HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2009; **24**: 165–175.
Published online 11 February 2009 in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.1011

REVIEW ARTICLE

The psychoneuroimmunology of depression

Brian E. Leonard[1,2]* and Ayemu Myint[2]

[1]*Pharmacology Department, National University of Ireland, Galway, Ireland*
[2]*Department of Psychiatry and Psychotherapy, Ludwig Maximillians University, Munich, Germany*

Chronic stress, by initiating changes in the hypothalamic-pituitary-adrenal (HPA) axis and the immune system, acts as a trigger for anxiety and depression. There is experimental and clinical evidence that the rise in the concentration of pro-inflammatory cytokines and glucocorticoids, which occurs in a chronically stressful situation and also in depression, contribute to the behavioural changes associated with depression. A defect in serotonergic function is associated with these hormonal and immune changes. Neurodegenerative changes in the hippocampus, prefrontal cortex and amygdalae are the frequent outcome of the changes in the HPA axis and the immune system. Such changes may provide evidence for the link between chronic depression and dementia in later life. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — inflammation; pro-inflammatory cytokines; glucocorticoids; serotonin; neurodegeneration; tryptophan-kynurenine pathway

INTRODUCTION

Psychoneuroimmunology (PNI) is concerned with the interaction between the nervous, immune and endocrine systems. The recent widespread interest in mind–body interactions and disease has undoubtedly stimulated the need to integrate, within a conceptual biological framework, the interactions within these systems. PNI therefore constitutes a rigorous attempt to address the complexity these interacting biological systems by re-establishing the philosophical balance between synthesis and analysis, the classical methodological approach that is used in the natural sciences. Such an approach contrasts with the reductionist view that currently bedevils both experimental and clinical neuroscience. For example, because of the complexity of the immune system, studies are frequently performed on cells in culture and the results extrapolated to the clinical situation. But immune cells in culture are not subject to the complex control mechanisms that arise *in vivo* in which the behaviour of a population of immune cells is determined by an interaction with different types of immune cells, immunomodulators, hormones and neurotransmitters for example. Furthermore, the frequently studied immortal human cell lines in culture are, by definition, not normal cells.

The purpose of this slight diversion, that has been developed recently into a critique on the limitations of psychoneuroimmunology (PNI) (see Leonard, 2007) is to caution the reader that the same rigorous scientific standards must be applied to this subject as they are to any other area of neuroscience. Only by applying these standards will PNI become a respectable and acceptable discipline and thereby help to return psychiatry to its rightful place in the medical hierarchy.

HISTORICAL BACKGROUND TO PSYCHONEUROIMMUNOLOGY

The adverse effects of stress, psychiatric illness, bereavement and social/marital discord on physical and mental health have been known since antiquity. In ancient Greece and Rome, the inter-relationship between mind and body was part of many of the schools of philosophy. The Roman poet Virgil proclaimed ‘mind moves matter’ while the Greek philosopher Aristotle advised physicians ‘Just as you ought not to attempt to cure eyes without a head or a head without a body, so you should not treat a body without a soul.’

In more recent times, Sir William Osler, the father of modern medicine, when predicting the possible

* Correspondence to: B. E. Leonard, Pharmacology Department, National University of Ireland, Galway, Ireland. E-mail: belucg@iol.ie

Received 1 February 2008
Accepted 2 January 2009

outcome of a tuberculosis infection stated that it was just as important to know what is going on in a man's head as in his chest! Such views would not be considered as eccentric today. It is a common experience, for example, that adverse events, stress etc. can increase susceptibility to upper respiratory tract infections, hostility can increase the likelihood of heart disease, while conversely, strong social support and an optimistic attitude by the patient can prolong the life expectancy of a cancer patient.

Conversely, physical illness can trigger psychological change. For example, some 6 months before patients develop clinical signs of pancreatic cancer, a significant proportion will develop a depressed mood. Similarly, approximately 10% of AIDS patients will show mood, behavioural, cognitive and memory changes before developing somatic signs of the illness (Blumenthal, 1995). It would now appear that many of the psychological changes associated with infections are directly caused by pro-inflammatory cytokines that are produced by infection or stress-induced activation of immune cells. This is indicated by the depressed mood state that occurs in a substantial minority of hepatitis patients treated therapeutically with the pro-inflammatory cytokine interferon (INF) α, the change in mood state being associated with the inflammatory state (Wichers *et al*., 2005a,b).

From the historical perspective therefore, PNI is a very old discipline that has re-surfaced in psychiatry as a result of the rise in psychosomatic medicine and in the holistic approach to health and disease. The bi-directional interaction between the nervous, immune and endocrine systems profoundly influence health and susceptibility to disease. Additionally, behavioural and lifestyle interventions, such as relaxation exercises, support groups, psychotherapy, can improve health outcomes and positively influence the course of physical and mental disorder.

The purpose of this chapter is to illustrate how PNI research impacts on our understanding of depression and how this may lead to a re-evaluation of the pathology of the disorder and its possible treatment.

CYTOKINES AND HOW THEY 'TALK' TO THE BRAIN

The chemical mediators of the endocrine and nervous systems are well defined and their effects on the immune system will be considered later. However, it is now apparent that immune cells also produce signalling molecules, the cytokines, that transmit information from the immune system to the endocrine and nervous systems and also within the immune system. Interactions imply reciprocity so that just as hormones and neurotransmitters convey information to the immune system so the immune system conveys information via the cytokines and the chemokines. The term 'cytokine' has been extended to include almost any protein released by an immune cell, including the glial cells in the brain that act as part of the central immune system, that can modulate its own function, or the function of other types of cell, in an autocrine or paracrine fashion.

Just as neurotransmitters and hormones elicit their biological responses by activating specific receptors on cell membranes (neurotransmitters) or by combining with intracellular receptors (most hormones), so the cytokines activate specific receptors on immune, endocrine or neural cells.

