PSYCHOIMMUNOLOGY SYMPOSIUM: THE IMPACT OF DYSFUNCTIONAL ENDOCRINE AND IMMUNE SYSTEMS ON PSYCHIATRIC DISORDERS

Immune dysfunction, depression and neurodegeneration

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The possible link between a dysfunctional immune system, depression and physical ill health has been known since antiquity. However, it is only recently that the possible mechanisms whereby chronic inflammation can initiate changes in the endocrine and cardiovascular system leading to type 2 diabetes, cardiovascular disease, cancers and psoriasis, have begun to be elucidated. Furthermore, evidence that inflammatory changes can initiate depression has arisen from observations of non-depressed patients who are undergoing interferon alpha or interleukin (IL)2 treatment for melanoma or chronic hepatitis. A substantial majority (approximately 40%) of these patients develop severe depression that abates when the inflammatory cytokine treatment is stopped (1). It is now known that in patients with major depression the peripheral macrophages and monocytes, and in the brain the microglia and astrocytes, are activated leading to an increase in pro-inflammatory mediators such as the pro-inflammatory cytokines (interleukins-1 and -6, interferon (IFN)gamma, tumour necrosis factor(TNF)-alpha) in addition to prostaglandin (PG)-E2 and nitric oxide (2). The changes in these immune parameters are largely reversed following effective antidepressant treatment..

Important advances in our understanding of the relationship between different types of stressor and changes in immune and endocrine function have been obtained from experimental studies mainly in rodents. These studies have indicated that there is an increase inIL-1 messenger RNA expression and IL-1 concentration in the hypothalamus (3,4), increased IL-1 beta and TNF –alpha in isolated alveolar macrophages (5) and an increase in IL-6 in the plasma (6,7)following different types of stress. In the olfactory bulbectomised rat model of depression, the blood and brain concentrations of the pro-inflammatory cytokines are also increased, changes that are associated with depressive-like behaviour and which are normalised following effective, but chronic, antidepressant treatments(8).

The inflammatory changes are known the impact upon the hypothalamic-pituitary-adrenal axis. The proinflammatory cytokines enhance the release of corticotrophin releasing factor(CRF) thereby resulting in an elevation in plasma corticosterone;such changes frequently occur in patients with major depression (9). The chronic increase in the corticosteroids results in glucocorticoid receptor tolerance as a consequence of the receptor desensitisation thereby impairing the negative feed-back mechanism whereby the rise in the plasma concentration of corticosteroids would normally inhibit the further activation of the CRF-ACTH pathway. In addition to the increase in CRF caused by the proinflammatory cytokines, IL-1 beta is known to increase the release of arginine vasopressin (AVP) from the anterior pituitary. AVP is usually released in response to chronic stress and maintains the activation of the adrenal glands, and therefore the secretion of corticosteroids.(10) Thus chronic, low grade inflammation that occurs in depression, and following chronic stress, is associated with hypercortisolaemia in experimental models of depression and in depressed patients.

The chronic increase in plasma and brain corticosteoids may contribute to the neurodegenerative changes that occur in elderly depressed patients that have suffered from chronic major depression (11,12) One of the key factors that contribute to neurodegeneration is the increase in corticosteroids that are known to impair the synthesis of neurotrophic factors (such as brain derived neurotrophic factor) that are responsible for the repair of damaged dendrites and axons(13) Thus the increase in corticosteroids, combined with the neuronal damage caused by the actions of the proinflammatory cytokines, probably contribute to the increase in apoptosis and therefore the neurodegenerative changes that frequently occur in patients with chronic major depression (14).

