

## Review

# Hormones and the immune response

Recent advances suggest that the immune system does not function in isolation but is influenced by other physiological systems such as the endocrine and neuroendocrine systems. This review discusses aspects of immune function altered by neuroendocrine peptides, sex hormones, and vitamin D metabolites.

### Neuroendocrine effects

A system of bidirectional communication between the immune and neuroendocrine system exists, in which the two systems share a common set of hormones and receptors.<sup>1,2</sup> Not only do immune cells possess receptors for neuroendocrine peptides, they are also capable of synthesising them and of responding to them. Products of immune cells affect the central nervous system, which possesses receptors for cytokines and can also synthesise them (Fig. 1).

Receptors for neuroendocrine peptides, such as adrenocorticotrophic hormone (ACTH),  $\beta$ -endorphin, thyroid stimulating hormone, and growth hormone are present on immune cells. High and low affinity ACTH receptors, similar to those on adrenal

cells, are present on mouse spleen cells<sup>3</sup> and human peripheral blood mononuclear cells.<sup>4</sup> Receptors, identical to those in the central nervous system, for methionine enkephalin are present on splenocytes and T lymphocytes.<sup>3</sup> In contrast, leucine enkephalin and  $\beta$ -endorphin receptors on T lymphocyte differ from those in the central nervous system as binding cannot be inhibited by opiate antagonists.<sup>5,6</sup> In the case of  $\beta$ -endorphin the bindings occur through its carboxy terminal, whereas opiates bind their receptor through the amino terminus. This raises an interesting possibility that a peptide such as  $\beta$ -endorphin could form a bridge between two lymphocyte subtypes by binding to one through its amino terminus to the opiate receptor and through its carboxy terminus to the non-opiate receptor on another lymphocyte.<sup>4</sup>

Other neuroendocrine peptide receptors present on leucocytes include those for neurotensin,<sup>7</sup> substance P,<sup>8</sup> prolactin,<sup>9,10</sup> growth hormone,<sup>11</sup> and vasoactive intestinal peptides.<sup>12</sup> Thus it is possible for many neuroendocrine peptides to influence the immune response through an interaction with their specific receptors as discussed below.

The pro-opiomelanocortin gene encodes a precursor protein from which neuropeptides such as ACTH,  $\beta$ -endorphin, and melanocyte stimulating hormone are derived. Pro-opiomelanocortin mRNA is present in Newcastle disease virus infected murine lymphocytes,<sup>13</sup> macrophages,<sup>14</sup> phytohaemagglutinin stimulated and corticotrophin releasing factor exposed human T lymphocytes.<sup>15,16</sup>

In contrast with anterior pituitary cells, the processing of pro-opiomelanocortin derived molecules in immune cells differs depending on the inducing signal. Corticotrophin releasing factor and Newcastle disease virus elicit the production of peptide hormones with a molecular weight of ACTH<sub>(1-39)</sub> and  $\beta$ -endorphin,<sup>16,17</sup> while lipopolysaccharide stimulated cells produce a similar peptide with a molecular weight of ACTH<sub>(1-24)</sub> and  $\alpha$ - or  $\gamma$ -endorphin.<sup>18</sup> In other respects leucocytes behave like anterior pituitary cells in that synthesis of ACTH and  $\beta$ -endorphin on exposure to corticotrophin releasing factor is inhibited by dexamethasone. In fact sufficient ACTH can be produced by lymphocytes to induce steroid production by the

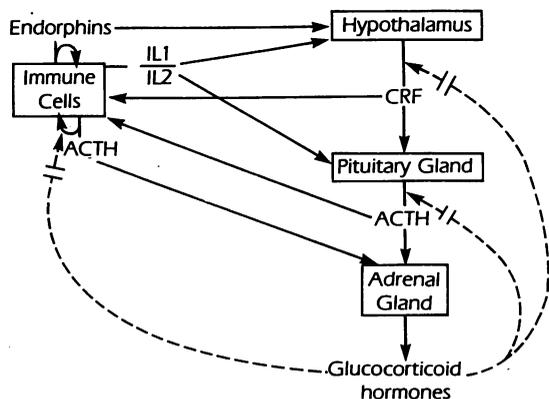


Fig. 1 Relation between the central nervous and neuroendocrine systems. The dashed lines represent feedback inhibition. ACTH=adrenocorticotrophic hormone; CRF=corticotrophin releasing factor; IL=interleukin.