The maintenance of homeostasis in the immune system requires the prevention of the uncontrolled activation of that system by the release of neuropeptides, hormones and neurotransmitters from immune, endocrine and nerve cells. Conversely, the immune system influences the brain and endocrine system by releasing cytokines. Studies of the behavioural changes elicited by the cytokines interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) α have demonstrated that cytokines activate specific cytokine receptors on neurons and glial cells and thereby directly influence brain function. Some 30 years ago, Besedovsky and Sorkin (1997) showed that there was an increase in plasma catecholamine concentrations at the peak of an antibody response; this effect was correlated with the activation of the central sympathetic system by cytokines from peripheral immune cells. Some 10 years later, the physiological changes that occur in the rat brain following an immune challenge with sheep erythrocytes have been studies by Saphier and Ovadia (1987) who showed that the immune response resulted in an increased electrical activity in the pre-optic area of the anterior hypothalamus.

In addition to the direct effects of cytokines on the brain, the cytokines also affect brain function by activating the hypothalamus and the hypothalamic-pituitary-adrenal (HPA) axis. Thus the systemic administration of IL-1 into rodents results in a marked rise in plasma adrenocorticotrophic (ACTH) hormone and corticosterone. As this occurs in mice that genetically lack T-cells that act as a source of IL-1 in the periphery, it would appear the IL-1 has a direct stimulant effect on the HPA axis via the corticotrophin releasing factor (CRF) receptors (Besedovsky *et al*., 1991; Berekenbosch *et al*., 1989). IL-6 and TNF α also activate the HPA axis but their effects are less potent.

IL-1, IL-6 and TNF α, together with INF γ, are pro-inflammatory cytokines that induce fever by activating

DOI: 10.1002/hup

brain cyclo-oxygenase (COX)-2 thereby initiating a rise in prostaglandin (PG) E2. In addition, sleep disturbance, anorexia, decreased libido and decreased social interaction, which are often associated with low mood in patients with depression, are common features of a rise in pro-inflammatory cytokines in the brain. These changes seen following an acute challenge with pro-inflammatory cytokines have led to the hypothesis that depression is a form of sickness behaviour (Bluthe *et al*., 1997). This hypothesis is supported by the observation that there is a rise in pro-inflammatory cytokines, and a fall in anti-inflammatory cytokines, in the blood of depressed patients (Maes *et al*.,1992a,b; Myint *et al*., 2005), and an increase in PGE2 in the cerebrospinal fluid (CSF) of depressed patients (Calabrese *et al*., 1986). This hypothesis has been extended to take into account the long-term consequences of the chronic inflammatory changes. As it is well established that there is an increase in apoptosis in patients with chronic depression that is associated with a reduction in the hippocampal volume, and in the volumes of the pre-frontal cortex and amygdalae, with an increase in the volume of the ventricles (Sheline *et al*., 1996), it has been postulated that depression can be a prelude to dementia (Leonard and Myint, 2006; Leonard, 2007).

The cytokines are large proteins that normally cannot enter the brain that is protected by a physical and metabolic blood–brain barrier. The question therefore arises, how can the cytokines gain access to the brain? One possible pathway is by diffusion across the vascular endothelial cells into the choroid plexus. However, the blood vessels in the brain are tightly adherent to each other and are surrounded by a basement membrane thereby forming an impenetrable barrier. Nevertheless the barrier is more permeable at the circumventricular organ at the base of the 4th ventricle and this might permit a sufficiently high concentration of the cytokines to enter the brain following immune activation (Banks *et al*., 1995). Another possibility is that the cytokines can enter the brain possibly by retrograde transport up the vagus nerve. It is well known that administration of pro-inflammatory cytokines produce profound behavioural changes in rodents (Song *et al*., 2006), but if the afferent branches of the subdiaphramatic cytokines are lesioned then the cytokines are without effect on behaviour (Bluthe *et al*., 1996).

SUMMARY OF THE MAIN POINTS OF THIS SECTION

(1) PNI is concerned with the interaction between the immune, endocrine and neurotransmitter systems and how they influence behaviour.
(2) Immune cells communicate by means of immune transmitters. These are large proteins that exercise both autocrine (alter the function of immune cells) and paracrine (alter the function of non-immune cells) activity through specific receptors.
(3) The cytokines may enter the brain either through the selective permeability of the blood–brain barrier and/or by retrograde transmission up the vagus nerve.
(4) The pro-inflammatory cytokines, when present in high concentrations (e.g. during an infection) not only cause fever but also cause profound changes in the sleep profile, anorexia, decreased libido, decreased social interaction and lowering of mood. Such symptoms are characteristic of major depression, which form the basis of the thickness hypothesis of depression. As inflammatory changes, when chronic, are associated with increased apoptosis and decreased hippocampal and cortical volumes, the sickness hypothesis has been extended to the dementia hypothesis of depression.

STRESS AND HOW IT AFFECTS THE IMMUNE AXIS

Stress may be defined as any environmental change, whether internal or external, that disturbs homeostasis. This definition emphasises the variability that may occur in the response of the individual to a stressful stimulus. It also emphasises the variability of the effect of the stressful stimulus; in one individual it has a major behavioural and physiological effect whereas another individual may experience little change. Coping strategies, that reflect adaptation to stressors, undoubtedly account for part of the variability.

The scientific basis of adaptation to stress was first suggested by Walter Cannon (1929) who, in the early part of the last century, introduced the concept of homeostasis. This concept involved the initiation of the fight or flight response whereby changes in the sympatho-adrenomedullary system co-ordinated the physiological basis of homeostasis. Hans Seyle (1936) developed the concept further by emphasising the connection between the hypothalamic-pituitary axis with the adrenomedullary system. Seyle also described how the early response to a noxious stimulus was characterised by a non-specific activation of the HPA axis. Continual exposure to the same stimulus results in adaptive changes in the endocrine and immune systems characterised by hypertrophy of the adrenal and pituitary glands, and changes in the composition of immune cells. This was termed the general adaptation syndrome.

