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Recent aspects of gonadal hormone and neurotransmitter interactions with synovial and immune cells: implications in rheumatoid arthritis

The hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) axis involvement, and/or response to the immune system activation, is now recognised in the development and maintenance of inflammatory and autoimmune conditions such as rheumatoid arthritis (RA).[1]

In female patients the immune response seems to depend more on the HPA axis, whereas in male patients it seems to depend more on the HPG axis. In particular, hypoandrogenism may have a pathogenetic role in male patients with RA, and in other autoimmune conditions (for example, systemic lupus erythematosus (SLE)), as androgens are considered natural immunosuppressors.[2]

Conversely, physiological concentrations of oestrogens seem to exert some immunoenhancing activities, at least on the humoral response. In addition, a range of physical/psychosocial stressors are also implicated in the activation of the HPA axis and the related altered HPG function in RA.[3 4]

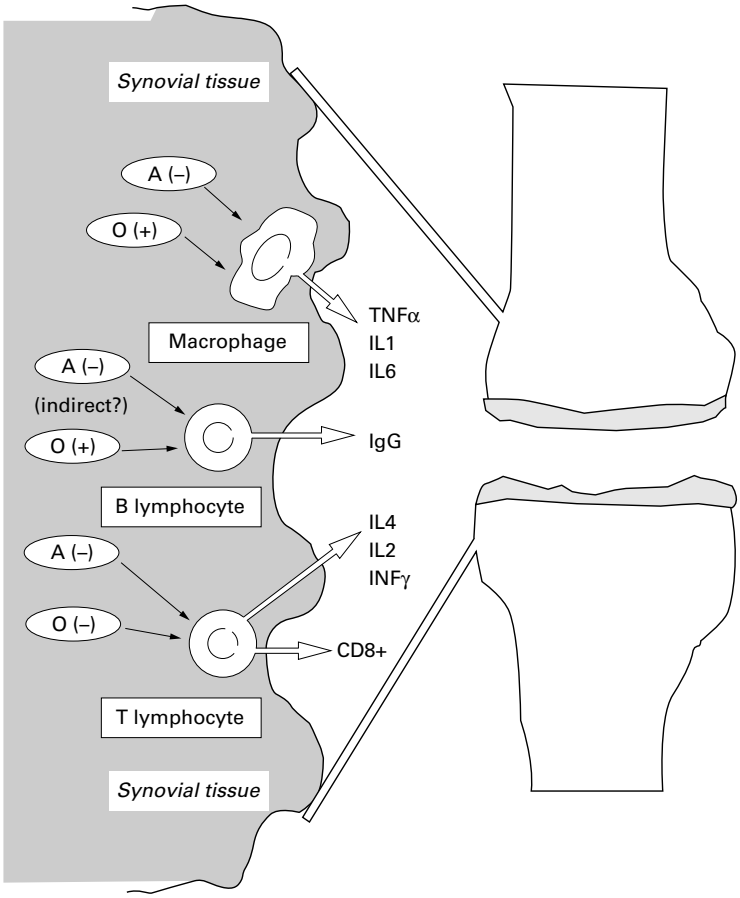

Figure 1 Major stimulatory (+) or inhibitory (−) effects (direct and indirect) of androgens (A) and oestrogens (O) on cytokine/immunoglobulin production by synovial/immune cells at the level of the synovial rheumatoid tissue.

Finally, the raised levels of neurotransmitters detected in RA synovial fluids, suggest that the peripheral nervous system also might contribute to the generation of the synovial inflammation (that is, neurogenic inflammation).[5–8]

A major unknown in the pathogenesis of RA is why immune mediated inflammation begins and develops within joints. A central role in understanding RA pathogenesis lies in the comprehension of arthrotropism of antigens and inflammatory cells for joints and in learning what specific receptors, mediators, and chemotactic gradients are active in focusing the immune mediated inflammation within the synovial tissue.

