INTERACTION BETWEEN THE NEUROENDOCRINE SYSTEM AND ARTHRITIS

Rheumatoid arthritis, an autoimmune disease of complex polygenic aetiology, is characterized by a chronic symmetric inflammation of peripheral joints. Ancillary clinical evidence shows that RA flare-ups usually coincide with period of increased 'stress' in the patient but strong scientific proof is lacking because of limitations in methods used to assess stress. The debilitating pain of RA, together with the stiffness and weakness, contribute to and is exacerbated by the depression so common in inflammatory arthritis. Persisting acute pain often results in physical and psychological stress which may in turn aggravate the initial pathological state. Recent developments in the field of neuroimmunoendoocrinology have provided biochemical markers for the hypothesis that an association between depression or stress and RA may lie in a common neuroendocrine defect.

Activation of the hypothalamo–pituitary–adrenal (HPA) axis is part of the normal physiological response to both inflammatory and behavioural stress. This activation in response to acute physical or psychological stress is indicated by increased corticotropin–releasing hormone (CRH) mRNA in the hypothalamic paraventricular nucleus (PVN), increased pro-opiomelanocortin (POMC) mRNA, the adrenocorticotropic (ACTH) precursor, in the anterior pituitary, and increased plasma levels of ACTH and corticosterone [1]. Stress is known to alter immune function, and a bidirectional communication between the immune and neuroendocrine systems exists, in which the immune system physiologically restrains its own response by causing release of glucocorticoids through activation of the HPA axis [2]. It has been suggested that this negative feedback loop between the HPA axis and the immune system is important in the modulation of inflammation [3]. Indeed glucocorticoids are the most potent anti-inflammatory agents that can alleviate the symptoms of RA. In man cortisol has a pronounced diurnal rhythm with peak plasma levels around 08.00 hours reaching a nadir about 20.00 hours. There appears to be a reciprocal correlation between plasma levels of cortisol and severity of disease which is heightened in the early hours of morning and reduced during the afternoon in RA patients. However there is less agreement regarding the plasma cortisol levels in patients with active RA. Both abnormally high and reduced plasma ACTH and cortisol levels have been observed in patients with significant ongoing joint inflammation. RA patients show a normal ACTH and cortisol response to CRH challenge. This would imply a hypothalamic dysfunction in control of cortisol secretion in RA patients.

Adjuvant arthritis (AA) is an experimental model of a chronic inflammatory arthritis in the rat elicited following an intradermal injection of adjuvant into the base of the tail [4]. AA is a T lymphocyte-dependent [5,6] strain-specific [7] immunologically mediated disease, which is associated with a number of neuroendocrine changes. We have recently shown that development of AA results in chronic activation of the HPA axis. Plasma levels of both ACTH and corticosterone [8] as well as anterior pituitary (POMC) mRNA accumulation [9] are increased during the development of AA. Paradoxically, CRF mRNA accumulation in the PVN and CRF peptide levels in the hypothalamo–hypophysial portal blood (HPB) are not increased [10] suggesting that the primary drive causing HPA axis activation is not hypothalamic CRH. The HPB levels of vasopressin, which acts synergistically with CRH to release ACTH, are increased in AA rats suggesting that vasopressin is one of the factors driving the pituitary adrenal axis. The nature of the inhibitory factor(s) and the mechanisms controlling or influencing these changes in CRH mRNA transcripts are currently unknown. The simultaneously elevated plasma ACTH and corticosterone levels during AA indicate that the normal negative feedback of corticosterone upon ACTH secretion is disrupted [8]. The decreases in CRH mRNA in the PVN and CRH-41 release into the HPB in response to chronic arthritis are however not solely due to increased glucocorticoid feedback as removal of endogeneous steroids by surgical adenalectomy only partially reverses the inhibition of CRH mRNA [11].

In 1938 Hench was the first to report remission of RA during pregnancy [12]. Subsequent clinical observations and studies have shown amelioration of RA during pregnancy in 75% of patients, with flares occurring during the postpartum period in 80% of patients. The pregnancy related hormonal changes have led to the suggestion that the hypothalamo–pituitary–gonadal axis may have a role in the pathology of RA [13]. During the third trimester progesterone, oestriadiol and testosterone plasma levels are markedly raised. The immunosuppressive effects of pregnancy associated hormones may in part account for the beneficial effects of pregnancy on RA. Prolactin and growth hormone are essential for the development of the immune system and act as predominantly pro-inflammatory hormones. Plasma levels of prolactin are also affected by AA and circulating prolactin has been shown to be crucial to the development of AA [14]. AA does not develop in hypophysectomized rats but can be induced after replacement of prolactin or growth hormone. Furthermore bromocriptine which inhibits prolactin secretion has been shown to suppress post-partum...
exacerbation of collagen-induced arthritis in the rat. During the chronic inflammatory stress of AA we also observed differential effects on the expression of pituitary POMC mRNA, which is increased, and pituitary GH and prolactin mRNAs, which are reduced. Changes in GH and prolactin mRNA levels remained unaffected by glucocorticoid status.

Immune system activation during AA leads to increased circulating levels of interleukin (IL)-1β, IL-6 and tumour necrosis factor-α (TNF-α) [15,16]. In addition we have demonstrated increased interleukin-6 mRNA expression in the pituitary and interleukin-1β (IL-1β) mRNA expression in the spleen which is subject to corticosterone inhibitory feedback [9]. Increased production of inflammatory cytokines during AA could play an important role in the pathogenesis of disease. The immunosuppressant cyclosporin A (CsA) has been shown to inhibit the development of AA and reduce the concomitant activation of the HPA axis [17]. It is now becoming clear that there is a complex interaction between the neuroendocrine system and activated cells of the immune system. Indeed the adoptive transfer of splenocytes from rats with AA results in activation of the HPA axis without any signs of arthritis [18]. Increased understanding of the mechanisms underlying the immune–neuroendocrine relationship and the role of endogenous corticosteroids in the development of arthritis will undoubtedly prove novel targets for the treatment of rheumatic disease.

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REFERENCES