The view that stress was physically and functionally damaging to the individual was initially attributed to the hypersecretion of adrenal glucocorticoids. This was supported by the observation that hyperactivity of the

DOI: 10.1002/hup

adrenals and pituitary were associated with pathological changes that were resolved once the HPA axis was normalised. However, it is now accepted that the stress response is often beneficial in protecting the individual from injury and that adaptation is a learned response that is important in adjustment to future adverse situations. Nevertheless, when stress becomes repetitive and sustained, adaptation is often impaired and pathological changes occur as a result of hypercortisolism, hypertension, abnormal immune changes and psychological changes. Anxiety, depression and psychotic disorders may result from such changes in the activity of the HPA axis (Arborehuis *et al*., 1999).

STRESS AND THE ROLE OF CORTICOTROPIN RELEASING FACTOR (CRF)

Stress is a frequent precipitant of major depression (Bjorntorp, 1999). Depression is often associated with the sustained hyperactivity of the stress axis caused by the stress neurotransmitter CRF. CRF initiates the changes in the HPA axis and also stimulates the sympatho-adrenal system (Bjorntorp, 1999). In addition to the psychological changes that reflect the maladaptation to chronic stress, physical changes can also occur that are associated with the metabolic changes initiated by the hypersecretion of the glucocorticoids and the hyperactivity of the sympatho-adrenal system. These changes include diabetes, accumulation of intimal and abdominal fat, hypertension and activation of peripheral and central macrophages that lead to the increase in pro-inflammatory mediators (Brambilla, 2000).

The physiological effects of CRF are mediated through the CRF 1 and CRF 2 receptors. Activation of the former receptors is responsible for the fight and flight response whereas the latter receptors are responsible for the slower adaptive response and recovery from stress.

Urocortin, rather than CRF, is primarily responsible for the activation of the CRF 2 receptors (Brambilla, 2000). The fight or flight response occurs when the CRF1 receptors on the paraventricular nucleus located in the hypothalamus are activated. These receptors are also activated on the corticotrophs located on the anterior pituitary and result in the release of ACTH hormone. ACTH then activates the adrenal cortex leading to the synthesis and release of glucocortioids. CRF also activates the locus coeruleus. This results in the activation of the central sympathetic system that forms part of the acute stress response system. The fast response system is particularly sensitive to negative feedback inhibition. Thus the acute rise in cortisol and other glucocorticoids activates the mineralocortioid receptors in the pituitary and hypothalamus and thereby decreases the release of CRF. This results in the reduction in ACTH release from the anterior pituitary and thereby decreases the release of glucocorticoids. Under conditions of high stress, or chronic stress, the glucocorticoid receptors in the brain are occupied. In patients with major depression, a condition characterised by a hypersecretion of cortisol (Sachar *et al*., 1970), desensitisation of the glucocortioid receptors frequently occurs. Under these conditions the negative feedback regulation malfunctions and the hypersecretion of cortisol persists. Clinical evidence in support of this is based on the lack of suppression of plasma cortisol following the administration of 1 mg of the synthetic glucocorticoid dexamethasone. This is the basis of the dexamethasone suppression test (DST), a test that was one time believed to be a biological marker of major depression (Carroll, 1982).

The adaptive response to stress is mediated by the peptides, urocortins 2 and 3, activating the CRF 2 receptors. The urocortins are synthesised in the hypothalamus and amygdalae and pass to their terminals that are located in the hypothalamus and brain stem where the CRF 2 receptors are mainly located; behavioural adaptation and coping strategies are associated with the activation of the CRF 2 receptors (Lovenberg *et al*., 1995). It is now apparent that activation of the CRF 1 receptors results in anxiety whereas activation of the CRF 2 receptors evokes anxiolytic-like effects (Chalmers *et al*., 1995).

In addition to CRF and the urocortins, arginine vasopressin (AVP), also plays an important role particularly in chronic stress. The secretion of CRF is usually accompanied by AVP but whereas AVP has a low efficacy for stimulating the release of ACTH, it potentiates the impact of CRF thereby enhancing ACTH release. Whereas chronic stress desensitises the CRF 1 receptors, the AVP receptors are sensitised thereby sustaining the release of ACTH and the activation of the adrenal cortex (Holsboer, 1999).

CRF neurons are activated by a number of neurotransmitters and neuromodulators in addition to CRF. Thus the excitatory inputs to the CRF neurons include serotonin, noradrenaline and such peptides as neuropeptide-Y while the inhibitory inputs include gamma-aminobutyric acid (GABA) and the opioid peptides (Heilig *et al*., 1994).

The precise CRF pathways that are activated by stress depend on the nature of the stress stimulus. Thus noxious stimuli (inflammatory substances, infections, hypoglycaemia for example) activate monosynaptic

DOI: 10.1002/hup

CRF pathways, whereas stressful psychological stimuli activate CRF neurons in the limbic-cortical region of the brain that sub-serve emotional and cognitive functions (Gray, 1993). This latter pathway functions to process cognitive and emotional aspects of stress.

SUMMARY OF THE MAIN POINTS OF THIS SECTION

(1) Chronic uncontrollable stress results in pathological changes in the brain as a consequence of hypercortisolism, hypertension and increased inflammatory changes. Anxiety and depression may result from such changes in the HPA axis.
(2) Chronic stress is associated with metabolic changes initiated by the hypersecretion of cotisol and the hyperactivity of the sympathoadrenal system. These changes include diabetes, accumulation of intimal and abdominal fat, hypertension and the activation of central and peripheral macrophages.
(3) The stress response is controlled centrally by CRF, urocortin and AVP. CRF, acting on CRF-1 receptors, is responsible for the fight or flight response whereas urocortin is primarily involved in the adaptive response to stress by activating the CRF-2 receptors. AVP plays a crucial role in chronic stress by activating AVP receptors that, unlike the CRF receptors that are desensitised by the chronic action of cortisol, are activated thereby increasing the release of ACTH and the consequent release of cortisol.
(4) Experimental and clinical studies have shown that chronic stress, as a result of the hypersecretion of cortisol, initiates a cascade of changes that impact on the serotonergic system. Thus acute stress is associated with an increase in the turnover of serotonin whereas chronic stress causes a decrease in serotonin turnover partly as a consequence of the increased metabolism of tryptophan due to the induction of tryptophan dioxygenase in the liver. Such changes are correlated with the onset of anxiety and depression.