Undoubtedly, the synovial tissue in RA can be regarded as the "target tissue", in which the sexual dimorphism in immune response to relevant trigger antigens is present and involves mainly synovial macrophages as well as fibroblasts and lymphocytes.[9–15]

Therefore, an intricate balance with bidirectional interactions between soluble mediators, released by the neuroendocrine system (that is, neurotransmitters and steroid hormones) and products of activated cells of the immune/inflammatory system (that is, cytokines from macrophages) maintains the homeostasis in the presence of immune/inflammatory synovitis.[16 17]

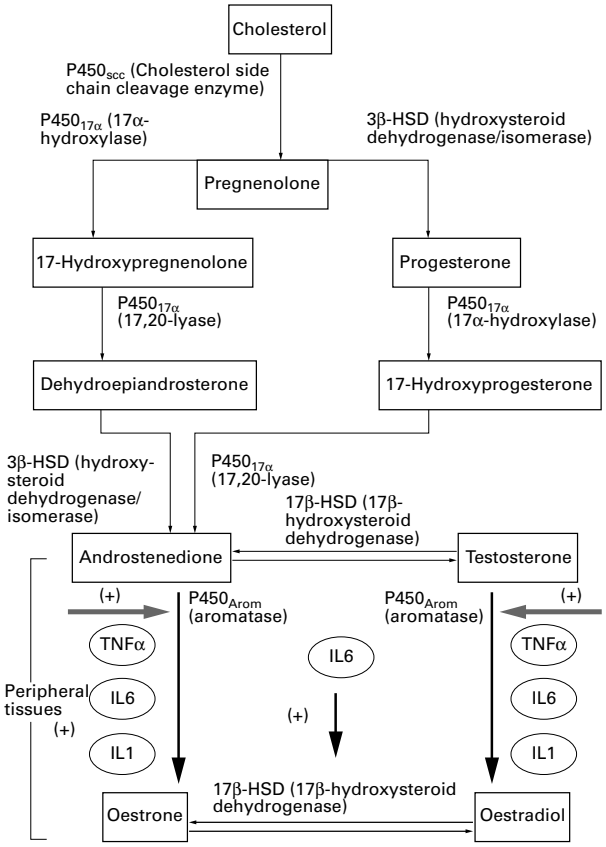

Figure 2 Locally produced inflammatory cytokines (that is, tumour necrosis factor α (TNFα), interleukin 1 (IL1), IL6) can markedly stimulate the aromatase activity ($P450_{Arom}$) in peripheral tissues (that is, synovial tissue) with subsequent increased conversion of androgens (testosterone and androstenedione) to oestrogens (oestrone and oestradiol, respectively). In addition, IL6 has been found to mediate an increase in reductive 17β-hydroxysteroid dehydrogenase (17β-HSD) activity that converts oestrone to the biologically more active 17β-oestradiol. These effects might explain the altered balance with lower androgens and higher oestrogens found in the synovial RA fluids, as well as their resulting effects on synovial cells.

Gonadal hormone interactions with synovial and immune cells

Generally, the macrophage derived inflammatory cytokines (that is, interleukin 6 (IL6), IL1, tumour necrosis factor α (TNFα)), as soluble products of the synovial arthritis, stimulate the production of corticotrophin-releasing hormone in the hypothalamus: this release leads to pituitary production of adrenocorticotrophic hormone, followed by glucocorticoid secretion by adrenal cortex and indirect perturbations of the gonadal function.[18]

As a matter of fact, significantly lower androgen concentrations (that is, testosterone, androstenedione, and dehydroepiandrosterone sulphate) are detected in the serum as well as in the synovial fluid of male and female patients with RA.[19 20] Low serum androgens seem also to characterise other immune mediated rheumatic diseases, such as systemic lupus erythematosus and systemic sclerosis.[21 22]

