Nuclear receptors and their role in regulation of inflammation

A special section consisting of proceedings from the EUROSTERONE Meeting, Huddinge, Sweden, 27 September 2000

Foreword

Introduction

EUROSTERONE is the acronym for a thematic network addressing the issue of ‘Steroids in health and disease’. This network is funded within the Fifth Framework Programme of the European Community and has gathered representatives from seven universities all over Europe: University of Edinburgh, University of Dublin, University of Göttingen, University of Innsbruck, Karolinska Institutet, Stockholm, University of Leiden and INSERM, Montpellier.

The overall objective of the network is to bring together the expertise and facilities of the participants of the EUROLIFE network of European Universities to promote European research in the area of steroid biology. The network has been effective since April 2000 and has funding for a three year period. The network is focusing on four major tasks: 1) to facilitate access to reagents, 2) to disseminate up-to-date information, 3) to access specialised facilities and technologies and 4) to initiate and support research and technological development (RTD) proposals within this area. More information about EUROSTERONE can be found at http://www.eurosterone.org.

A number of thematic conferences are currently being planned to take place within the EUROSTERONE network. The first thematic conference took place under the umbrella of a Joint International Symposium arranged by the Center for Biotechnology at Novum, Karolinska Institutet, and the Summer School of Southern Stockholm, Sweden. This meeting was limited to 200 participants, who came from all over the world, and a one-day theme of ‘Nuclear receptors and inflammation’ constituted the EUROSTERONE part of the meeting. A number of commentary articles from this symposium are provided by the participating lecturers in this special section of the Journal of Endocrinology.

Glucocorticoids, glucocorticoid receptors and HPA-axis regulation

Several aspects of the role of nuclear receptors in inflammation were elucidated during this meeting. Dr Ester M Sternberg, Bethesda, MD, USA gave an overview of ‘Neuroendocrine regulation of autoimmune/inflammatory disease’, describing the importance of the hypothalamic-pituitary-adrenal (HPA) axis in determining disease susceptibility. Based on studies in inbred rat strains, Dr Sternberg and her co-workers have found that a high setpoint of the HPA-axis with high diurnal corticosterone secretion (i.e. an excess stress
hormone response) increases both the risk of acquiring infections and their subsequent severity. This is supposedly due to an immunosuppressive effect of glucocorticoids exerted on virtually every level of innate and specific immune responses. A low-set HPA-axis with low, inadequate corticosterone secretion and a small amplitude of secretion increases susceptibility to autoimmune and inflammatory diseases. Dr Sternberg also discussed connections between the nervous, endocrine and immune systems, how cytokines affect the HPA-axis and how the rich innervation of immune organs as well as local neural secretion of corticotrophin-releasing hormone (CRH) may affect inflammatory responses. A distinction of physiological levels of glucocorticoids from pharmacological glucocorticoid treatment levels was made. A physiological dose may act in a more immunomodulatory rather than immunosuppressive manner, driving the T-cell responses from the Th1 to the Th2 subtype.

Dr George P Chrousos, Bethesda, MD, USA discussed animal models for inflammatory disorders. He explained the interplay of glucocorticoids with T-cell subsets and cytokines such as IL-6, which can act as activators of the HPA-axis. Dr Chrousos also discussed the perturbations caused by HIV infection, which can give rise to a seemingly glucocorticoid hypersensitive state, and the Cushing-like appearance of a subset of AIDS patients treated with protease inhibitors. This may be linked to the ability of the viral protein vpr to act as a coactivator for the glucocorticoid receptor (GR). Studies by Chrousos and co-workers, summarised in this issue of the *Journal of Endocrinology*, also detail mechanisms for the impairment of steroid hormone receptor signalling based on point mutations and other structural changes in the GR.