THE HPA AXIS AND SEROTONIN: THE CONNECTION BETWEEN STRESS AND DEPRESSION

Serotonin is an important excitatory transmitter that modulates the release of both CRF and AVP (Calogero *et al*., 1993). In addition, serotonin activates CRF neurons in the PVN and also increases the release of ACTH (Owens *et al*., 1990). There is a close relationship between plasma cortisol concentrations and serotonin. Thus acute stress induced rise in cortisol is associated with an increase in the turnover of serotonin, a change that is linked to the stimulation of tryptophan hydroxylase activity (Davis *et al*., 1995). Chronic stress that results in a sustained increase in plasma cortisol has the opposite effect, namely a reduction in serotonin turnover and release. This may be due to the activation of tryptophan dioxygenase (pyrrolase) in the liver whereby tryptophan in metabolised through the tryptophan–kynurenine pathway (Myint *et al*., 2007). Thus the changes in the function of the serotonergic system reflect the nature and duration of the stressful stimulus; acute stress being associated with an increased turnover of serotonin while chronic stress has the opposite effect.

The changes in the $5HT_1A$ receptor reflect the turnover of serotonin, the receptor responsiveness increases during acute stress and decreases following chronic stress (Meijer and De Kloet, 1998). Experimental studies have shown that when rats are raised in a stressful, overcrowded environment they showed an increase in anxiety that correlated with a decrease in the functional activity of the $5HT_1A$ receptors in the hippocampus. Under conditions of chronic stress there is evidence that the hippocampal $5HT_1A$ receptors are inhibited by cortisol, effects that are primarily mediated by mineralocorticoid, and to a lesser extent, glucocorticoid, receptors (Chaouloff, 1995; Meijer and De Kloet, 1998). Unlike the $5HT_1A$ receptors, the $5HT_2$ receptor affinity for serotonin is increased by chronic stress (McKittrick *et al*., 1995) It is possible that the changes in the $5HT_1A$ and $5HT_2$ receptors following chronic stress are linked (Renyi *et al*., 2001). The connection between the decrease in the turnover of serotonin following chronic stress and the stress-induced changes in serotonin receptor function is indicated by the increase in the density of the presynaptic $5HT_1B$ receptors (Neumaier *et al*., 1997). The $5HT_1B$ receptors act as autoreceptors that, when activated, reduce the release of serotonin. Thus the effects of chronic stress on serotonergic function can be explained in terms of the differential effects of stress on serotonin receptor function.

The increase in anxiety and the impaired adaptation that has been observed in animals following exposure to chronic stress can also be explained by the changes in the functional activity of the serotonin receptors, particularly the $5HT_1A$ receptors located on the median raphe neucleus and hippocampus (Deakin, 1996). In addition, the dorsal raphe neurons that project to the hippocampus and the amagdalae are thought to contribute to the anxiety producing effects of stress by activating the $5HT_2$ receptors (McEwen and Stellar, 1993).

The unravelling of the relationship between the behavioural effects of chronic stress and changes in the serotonergic system has largely been based on experimental studies mainly on rodents. In clinical studies however, there is also evidence that the

DOI: 10.1002/hup

hypersecretion of cortisol results in a reduction of tryptophan, the precursor of serotonin. In some depressed patients during remission, tryptophan depletion also triggers depression, a change that is associated with a hypersecretion of cortisol (Aberg-Wistedt *et al*., 1998). The elevation of cortisol and prolactin secretion following an acute fenfluramine challenge is also reduced in patients with depression (O'Keane and Dinan, 1991). In regard to changes in serotonin receptor function in depressed patients, there is clinical evidence that the secretion of growth hormone in response to tryptophan is attenuated by pre-treatment with the naturally occurring glucocorticoid hydrocortisone but, somewhat surprisingly, not the synthetic glucocorticoid dexamethasone (Porter *et al*., 1998).

Finally, a relationship has been established between the 5HT transporter gene and the susceptibility of the depressed patient to the effects of stress. The double short allelic form of the 5HT transporter gene and the susceptibility to depression and anxiety-related personality traits has been observed by some (Ogilvie *et al*., 1996; Lesch *et al*., 1996) but not by other (Little *et al*., 1997; Mazzanti *et al*., 1998) investigators.

The results of these experimental and clinical studies lend credibility to the view that chronic stress, largely as a result of the hypersecretion of cortisol, initiates a cascade of changes particularly involving the serotonergic system. These changes are correlated with the onset of depression and anxiety. Qualitatively similar changes have been reported to occur in anxious, depressed patients (van Praag, 1996).

INFLAMMATORY CHANGES THAT OCCUR FOLLOWING STRESS

Stress activates both the HPA axis and the sympathetic nervous system, and therefore it is not surprising to find that most acute and chronic stressors affect the immune system. Lymphocytes contain adrenoceptors which respond to the actions of catecholamines that are released during stress. Glucocorticoids also reduce lymphocyte function by stimulating glucocorticoid receptors situated on the outer membrane. However, not all stressors produce identical changes in the immune system. Different types of stress produce different degrees of endocrine and sympathetic activation (Mason, 1971), while coping strategies can modify the impact of stress on these systems. Thus the response of the immune system to stress involves a complex cascade of events in which catecholamines, glucocorticoids, endorphins and other neuropeptides play vitally important parts (Croiset *et al*., 1987). These interconnections between the HPA axis, immune and sympathetic nervous system are illustrated in Figure 1.

