6 and CXCL1, and significantly reduced CXCL1 and TNF-α levels in unstressed mice.

This thesis has provided important information on how social stress accelerates atherosclerosis, and has suggested the release of pro-inflammatory cytokines as an underlying mechanism. Our hope is that our results, and further studies exploring mechanisms converting psychosocial stress into physical disease, will help to reduce the deleterious effects of psychosocial stress.

Keywords: Social isolation, stressors, social disruption stress, atherosclerosis, cytokines, corticosterone, metoprolol

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