We investigated the ability of cultured synovial macrophages to metabolise androgens and we found that these cells could metabolise testosterone into the bioactive metabolite dihydrotestosterone.[23] Therefore, macrophages contain the key enzymes of steroidogenesis, in particular the 5α reductase. Furthermore, we analysed the IL1β production by primary cultures of synovial RA macrophages. Following exposure to physiological concentrations of testosterone (10^{-8} mol/l) a significant decrease of IL1β levels in conditioned media was found after 24 hours (fig 1).[23] In addition, testosterone treatment was found to reduce the monocyte IL6 production when compared with controls.[24]

On the contrary, physiological concentrations of oestrogens (10^{-8} mol/l) seem to stimulate both IL1 mRNA levels and IL1 protein synthesis in human peripheral monocytes (precursors of tissue macrophages) and pelvic macrophages.[25] Similar results were also obtained when TNF mRNA levels were evaluated on cultured RA synovial macrophages treated with oestrogens (fig 1) (Di Giovine F, personal communication).

Therefore, gonadal steroids may act directly on human macrophages and may interfere with some of their functions (for example, proinflammatory cytokine production) through receptor dependent mechanisms (fig 1).

The presence in the RA synovial fluids of an altered sex hormone balance, resulting in lower immunosuppressive androgens and higher immunoenhancing oestrogens, might provide a favourable condition for the development of the immune mediated RA synovitis.[26]

How can one explain the recent detection of lower androgen and higher oestrogen levels in both female and male RA synovial fluids?[27 28]

The appropriate explanation might originate from studies showing that the inflammatory cytokines (that is, IL6, IL1, TNFα) can markedly stimulate the aromatase activity in peripheral tissues (fig 2).[29–31] As a matter of fact, the aromatase enzyme complex plays a part in the peripheral conversion of androgens (testosterone and androstenedione) to oestrogens (oestrone and oestradiol, respectively). In tissues rich with macrophages a significant correlation was found between the aromatase activity and the IL6 production.[31] Therefore, the increased aromatase activity induced by locally produced inflammatory cytokines (that is, IL1, IL6, TNFα) might explain the altered balance resulting in lower androgens and higher oestrogens in the synovial RA fluids, as well as their effects on synovial cells (fig 2).[5]

In addition, IL6 has been found to mediate an increase in reductive 17β-hydroxysteroid dehydrogenase activity that converts oestrone to the biologically more active 17β-oestradiol.[32]

Oestrogen and androgen receptors have been investigated in B lymphocytes to evaluate their possible functional role in cell proliferation and immunoglobulin secretion during the immune response. Oestrogen receptors have been detected in cell lines derived from patients with multiple myeloma (and mouse hybridomas), whereas androgen receptors have not been found in these cell lines.[33] Immunoglobulin production by 17β-oestradiol treated B cells at physiological concentrations is higher than that of controls both in men and women (fig 1).[34 35] Interestingly, 17β-oestradiol increases IL10 production by monocytes, and exogenous IL10 further enhances 17β-oestradiol induced increases in antibody production by B cells. A more recent study confirms that 17β-oestradiol can increase polyclonally the production of IgG, including IgG anti-dsDNA in the peripheral blood mononuclear cells (PBMCs) of patients with SLE, by enhancing B cell activity and promoting IL10 production by monocytes (fig 1).[36] Antibody production in B lymphocytes was found to be suppressed by testosterone, though the magnitude of its effect on B cells was lower than on PBMCs (fig 1).[37] Furthermore, testosterone reduced IL6 production by normal monocytes, whereas, exogenous IL6 partially restored the testosterone induced decrease in antibody production by PBMCs. Thus these data indicate that testosterone may modulate, at least indirectly, susceptibility to human autoimmune diseases, including RA, through actions on monocytes. The final result is the induction of decreased B cell activity.