Changes in the brain and endocrine system inevitably alter the immune system and, conversely, changes in immune function directly or indirectly impact on the endocrine system and the brain (Leonard and Song, 1999). There is a structural and functional basis to the close interrelationship between these systems. Thus both noradrenergic and cholinergic terminals innervate the thymus gland and the bone marrow thereby directly influencing the development of immune cells. In addition, lymphocytes and monocytes contain adrenoceptors, as well as other biogenic amine and peptide receptors that respond to these neurotransmitters when they are released following a physiological stimulus.

There is also abundant evidence that the immune system can modulate both central neurotransmitter and endocrine function. Thus some pro-inflammatory cytokines that are released from monocytes, macrophages and other immune cells in the periphery, and from microglia and astrocytes in the brain, profoundly affect central monoamine function and also activate the HPA axis (Song *et al*., 1994). In addition, pro-inflammatory cytokines such as IL-1, -6 and TNF α enhance inflammatory changes in the brain and elsewhere by stimulating COX to produce PG-E2. This prostenoid modulates monoamine release in the brain (Connor and Leonard, 1998). The 'cross-talk' between these three systems account for the changes seen following different types of stress but also those changes that arise in major depression. Such changes include a reduction in natural killer cell activity, T-cell proliferation and neutrophil phagocytosis but also a rise in macrophage and monocyte activity, in positive acute phase proteins, immunoglobulins A and M, and complement factors C3 and C4 (Maes *et al*., 1992; Sluzewska *et al*., 1996; Leonard and Song, 1999). Such changes are largely a reflection of the increased release of the pro-inflammatory cytokines from activated macrophages and a reduction in the anti-inflammatory cytokines such as IL-4 and IL-10.

In addition to the functional changes in the immune system associated with chronic stress and depression, structural changes in some organs also occur. Thus the weights of the thymus gland and spleen are decreased while the adrenals increase (Dohmus and Metz, 1991), changes that reflect the hypercortisolaemia. In chronic depression, secondary changes also occur in the structure of the brain. Thus the enlargement of the ventricles and the atrophy of the hippocampus is associated with glucocorticoid induced apoptosis

DOI: 10.1002/hup

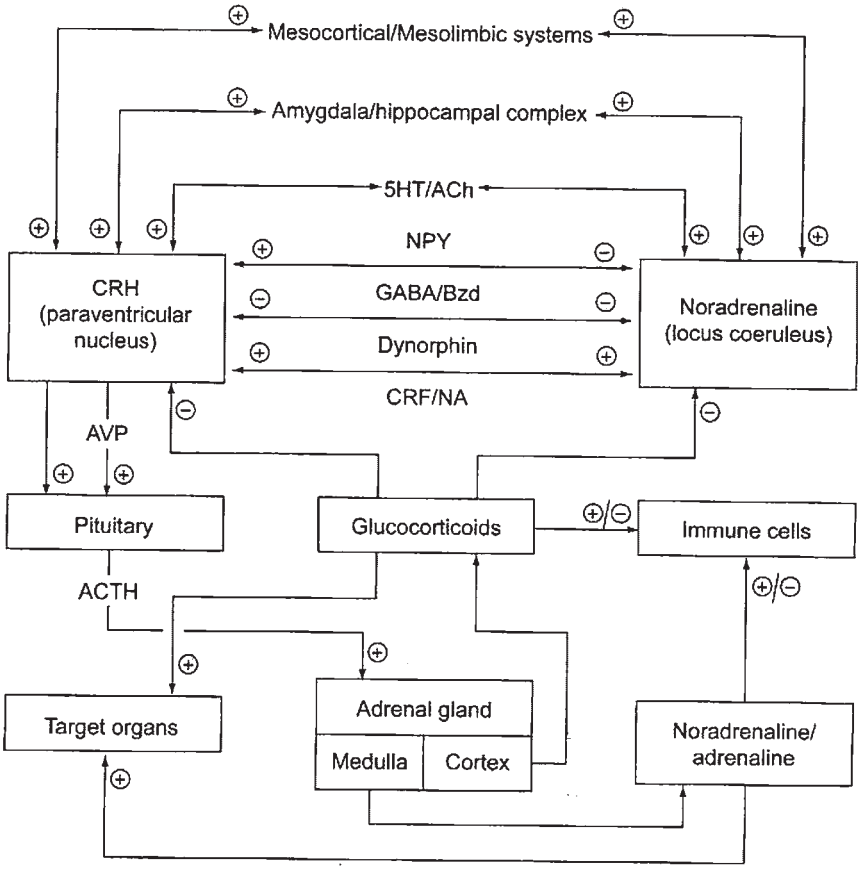

Figure 1. Diagrammatic representation of the central and peripheral components of the stress system. (Modified with permission, from Chrousos and Gold, 1992). Key: CRH, corticotrophin releasing hormone; NPY: neuropeptide Y; NA: noradrenaline; AVP: arginine vasopression; ACTH: adrenocorticotrophic hormone; GABA–Bzd: gamma aminobenzoic acid/benzodiazepine receptor complex; 5HT/ACh: serotonin/acetylcholine; +: activation; −: inhibition.

(Duman *et al*., 1997); pro-inflammatory cytokines contribute to these changes (Leonard and Myint, 2006).

Besides the changes in the pro-inflammatory cytokines that occur in the plasma of depressed patients, the role of such cytokines in the aetiology of depression is further supported by their behavioural effects in non-psychiatric patients being treated with INF for hepatitis and some types of cancer. A substantial minority of these patients develop symptoms such as depressed mood, anxiety, cognitive dysfunction, anorexia, deficits in short-term memory and a disturbed sleep profile, symptoms that commonly occur in patients with major depression. These behavioural changes are associated with a rise in plasma pro-inflammatory cytokines (Wichers *et al*., 2005). It is perhaps not surprising to find that depressed mood is frequently reported in patients recovering from a chronic infection, those with multiple sclerosis, allergies and rheumatoid arthritis. In all these conditions, inflammatory changes are evident and pro-inflammatory cytokines are over-expressed. A possible causal connection between the inflammatory changes and the symptoms of depression is indicated by the reduction in the symptoms once the inflammatory changes return to normal. Interestingly, effective antidepressant treatment of patients with depression also reduces the inflammatory changes (Sluzewska *et al*., 1996; Connor and Leonard, 1998; Leonard and Song, 1999).