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adrenal gland in hypophysectomised animals, which can be inhibited by dexamethasone.<sup>19</sup>

Neuropeptides, whether pituitary derived or produced by immune cells, affect immune cell function through binding to specific receptors. ACTH directly inhibits the production of antibody and interferon gamma by murine lymphocytes<sup>3 20</sup> and blocks the activation of macrophage by interferon gamma.<sup>21</sup> The immunosuppressive effects of ACTH require ACTH<sub>(1-39)</sub>, whereas ACTH<sub>(1-29)</sub> is ineffective. In contrast, both peptides have a steroidogenic activity.<sup>3</sup> As the pro-opiomelanocortin mRNA is processed differently in leucocytes, depending on the inducing stimulus (see above), the effect on the immune response will differ accordingly.

The endogenous opioid peptides also modulate immune cell function and have been proposed as the mediators by which stress induces rheumatoid arthritis.<sup>22 23</sup> Host defence mechanisms are enhanced by opioid peptides.  $\beta$ -Endorphin and methionine enkephalin stimulate the generation of cytotoxic T lymphocytes<sup>24</sup> and enhance human natural killer cell cytotoxicity.<sup>25 26</sup> The effect of  $\beta$ -endorphin on lectin induced lymphocyte proliferation may be either positive or negative, however.<sup>27 28</sup>  $\beta$ -Endorphin, unlike the related neuropeptide  $\alpha$ -endorphin, does not suppress antibody production.<sup>3</sup> The suppression of antibody production by  $\alpha$ -endorphin is effected at the T helper cell level as well as at the B cell level.<sup>29</sup>

Prolactin and growth hormone are essential for the development of the immune system and function as immunostimulators.<sup>30</sup> Prolactin restores the immune response in hypophysectomised rats, and one mechanism by which cyclosporin exerts its immunosuppressive effects is by displacing prolactin from its receptors on lymphocytes.<sup>9 10</sup> The effect on lymphocyte function of neuropeptides such as substance P and vasoactive intestinal peptides, which are released by fibres of the peripheral nervous system, has been reviewed and will not be discussed here.<sup>31 32</sup>

In the model of bidirectional communication not only do peptides of the neuroendocrine system affect the immune response, but the hormone like products of the immune system exert an influence on the cells of the neuroendocrine system (Fig. 1). Interferon alfa raises circulating cortisol levels in humans<sup>33</sup> and binds to opiate receptors to cause analgesia.<sup>34</sup> Interferon gamma enhances the role of astrocytes as antigen presenting cells.<sup>35</sup> Binding sites for interleukin 1 (IL1) are present in the brain,<sup>15</sup> and the cytokine is synthesised by brain astrocytes and microglial cells.<sup>35</sup> IL1 induces ACTH and glucocorticoid synthesis by acting on the hypo-

thalamus and the pituitary gland.<sup>36</sup> Interleukin 2 (IL2) raises circulating ACTH and cortisol levels<sup>37</sup> probably by causing the production of the pro-opiomelanocortin molecule by pituitary cells.<sup>15</sup>

### Sex hormones

The concept that sex hormones can influence the immune response is suggested by many observations, including the following: autoimmune disorders are more common in women, especially in childbearing years; orchidectomy delays thymic involution and causes thymic hypertrophy; and mitogenic and cell mediated responses are depressed during pregnancy.<sup>38-40</sup> High progesterone levels are immunosuppressive and may account for the beneficial effect of pregnancy on rheumatoid arthritis (RA).<sup>40 41</sup> The oral contraceptive pill may protect against RA and improve its clinical manifestations, although the constituent hormone responsible for this effect, and the underlying mechanism, remain unclear.<sup>41 42</sup> Male patients<sup>43</sup> and postmenopausal women with RA, but not premenopausal women,<sup>44</sup> have relatively high androgen levels. These observations need to be confirmed and the mechanism for altered androgen metabolism evaluated.