Effects of oestrogen on T lymphocytes are less well documented than effects on B lymphocytes. However, oestrogen receptors are present in human CD8+CD29+ CD45RO+ T lymphocytes (memory cells) from synovial tissue.[38 39] Because oestrogen receptors are expressed on CD8+ T lymphocytes that display inhibitory properties on antibody producing B lymphocytes, the role of 17β-oestradiol on B autoreactive cells is probably both direct and indirect (fig 1). Nevertheless, the role of oestrogens in modulating susceptibility to human autoimmune diseases, including RA, does not seem, from the available evidence, critically determined by actions on T lymphocytes. The influences of androgens on T cells are also complex and have been inadequately studied in both humans and animals. Direct exposure of murine T cells to dihydrotestosterone reduces the amount of IL4, IL5, and interferon γ (IFNγ) produced after activation with anti-CD3 without affecting the production of IL2 (fig 1).[40] A recent experimental study showed that testosterone exerts a protective effect on experimental autoimmune encephalomyelitis and was the first to show the ability of testosterone to shift an autoantigen-specific T lymphocyte response toward the T helper 2 phenotype, in vivo, coupled with an observed effect on a clinical autoimmune disease (fig 1).[41]

Neurotransmitter interactions with immune cells

Besides the paracrine and systemic gonadal hormone influence on synovial cells, we have to discuss paracrine neurotransmitter effects because the synovial tissue is richly innervated.[42] At least three different types of nerve fibres enter the synovial tissue by various routes: Firstly, the sympathetic nervous system accompanies blood vessels and the small nerve fibres end in the surrounding of these vessels.[43] These efferent nerve fibres store neurotransmitters, such as norepinephrine, neuropeptide Y, endogenous opioids (that is, methionine enkephalin), and adenosine triphosphate (ATP) in the peripheral nerve endings.[44] ATP is converted to adenosine in the extracellular space by the ecto-5'-nucleotidase, which is located at the surface of macrophages and other cells (CD73) in the vicinity of the nerve terminal.[45] Secondly, the primary sensory afferent nerve fibres with the two neurotransmitters, substance P and calcitonin gene-related peptide, also innervate the synovial tissue.[46] Thirdly, vasoactive intestinal peptide belongs to the non-adrenergic non-cholinergic type of peripheral nerve fibres which are also present in this tissue.[47] From the present point of view, the effects of these neurotransmitters on immune cells are not uniform (fig 3). Generally, it seems that high concentrations of neurotransmitters of the sympathetic nervous system (norepinephrine, adenosine, methionine enkephalin) are anti-inflammatory, whereas the main neurotransmitter of the sensory nervous system—substance P—is proinflammatory in all aspects (fig 3).

At the moment, it is widely accepted that substance P, a neurotransmitter of the sensory afferents, is proinflamma-

