Role of environmental toxins in chronic experimental arthritis

- in search of anti-inflammatory pathways for ethanol and nicotine

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid
Göteborgs universitet, kommer att offentligen försvaras i
föreläsningssalen, våning 3, Guldhedsgatan 10 A, Göteborg

fredagen den 10 december kl. 09.00

av
Sofia Silfverswärd Lindblad

Fakultetsopponent:
Patrick Venables,
Kennedy Institute, Imperial College, London, Storbritannien

Avhandlingen baseras på följande delarbeten:

I. Ing-Marie Jonsson, Margareta Verdrengh, Mikael Brisslert, Sofia S. Lindblad, Maria Bokarewa, Ulrika Islander, Hans Carlsten, Claes Ohlsson, Kutty Selva Nandakumar, Rikard Holmdahl, Andrej Tarkowski.
Ethanol prevents development of destructive arthritis
Proc Natl Acad Sci U S A. 2007 Jan 2;104(1):258-63

II. Sofia S. Lindblad, Piotr Mydel, Ing-Marie Jonsson, Robert Senior M, Andrej Tarkowski, Maria Bokarewa
Smoking and nicotine exposure delay development of collagen-induced arthritis in mice
Arthritis Research & Therapy 2009;11(3):R88

III. Sofia S. Lindblad, Piotr Mydel, Annelie Hellvard, Ing-Marie Jonsson, Maria Bokarewa
The NMDA receptor antagonist memantine ameliorates and delays development of collagen-induced arthritis by intensifying development of regulatory T cells
Arthritis & Rheumatism, revision submitted

UNIVERSITY OF GOTHENBURG

Role of environmental toxins in chronic experimental arthritis - in search of anti-inflammatory pathways for ethanol and nicotine

Sofia Silfverswärd Lindblad, Department of Rheumatology and Inflammation Research,
The Sahlgrenska Academy at Göteborg University, Guldhedsgatan 10A, 413 46 Göteborg, Sweden

Abstract

Rheumatoid arthritis (RA) is a common systemic autoimmune disorder and a debilitating disease affecting 1% of the world population. The etiology of RA is an unresolved issue. Environmental factors such as alcohol intake and cigarette smoke have been described as contributing to the pathogenesis of RA. These assumptions are based on epidemiological studies, while experimental proof on this issue is limited. This thesis studies the effect of common environmental toxins on experimental arthritis induced by collagen type II (collagen-induced arthritis, CIA), an established murine model closely resembling human RA. We propose biological mechanisms behind the anti-inflammatory properties of environmental stimuli such as ethanol and nicotine, and provide new insights into the pathogenesis of RA.

Paper I shows that a continuous intake of ethanol delays the onset and halts the progression of CIA in mice. This anti-arthritic effect is mediated by increased testosterone secretion leading to (i) decreased activation of transcription factor NF-κB, (ii) down-regulation of pro-inflammatory cyto- and chemokines and (iii) down-regulation of leukocyte migration into the joints.

Paper II studies the effect of cigarette smoking and nicotine exposure in CIA mice. Results show that mice exposed to cigarette smoke develop a significantly milder arthritis with reduced destruction of joints. Nicotine-exposed mice show a tendency to decreased inflammation. Notably, exposure to cigarette smoke reduces antigen response and decreases the level of CII-specific antibodies.

Paper III handles intervention with ethanol-sensitive glutamate receptors. CIA mice subjected to the NMDA receptor antagonist memantine show significantly decreased severity of arthritis and reduced destructive disease. We show that memantine up-regulates transcription factor Foxp3 and enhances formation of $CD4^+CD25^+Foxp3^+$ regulatory T cells, which may be a potential reason for the anti-arthritic properties of the NMDA receptor blockade.

In conclusion, our results provide new insights into the anti-inflammatory properties of environmental toxins such as ethanol and nicotine, as well as of blockade of the ethanol-sensitive NMDA receptor. Our findings from experimental studies need further validation in the population of RA patients.

Key words: rheumatoid arthritis, collagen-induced arthritis, ethanol, testosterone, NF-κB, cigarette smoking, nicotine, NMDA, $CD4^+CD25^+Foxp3^+$ regulatory T cells

ISBN 978-91-628-8194-8 Göteborg 2010