Evidence for altered sex hormone metabolism is clearer in systemic lupus erythematosus (SLE).<sup>45</sup> Increased 16- $\alpha$ -hydroxylation of oestrone in SLE results in the production of agonist metabolites, 16 $\alpha$ -hydroxyoestrone and oestriol,<sup>46</sup> which are highest in those patients with clinically active disease.<sup>47</sup> It remains to be seen, however, whether altered oestrogen metabolism is involved in the pathogenesis of SLE or is an epiphenomenon. One possibility is that 16 $\alpha$ -hydroxyoestrone reacts with lysine residues on plasma membranes to induce the formation of antibodies to the 16 $\alpha$ -hydroxyoestrone-protein complex. Increased levels of such complexes occur in the membranes of red cells and lymphocyte of patients with SLE,<sup>48</sup> and 26% of patients with SLE have autoantibodies to this complex which correlate with the presence of active disease.<sup>49</sup> Male patients with SLE have decreased levels of androgen, which are unaltered by injection of luteinising hormone releasing hormone.<sup>50</sup> The situation of raised oestrogen and lower androgen levels alters the oestrogen to androgen ratio and provides a favourable setting for the development of autoimmune disorders.<sup>45</sup> Attempts to correct the ratio by using cyproterone acetate resulted in an improvement in disease activity in SLE.<sup>51</sup>

The precise mechanism by which sex hormones modulate the immune response is unknown. Sex hormone receptors are present in the human thymus and spleen.<sup>40</sup> By affecting thymic factors, sex

hormones indirectly affect immune regulation.<sup>39 40</sup> Direct immunomodulation takes place through interaction with specific receptors on lymphocytes. Oestrogen receptors are present on suppressor/cytotoxic T lymphocytes,<sup>52</sup> which suggests that suppressor T cell function is directly influenced by oestrogen. Support for this hypothesis is provided by the observation that oestrogens enhance mitogen induced immunoglobulin production.<sup>38</sup> In general, androgens have an immunosuppressive effect. They have a beneficial effect on autoimmune disease in the NZB-NZW lupus mouse model<sup>38 39</sup> and increase T cell suppressor activity.<sup>53</sup> Progesterone also suppresses immune responses and has been shown to depress cell mediated immunity, enhance suppressor cell activity, and inhibit mitogen induced lymphocyte proliferation.<sup>39 53</sup>

### Vitamin D

The biologically active metabolite of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub>, exerts its effects by initially binding to specific intracellular receptors. The observation that such receptors are present in immature monocyte cell lines, peripheral blood monocytes, and activated but not resting lymphocytes suggested that 1,25-dihydroxyvitamin D could modulate the function of immune cells.<sup>54-56</sup> 1,25-Dihydroxyvitamin D causes differentiation of immature monocyte cell lines<sup>57</sup> and augments IL1 and tumour necrosis factor production by human monocytes and cell lines.<sup>57-59</sup> The hormone restores phagocytic function of peritoneal macrophages obtained from mice deficient in vitamin D,<sup>60</sup> increases adherence of human monocytes and protects them from thermal injury by increasing the synthesis of heat shock proteins,<sup>61</sup> and promotes multinucleation.<sup>62</sup> By altering class II major histocompatibility complex expression and by increasing IL1 production, 1,25-dihydroxyvitamin D may enhance antigen presentation and thus modify immune cell responses.<sup>63</sup> Alveolar and lymph node macrophages from patients with sarcoidosis,<sup>64 65</sup> as well as normal peripheral blood monocyte/macrophage cultured with interferon gamma or lipopolysaccharide, have the capacity to synthesise 1,25-dihydroxyvitamin D.<sup>66</sup> The production of 1,25-dihydroxyvitamin D by macrophage may be sufficient to cause hypercalcaemia,<sup>67</sup> and at sites of inflammation the concentration of the hormone may be sufficiently high to exert a paracrine or autocrine influence on immune responses (Fig. 2).