In addition to the rise in plasma pro-inflammatory cytokines in depression, there is also evidence of an increased number of T-helper, T-memory, activated T cells and B-cells that act as a source of plasma cytokines. This has led to the hypothesis that major depression involves an imbalance between inflammatory and anti-inflammatory arms of the system, the cytokines from the inflammatory Th-1 pathway (such as INF-α) being predominant over the Th-2 anti-inflammatory (such as IL-10) pathway. Recent evidence has also shown that the Th-3 cytokine, transforming factor β 1, that plays a key role in maintaining the balance between the Th-1 and Th-2

DOI: 10.1002/hup

pathways, is increased in response to effective antidepressant treatment (Myint *et al*., 2005). The mechanism whereby this occurs is presently uncertain. However, the results of these studies suggest that antidepressants have an anti-inflammatory action and may indirectly modulate central monoamine dysfunction in depression by correcting the changes in the immune and endocrine systems.

SUMMARY OF THE MAIN POINTS OF THIS SECTION

(1) The response of he immune system to stress involves a complex cascade of events in which catecholamines, glucocorticoids, endorphins and other neuropeptides play a role. These changes are interlinked with the endocrine and neurotransmitter systems via the immunotransmitter receptors on endocrine cells and the neurons; hormone and neurotransmitter receptors also occur on immune cells.
(2) Evidence that the activation of the immune system is associated with the symptoms of depression is provided by the increase in depressive symptoms in otherwise psychiatrically normal patients being therapeutically treated with the pro-inflammatory cytokine INF. In depressed patients, there is evidence that the pro-inflammatory arm of the immune pathway is increased while that of the anti-inflammatory arm is decreased. Effective antidepressant treatment restores the imbalance and reduces both the stress induced hypercortisolism and the increase in the inflammatory mediators.

STRESS, DEPRESSION AND NEURODEGENERATION

In depressed patients during a period of remission, the depletion of tryptophan from the diet by the administration of an amino acid mixture that lacks tryptophan results in a reduction in brain serotonin, as indicated by a fall in the CSF concentration of 5-hydroxyindole acetic acid, that correlates with the onset of a depressed mood (Young *et al*., 1985). Tryptophan is metabolised through two main pathways, one leading to the synthesis of serotonin following the action of tryptophan hydroxylase and the other by the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), leading to the formation of kynurenine and kynurenic acid (Hayaishi, 1980; Guillemin *et al*., 2001). In depression, there is evidence that the metabolism of tryptophan through the kynurenine pathway is increased, thereby reducing the availability of tryptophan for serotonin synthesis in the brain (Myint and Kim, 2003). Thus TDO in induced by cortisol while IDO is induced by the pro-inflammatory cytokines and inhibited by the anti-inflammatory cytokines (Carlin *et al*., 1987; Musso *et al*., 1994).

There are two main stages in the metabolism of tryptophan through the kynurenine pathway (Chiarugi *et al*., 2001). Following the conversion of tryptophan to kynurenine, kynurenine hydroxylase metabolises kynurenine to 3-hydroxykynurenine and then to 3-hydroxyanthranilic acid and quinolinic acid. This pathway is increased in depression and dementia (Kim *et al*., 1987; Stone and Darlington, 2002). The neurotoxic effects of these end products of kynurenine metabolism is due to their agonistic affinity for the *N*-methyl-D-aspartate glutamate receptors. By contrast, kynurenine may be metabolised by kynurenine aminotransferase to form the neuroprotective end product kynurenic acid (Perkins and Stone, 1982); this acts as an antagonist of NMDA glutamate receptors and its rate of synthesis is decreased in depression.

In the brain, the metabolism of tryptophan by IDO occurs in both the microglia and astrocytes (Grant and Kapoor, 1998). The microglia are known to produce both 3-hydroxyanthranilic acid and quinolinic acid in depression while the astrocytes produce mainly kynurenic acid. Astrocytes also metabolise quinolinic acid and thereby reduce the neurotoxic impact of microglia activation (Sheline *et al*., 1999). In chronic depression, there is evidence that the activated microglia produce an excess of quinolinic and 3-hydroxyanthranilic acid that cannot be adequately metabolised by the astrocytes. This eventually results in a reduction in astrocytes that, due to the role of astrocytes as metabolic buffers for the neurons, further exposes the neurons to the neurodegenerative actions of quinolinic acid.

The evidence for an increase in the neurodegenerative end products of the kynurenine pathway being associated with depression comes from two major clinical studies. Thus Wichers *et al*. (2005) showed that the blood kynurenic acid concentration was reduced in patients being treated therapeutically with the pro-inflammatory cytokine INF α. Myint *et al*. (2007) also showed that effective antidepressant treatments reversed the increase in the neurotoxic end products in those patients in their first depressive episode but not in those suffering from chronic depression. This suggests that neurodegenerative changes in the brain may increase in the brain of the depressed patient as the disorder becomes chronic.

The structural deterioration of the brain of patients with chronic depression lends support to the neurodegenerative hypothesis of depression. In patients with major depression, there is a shrinkage of the hippocampus (Ongur *et al*., 1998), a decrease in the

DOI: 10.1002/hup

number of astrocytes and a neuronal loss in the prefrontal cortex (Rajkowska *et al*., 1999; Leonard, 2001) and in the striatum. These changes may be a reflection of the increase in the concentration of pro-inflammatory cytokines and other inflammatory mediators such as PG-E2 and nitric oxide whose synthesising enzymes are also induced by these cytokines (Nibuya *et al*., 1999). The inhibition of neuronal repair mechanisms resulting from a reduction in the synthesis of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) by cortisol (Chen *et al*., 1999) further adds to the impact of the inflammatory changes and the presence of neurotoxic metabolites of the kynurenine pathway.