For over 40 years there has been widespread acceptance of the hypothesis that a dysfunctional serotonergic system plays a fundamental role in the aetiology of depression. It now seems possible to link the deficit in serotonergic function with the increase in proinflammatory cytokines in depression. It is now known that IFN-gamma, and other proinflammatory cytokines, induce the widely distributed enzyme indoleamine 2,3 dioxygenase (IDO) thereby enhancing the metabolism of tryptophan through the kynurenine pathway, and away from serotonin synthesis. Kynurenine is then metabolised either to kynurenic acid (an N-methyl-D-aspartate glutamate (NMDA) receptor antagonist) or to 3-hydroxykynurenine (3OHK) and quinolinic acid (a NMDA receptor agonist). This neurodegenerative quinolinic acid pathway is induced by IFN-gamma and by TNF-alpha (15,16). Of these neurotoxins that are produced by proinflammatory cytokines, quinolinic acid is excitotoxic and 3OHK induces apoptosis.

In the brain, the astrocytes have been shown to metabolise tryptophan to kynurenic acid whereas the microglia, and peripheral macrophages that produce the proinflammatory cytokines in the blood, produce mainly 3OHK and quinolinic acid(17,18). Furthermore the astrocytes metabolise quinolinic acid produced by the neighbouring microglia. In addition, kynurenic acid has been shown to antagonise the excitotoxic action quinolinic acid.

In the plasma of depressed patients, tryptophan breakdown has been reported to be increased but the neuroprotective, kynurenic acid pathway is decreased (19). This suggests that the neurodegenerative arm of the tryptophan-kynurenine pathway is increased in depression, a view that is supported by the recent finding that the plasma 3OHK concentration is increased in the plasma of depressed patients. Preliminary *in vitro* studies have also shown that in a human cell culture the astrocytes are particularly

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vulnerable to the toxic effects of IL-1 beta. Thus a combination of raised proinflammatory cytokines, an increase in the neurotoxins 3OHK and quinolinic acid and a decreased protection against quinolinic acid by the astrocytes contribute to the neurodegenerative changes that predispose the elderly depressed patient to dementia.

Chronic IFN-gamma treatment of rats results in depressive-like behaviour (20) together with a loss of astrocytes in the dentate gyrus of the hippocampus, changes that are not reversed by the chronic administration of antidepressants. This may have some clinical relevance where it has been shown that aspects of cognitive dysfunction remain even after the mood of the patients has improved. Furthermore, the interval between the episodes of depression tends to become shorter as the chronicity of the disorder increases. Such factors lead to the hypothesis that in chronic depression changes occur that not only lead to neuronal loss in selected regions of the mesocortical and mesolimbic systems but also enhance the synthesis of neurotoxic factors (such as beta amyloid) that contribute to dementia (21) Thus the interaction between the increase in proinflammatory mediators, corticosteroids and the resulting dysfunction in neurotrans mitter systems play a fundamental role in major depression that not only contributes to profound mood and cognitive changes but also predisposes the patient to dementia in later life.

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Changes in immune and endocrine systems in posttraumatic stress disorder – prospective study

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Abstract:

Introduction and aim: Posttraumatic stress disorder (PTSD) is associated with increased medical morbidity, particularly from the autoimmune and cardiovascular diseases. Changes in the endocrine and immune system are key mediators in this process. The aim of our study was to investigate weather hormones (cortisol and prolactin), proinflammatory cytokines (interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)), components of HPA-axis (lymphocyte expression of glucocorticoid receptor (GR)), immune function (natural killer cell cytotoxicity) and peripheral blood percentages of various lymphocyte subpopulations (T cells, helper T cells, cytotoxic T cells, B cells and natural killer cells) change in patients with posttraumatic stress disorder over time.

Subjects and methods: We assessed 39 patients with PTSD and 37 sex and age matched healthy volunteers in two time points separated by 5.6 years (median; interquartile range: 5.4–6.3). Hormones were measured by radioimmunoassay and cytokines were determined by immunoenzyme assays. Immune function was assessed with the *in vitro* natural killer cell cytotoxicity (NKCC) toward 51Cr-labeled K562 target cells. Lymphocyte counts, immunophenotye and intracellular glucocorticoid receptor expression were determined by three-color flow cytometry.

Results: In the first time point cortisol, prolactin, NKCC, lymphocyte count, total T cells and helper T cells were increased, while glucocorticoid receptor expression was decreased in all lymphocyte subpopulations in PTSD patients compared to controls. In the second time point only prolactin levels and

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