1,25-Dihydroxyvitamin D inhibits lectin and antigen induced T cell proliferation by decreasing the production of IL2<sup>59 68</sup> and blocking the progression of lymphocytes from early G1 to late G1 phase

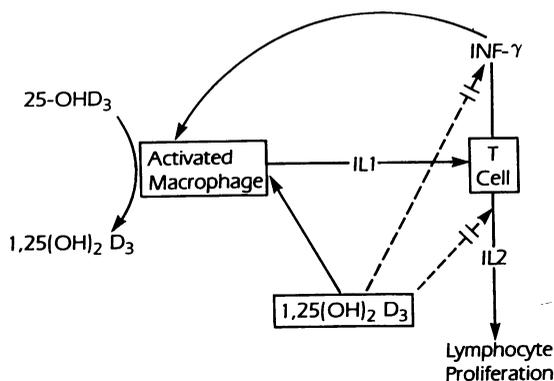


Fig. 2 Role of vitamin D on immune cells. Activated macrophages produce 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) from 25-hydroxyvitamin D<sub>3</sub> (25-OHD<sub>3</sub>). Dashed lines illustrate negative effects of 1,25(OH)<sub>2</sub>D<sub>3</sub>. IL=interleukin; INF-γ=interferon gamma.

of the cell cycle.<sup>69</sup> The production of interferon gamma is also inhibited but is not secondary to decreased IL2 synthesis as there is coordinated inhibition of mRNA for both lymphokines.<sup>70</sup> These effects on lymphocytes require the presence of the specific 1,25-dihydroxyvitamin D receptor and cannot be demonstrated in patients with vitamin D dependent rickets, type II, who either lack or have a defective receptor.<sup>71</sup>

As it was necessary to have monocytes present in the experiments discussed above it is unclear whether the effects observed were mediated directly by the hormone acting on lymphocytes or through an initial interaction with monocytes. By using a mouse model of T cell hybridomas which produce IL2 when activated, it has been shown that 1,25-dihydroxyvitamin D directly inhibits alloantigenic and antigen specific T cell proliferation by decreasing IL2 production.<sup>72</sup> Unlike dexamethasone, 1,25-dihydroxyvitamin D failed to inhibit lectin induced T cell proliferation, thereby distinguishing between these steroid hormones.<sup>72</sup> Thus the immunomodulating effects of 1,25-dihydroxyvitamin D in this model are dependent on the type of activating signal delivered to the T cell.

The relation between the presence of the 1,25-dihydroxyvitamin D receptor and proliferation of T lymphocytes<sup>55</sup> also applies to thymocytes. The larger dividing murine medullary thymocytes, but not the non-dividing cortical thymocytes, possess the 1,25-dihydroxyvitamin D receptor.<sup>73</sup> 1,25-Dihydroxyvitamin D inhibits the proliferation of medullary but not cortical thymocytes. The function of the receptor in medullary thymocytes is unclear,

but one possibility is that the hormone influences the differentiation of thymocytes to a stage where they lose the 1,25-dihydroxyvitamin D receptor and are ready to leave the thymus.

In vitro immunoglobulin production by human B lymphocyte is inhibited by 1,25-dihydroxyvitamin D.<sup>74-75</sup> It is unclear whether this is due to a direct effect on B cells<sup>75</sup> or the consequence of decreased T helper/inducer cell activity.<sup>74</sup> Direct suppression of immunoglobulin production requires the presence of the 1,25-dihydroxyvitamin receptor and has been observed in Epstein-Barr virus infected B cells<sup>76</sup>; no effect is seen in B cell clones lacking the receptor (A K Bhalla and P Lydyard, unpublished observations).

In the clinical setting the administration of vitamin D metabolites has been shown to alter immune cell function. The administration of  $1\alpha$ -hydroxyvitamin D<sub>3</sub>, which is metabolised to 1,25-dihydroxyvitamin D, restores mitogen stimulated T cell responses to normal in patients on haemodialysis.<sup>77</sup> In elderly osteoporotic patients  $1\alpha$ -hydroxyvitamin D<sub>3</sub> restores their ability to respond to recall antigens and improves the T4 to T8 cell ratio towards a normal value.<sup>78</sup> Children with vitamin D deficiency rickets have anaemia and extramedullary haematopoiesis, which improves after supplementation of the diet with vitamin D.<sup>79</sup>

A clearer understanding of the regulation of immune responses by hormones, particularly at the level of hormone-receptor interaction, may provide a novel way of treating autoimmune disorders using synthetic analogues that preferentially affect the immune but not the endocrine system. Such analogues may prove to be less toxic than many of the drugs currently used to treat these disorders.

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