Estrogen and 2-methoxyestradiol Regulation of arthritis, inflammation and reactive oxygen species

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ABSTRACT

Rheumatoid arthritis (RA) is characterized by severe synovial inflammation, cartilage destruction, and immune-mediated bone loss. Estrogen ameliorates experimental RA, reducing both inflammation and bone loss. The inflamed tissues are damaged partly by innate immune cells producing reactive oxygen species (ROS). ROS can also regulate the immune system. This thesis aimed to investigate the regulation of inflammation and joint destruction by 17β -estradiol (E2) and its metabolite 2-methoxyestradiol (2me2).

E2's and 2me2's immunomodulation were investigated both in experimental arthritis and in an unprovoked immune system. Both wild type (WT) mice and Catechol-*O*-methyltransferase (COMT)-deficient mice were used, as COMT metabolizes E2 into 2me2. Further, E2's regulatory role was investigated in WT mice or ROS-deficient mice (B10.Q.Ncf1*/*), in a model of osteoporosis and a local (LPS-induced) inflammation model.

2me2 ameliorated arthritis and bone mineral density (BMD), and regulated immune cells differently compared with E2. Treatment with high doses of 2me2 increased uteri weight, implying estrogen-receptor activation; 2me2 activated estrogen-response elements in a tissue, and dose-dependent manner. Deficiency in the COMT enzyme only moderately affected the immune system, and males were more affected than females.

In ovx-induced bone loss, ROS-deficient mice displayed reduced osteoclastogenesis compared to controls, but similar bone mineral density and immunological profiles. In LPS-induced inflammation, E2 treatment in WT mice shifted neutrophil infiltration to macrophage infiltration, while in ROS-deficient mice E2 treatment induced neutrophil infiltration and reduced the macrophages.

In conclusion, E2's metabolite 2me2 can modulate arthritis and inflammation-triggered osteoporosis. At high doses 2me2 can induce estrogen receptor signaling. E2 together with ROS regulate inflammation and osteoclastogenesis. Understanding estrogenic cellular and molecular mechanisms are important for developing new arthritis and inflammation-treatments. Our results increase the understanding of estrogens' role in inflammation and motivate further investigations.

Keywords: Estrogen, arthritis, reactive oxygen species

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 I. <u>Alexandra Stubelius</u>, Emil Andréasson, Anna Karlsson, Claes Ohlsson, Åsa Tivesten, Ulrika Islander, Hans Carlsten

Role of 2-methoxyestradiol as inhibitor of arthritis and osteoporosis in a model of postmenopausal rheumatoid

Clinical Immunology 2011: 140, 37-46.

- II. <u>Alexandra Stubelius</u>, Malin C. Erlandsson, Ulrika Islander, Hans Carlsten. <u>Immunomodulation by the estrogen metabolite 2-methoxyestradiol</u> Clinical Immunology 2014, in press.
- III. <u>Alexandra Stubelius</u>, Anna S. Wilhelmson, Joseph A. Gogos, Åsa Tivesten, Ulrika Islander, Hans Carlsten

Sexual dimorphisms in the immune system of catechol-*O*-methyltransferase knockout mice.

Immunobiology 2012: 217, 751-760.

IV. <u>Alexandra Stubelius</u>, Annica Andersson, Rikard Holmdahl, Claes Ohlsson, Ulrika Islander, Hans Carlsten

 $NADPH\ oxidase\ 2\ influences\ osteoclast\ formation\ but\ is\ not\ critical\ for\ ovariectomy-induced\ bone\ loss$

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V. <u>Alexandra Stubelius</u>, Annica Andersson, Rikard Holmdahl, Ulrika Islander, Hans Carlsten

Role of estrogen in regulating LPS-induced inflammation in NADPH oxidase 2 deficient mice

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