In a lecture by Dr Michael Karin, La Jolla, CA, USA, the interaction and transcriptional interference between GR and the transcription factor AP-1 were addressed. This action of glucocorticoids is important for anti-inflammatory and immunosuppressive effects mediated via repression of both nuclear factor-κB (NF-κB) and AP-1, and is now considered to be even more important than the classic mode of transactivation exerted by GR. This notion is further supported by the findings of Reichardt et al. (1998) who generated mice with a GR that cannot bind a glucocorticoid response element (GRE) due to a dimerisation deficiency, but does retain the capacity to repress both AP-1 and NF-κB. Adding another level of control into this system, Dr Karin reported on experiments showing that the protein kinase Jun N-terminal kinase (JNK) is activated by, for example, IL-1. As a consequence of this, JNK is able to activate AP-1 and NF-κB, and hence can act as an HPA-axis activator. This feedback mechanism finally leads to an increase of glucocorticoids, which in turn via GR can interfere with AP-1, and this enables an adequate stress response.

**Peroxisome proliferator-activated receptors and anti-inflammation**

Several speakers addressed exciting new developments in the quickly expanding field of the peroxisome proliferator-activated receptors (PPARs). Subforms of this receptor regulate various steps in lipid and lipoprotein metabolism and, more recently, PPARs have been indicated as regulators of various inflammatory responses. Further development of ligands to these receptors may enable anti-inflammatory therapies with a decreased risk of unwanted side-effects.

Dr Bart Staels, Lille, France discussed the role of PPARs in modulating immune and inflammatory responses. Ligands that can activate PPARs (such as fibrates in the case of PPARα) lead to inhibition of pro-inflammatory genes via antagonism of, for example, NF-κB and AP-1 activity. Additional anti-inflammatory mechanisms such as control of cellular redox status and catalase activity have also been suggested. Furthermore, data from clinical trials suggest there are effects of PPARα agonists such as fenofibrates on inflammation control,
reducing inflammatory markers such as IL-6, fibrinogen and C-reactive protein. PPARγ ligands have also been suggested to act as potential anti-inflammatory agents. However, results obtained in various model systems for inflammatory diseases are not conclusive and sometimes such effects could not be demonstrated. The role of PPARγ was further addressed by Dr Christopher K Glass, La Jolla, CA, USA. He focused on the role of PPARγ in inappropriate activation of macrophages, which has been shown to contribute to the development of diseases like atherosclerosis, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Although glucocorticoid treatment of both IBD and RA is part of established, efficient therapeutic strategies, the treatment is unfortunately hampered by the development of detrimental side-effects and a new mode of treating these diseases with PPAR ligands could be beneficial.

Dr Glass reported on investigations of the function of PPARγ in macrophages. The interplay of PPARγ and IL-4 in the macrophage and the putative role of PPARγ in the development and progression of atherosclerosis were also discussed. PPARγ has natural ligands such as metabolites of polyunsaturated fatty acids, but synthetic ligands called thiazolidinediones, used clinically as insulin sensitisers, are also potent agonists for PPARγ. Both synthetic and natural PPARγ agonists could inhibit the expression of genes induced in experimental inflammatory macrophage models, and this indicates that PPARγ may serve as a target for further anti-inflammatory drug development where aberrant macrophage activation is involved.

A step in this direction has been taken by Johan Auwerx and his colleagues, who reported on the development of PPARγ modulators that can exert a more beneficial effect on insulin sensitivity in spite of lower potency. Dr Auwerx also discussed studies reported elsewhere (Dubuquoy et al. 2000) indicating that PPARγ agonists decrease the intensity of trinitrobenzene sulfonic acid (TNBS)-induced colitis, through normalisation of IL-1β and tumor nicrosis factor-α expression.

Research in the field of nuclear receptors is rapidly expanding and attracting greater interest. Several of these receptors are involved in modulating immunological and inflammatory responses. A number of these effects are well established and widely used for clinical purposes, such as the immunosuppressive and anti-inflammatory effects of glucocorticoids. Several recent discoveries may point to new ways of treating chronic inflammation in various diseases, employing ligands to the PPARs or to other nuclear receptors. The EUROSTERONE part of the Stockholm Center for Biotechnology meeting in September 2000 demonstrated an exciting overview of the role of glucocorticoids and the HPA-axis in inflammation, and the possibilities of using PPAR ligands for anti-inflammatory purposes.

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Chair

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