IS THERE A POSSIBLE LINK BETWEEN DEPRESSION AND DEMENTIA?

There is epidemiological evidence that a life-time history of major depression is an increased risk factor for Alzheimer's disease in later life (Steffens *et al*., 2002; Green *et al*., 2003). Hippocampal atrophy provides a link between these disorders (Rapp *et al*., 2005), in addition to a dysfunction of the temporal lobes (Myint and Kim, 2003). Furthermore, patients with a history of major depression before the onset of Alzheimer's disease had a higher density of hippocampal plaques and neurofibrillary tangles than is found in patients who had never suffered from depression before the onset of Alzheimer's disease.

While such studies support the hypothesis that chronic major depression may be a prelude to Alzheimer's disease, the final common pathway leading to the formation of β-amyloid plaques and tangles is uncertain. Nevertheless, there is evidence that a dysfunctional serotonergic system may play a role in increasing amyloid plaque formation. Experimental studies have shown that stimulation of $5HT_2A$ and $5HT_2C$ receptors by serotonin activates the secretion of the soluble, non-amyloidogenic, form of amyloid precursor protein that can be cleaved by α- and β-secretases (Nitsch *et al*., 1996). This implies that a chronic reduction in serotonergic function, that is assumed to occur in major depression, would result in more amyloidogenic precursor protein thereby leading to an increase in amyloid plaque formation.

Although most attention has been directed towards the neurotoxic effects of amyloid plaques and neurofibrillary tangles in Alzheimer's disease, there is evidence that the kynurenine pathway, and an increase in lipid peroxidation of the neuronal membranes, also plays a role that is similar to that occur in major depression (Heyes *et al*., 1993; Butterfield *et al*., 2002). The change in the kynurenine pathway reflected the increase in IDO activity, presumably associated with an increase in pro-inflammatory cytokines, in patients with Alzheimer's disease (Butterfield *et al*., 2002). This could account for the decrease in the concentration of kynurenic acid in the CSF and in the eythrocytes of patients with Alzheimer's disease (Heyes *et al*., 1993; Hartai *et al*., 2006). Such results suggest that the neurodegenerative arm of the kynurenine pathway is increased in dementia thereby leading to similar neurodegenerative changes to those seen in patients with major depression.

SUMMARY OF MAIN POINTS OF THIS SECTION

(1) Chronic, major depression is associated with a reduction in the volume of the hippocampus, frontal cortex and amygdalae. At the cellular level, the microglia are activated to increase the release of pro-inflammatory cytokines while there is loss of astrocytes and neurons. The structural changes in the brain are a reflection of neurodegeneration caused by the inflammatory mediators (pro-inflammatory cytokines, PG-E2, nitric oxide) and a reduction in neuronal repair due to the decreased synthesis of neurotrophic factors such as BDNF.

(2) Epidemiological evidence shows that a life-time history of major depression is an increased risk factor for Alzheimer's disease. The frequency of neuropathological changes, as shown by the density of amyloid plaques and neurofibrillary tangles, is greater in depressed patients who develop Alzheimer's disease than in those that were not depressed before getting the disease.

(3) In addition to the increase in similar inflammatory markers, and in hypercortisolism, in both depression and in Alzheimer's disease there is also evidence that the neurotoxins derived from the tryprophan-kynurenine pathway play a key role. Thus the neurotoxins quinolinic acid and 3-hydroxykynurenine are known to accumulate in the brains of patients with Alzheimers disease and depression and are therefore likely to cause the neurodegenerative changes that form the basis of dementia.

CONCLUSION

Experimental and clinical evidence suggests that chronic stress that increase the activity of the HPA axis plays a major role in initiating anxiety and ultimately depression. The principal components that are causally connected to depression include the glucocorticoids, the pro-inflammatory cytokines and such dysfunctional neurotransmitters as noradrenaline and serotonin. The long-term outcome of these stress-induced changes is neurodegeneration particularly

DOI: 10.1002/hup

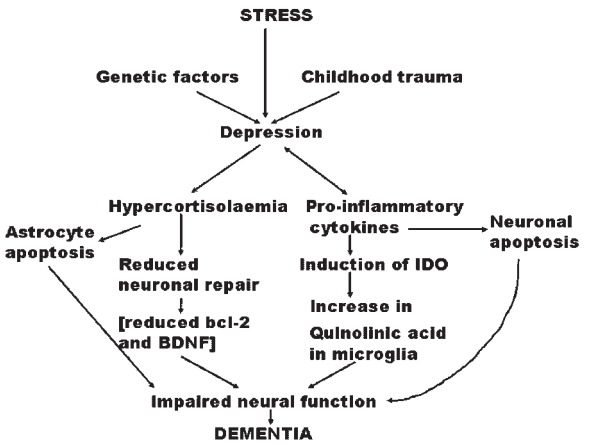

Figure 2. Summary of the cascade of changes linking depression with the possible onset of dementia.

affecting limbic regions of the brain. As qualitatively similar changes in inflammatory mechanisms, combined with an increase in neurotoxic metabolites from the tryptophan-kynurenine pathway, have been found in patients with Alzheimer's disease, it is hypothesised that major depression may be a prelude to dementia in later life. Figure 2 summarises the possible links between chronic stress, depression and dementia in later life.

REFERENCES

Aberg-Wistedt A, Hasselmark L, Stain-Malingren R, Aperia B, Kjellman BF, Mathe AA. 1998. Serotonergic vulnerability in affective disorder. *Acta Psychiat Scand* **97**: 374–380.

Arborehuis L, Owens MJ, Plotsky PM, Nemeroff CB. 1999. The role of corticotrophin-releasing factor in depression and anxiety disorders. *J Endocrinol* **160**: 1–12.

Banks WA, Kastin AJ, Broadwell RD. 1995. Passage of cytokines across the blood-brain barrier. *Recent Prog Neuroimmunomod* **2**: 241–248.