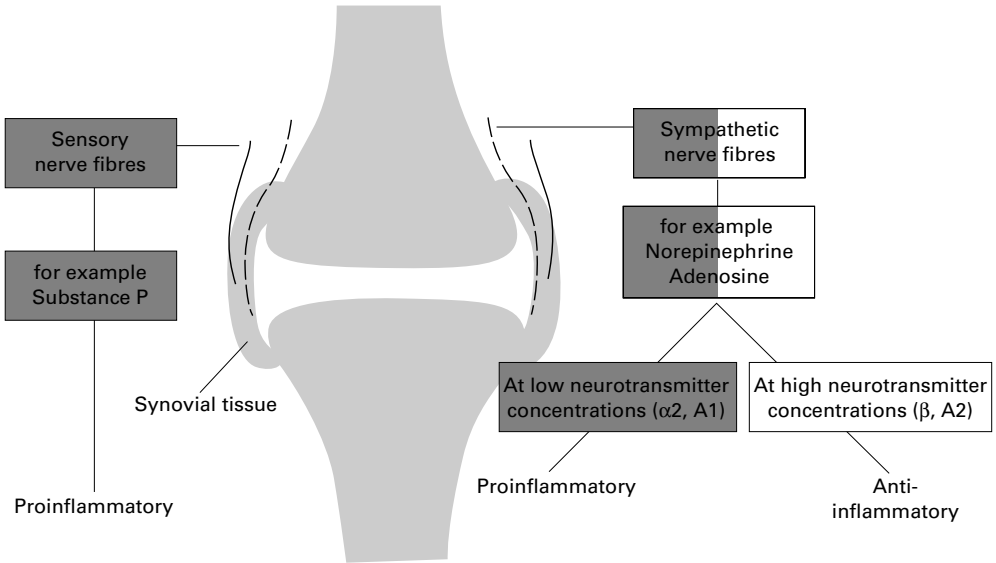

Figure 3 Impact of sensory and sympathetic nerve fibres on inflammation in the synovial tissue. The diagram shows the balance of proinflammatory and anti-inflammatory mechanisms. Substance P of sensory nerve fibres and norepinephrine/adenosine at low concentrations seem to be proinflammatory, whereas norepinephrine/adenosine at high concentrations seem to be anti-inflammatory. α2 = alpha 2 adrenergic; β = beta adrenergic; A1 = adenosine receptor 1; A2 = adenosine receptor 2.

tory. For example, substance P stimulates IL1, IL2, IL8, TNF, NF-κB, and superoxide anion production from various cell types.[48–52] Local administration of substance P antagonists markedly reduces the severity of inflammation in animal models.[53 54] Furthermore, substance P is chemotactic for human monocytes and it sensitises articular afferent nerve fibres in normal and inflamed knee joints, which leads to increased mechanosensitivity, pain, and continuously increased substance P release into the lumen of the joint.[55 56] Aside from the proinflammatory mechanisms influenced by substance P, the effects of substance P also continuously sense painful stimuli in the periphery.

For the sympathetic nervous system and its neurotransmitters, the situation is not as uniform as with substance P. Because norepinephrine or adenosine, which are colocalised in vesicles of the sympathetic nerve terminal, are ligands of different receptor subtypes with opposing intracellular signal transduction pathways, different effects may arise depending on the local concentration (summarised[57], fig 3). At high concentrations in the vicinity of the nerve terminal, norepinephrine acts on α and β adrenoceptors and adenosine on A1, A2, and A3 adenosine receptors, respectively. However, at low concentrations (equal or below 10^{-7} mol/l) effects are mediated mainly through α receptors or A1 adenosine receptors, respectively. Stimulation of the β adrenoceptor and the A2 receptor leads to an intracellular increase of cyclic AMP and, thus, marked downregulation of arthritogenic TNF, IL12, or IFNγ.[58–61] In contrast, stimulation through the α2 adrenoceptor (cAMP decrease) even stimulates TNF secretion.[62] Taken together, an increased sympathetic nervous system activity is accompanied by release of high amounts of norepinephrine, adenosine, and opioids, which induces an anti-inflammatory effect (fig 3).

However, recent studies suggest that the proinflammatory sensory nerve fibres remain high in the inflamed tissue whereas the density of sympathetic nerve fibres decreases.[63] This may lead to a shift towards a more proinflammatory situation. Since norepinephrine (through β adrenoceptors) and cortisol help each other to maintain the respective signal transduction pathway, a decrease in their relative concentrations in the synovial tissue may synergistically lead to a more proinflammatory state.[64 65] Thus loss of norepinephrine and other sympathetic neurotransmitters due to retraction of sympathetic nerve fibres will be accompanied by a more proinflammatory state.

Conclusions

In conclusion, neuroendocrine mechanisms represent modulating factors for the immune response and the inflammatory reaction. The participation of the neuroendocrine immune system in the pathophysiology of RA is now clearer and suggests a common pathway also for other chronic inflammatory rheumatic diseases.[66 67] However, further studies are in progress to consider the effects of the neurotransmitters together with gonadal hormones in target cells of the synovial tissue.[68 69]

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