Berekenbosch F, de Goeij DEC, del Rey A, Besedovsky HO. 1989. Neuroendocrine,sympathetic and metabolic responses induced by IL-1. *Neuroendocrinology* **50**: 570–576.

Besedovsky HO, del Rey A, Klusman I, *et al*. 1991. Cytokines as modulators of the HPA axis. *J Steroid Biochem Mol Biol* **40**: 613–618.

Besedovsky HO, Sorkin E. 1997. Network of immune-neuroendocrine interactions. *Clin Exp Immunol* **27**: 1–12.

Bjorntorp P. 1999. Neuroendocrine perturbations as a course of insulin resistance. *Diabetes Metab Res Rev* **15**: 1–15.

Blumenthal SJ. 1995. Overview of mind-body interactions. *Proceedings of Conference of Stress, Immunity and Health, National Institutes of Health*. Hall NRS, Altman F, Blumenthal SJ (eds). Health Dateline Press: USA; 15–22.

Bluthe RM, Dantzer R, Kelley KW. 1997. Central mediation of the effects of IL-1 on social exploration and body weight in mice. *Psychoneuroendocrinology* **22**: 1–11.

Bluthe RM, Michaud B, Kelley KW, Dantzer R. 1996. Vagotomy attenuates behavioural effects of IL-1 injected peripherally but not centrally. *Neuroreport* **7**: 1485–1488.

Brambilla F. 2000. Psychoneuroendocrinology: research on the pituitary-adrenal-cortical system. *Psychosom Med* **30**: 576–607.

Butterfield DA, Casegna A, Lauderbach CM, Drake J, 2002. Evidence that amyloid beta peptide induced lipid peroxidation and its sequelae in Alzheimer's brain contributes to neural death. *Neurobiol Aging* **23**: 655–664.

Calabrese JR, Skwerer AG, Barna B, *et al*. 1986. Depression, immunocompetence and prostaglandins of the E series. *Psychiatr Res* **17**: 41–47.

Calogero AE, Bagdy G, Moncada ML, D'Agata R. 1993. Effect of selective serotonin agonists on basal CRH and VP-induced ACTH release in vitro from rat pituitary cells. *J Endocrinol* **136**: 381–387.

Cannon WB. 1929. *Body Changes in Pain, Hunger, Fear and Rage*. Appleton: New York.

Carlin JM, Borden EC, Sordel PM, Byrne GI. 1987. Biologic response modifier induced IDO activity in human peripheral blood mononuclear cell cultures. *J Immunol* **139**: 2414–2418.

Carroll BJ. 1982. Use of dexamethasone suppression test in depression. *J Clin Psychiatry* **43**: 44–50.

Chalmers DT, Lowenberg TW, de Souza EB. 1995. Localization of novel CRF R2 mRNA expression. *J Neurosci* **15**: 6340–6350.

Chaouloff F. 1995. Regulation of 5HT receptors by corticosteroids: where do we stand? *Fundam Clin Pharmacol* **9**: 219–233.

Chen P, Ganguli M, Mulsant BH, De Kosky ST. 1999. Then temporal relationship between depressive symptoms and dementia: a community based prospective study. *Arch Gen Psychiatry* **56**: 261–266.

Chiarugi A, Calvani M, Meli E, Traggiai E, Moroni F. 2001. Synthesis and release of neurotoxic kynurenine metabolites by human derived macrophages. *J Neuroimmunol* **120**: 190–198.

Chrousos GB. 1998. Stressors, stress and neuroendocrine integration of the adaptive response. *Ann NY Acad Sci* **750**: 311–335.

Connor TJ, Leonard BE. 1998. Depression, Stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci* **62**: 583–606.

Croiset G, Heijnen CJ, Veldhuis HD, de Wied D, Ballieux RE. 1987. Modulation of the immune response by emotional stress. *Life Sci* **40**: 775–782.

Davis S, Heal DJ, Stanfort SC. 1995. Long lasting effects of acute stress on the neurochemistry and function of 5HT neurons in mouse brain. *Psychopharmacology* **118**: 267–272.

Deakin JE. 1996. Does selectivity matter? *Int Clin Psychopharmacol* **11**(Suppl 1): 13–17.

Dohmus JE, Metz A. 1991. Stress mechanisms of immune suppression. *Vet Immunol Immunopathol* **30**: 89–109.

Duman RS, Henninger GR, Nessler EJ. 1997. A molecular and cellular theory of depression. *Arch Gen Psychiatry* **54**: 597–606.

Grant RC, Kapoor V. 1998. Murine glial cells regenerate NAD after peroxide-induced depletion, using nicotinic acid, nicotinamide or quinolinic acid as substrates. *J Neurochem* **70**: 1759–1763.

Gray TS. 1993. Amygdaloid CRF pathways: role in autonomic neuroendocrine and behavioural responses to stress. *Ann NY Acad Sci* **697**: 53–60.

Green RC, Cupples LA, Kurz A, Auerbach S, Go, Sadovnick D. 2003. Depression as a risk factor for Alzheimer's disease: the MIRAGE study. *Arch Neurol* **60**: 753–759.

Guillemin GJ, Kerr SJ, Smyth GA, Smith DG, Kapoor PJ. 2001. The kynurenine pathway metabolism in human astrocytes: pathway for neuroprotection. *J Neurochem* **78**: 842–853.

Hartai Z, Juhasz A, Rimanoczy A. 2006. Decreased serum RBC kynurenic acid in Alzheimer's disease. *Neurochem Int* neuint. 2006.08.012:10. 1016/j

Hayaishi O. 1980. *Biochemical and Medical Aspects of Tryptophan Metabolism*. Elsevier, North Holland Biomedical Press: Amsterdam.

Heilig M, Koob GF, Ekman R. 1994. CRF and NPY: role in emoptional integration. *Trends Pharmacol Sci* **17**: 80–85.

Heyes MP, Saito K, Major EO, Milstien S, Markey SP, Vickers JH. 1993. A mechanism of quinolinic acid formation by brain inflammatory neurological disease. *Brain* **16**: 1425–1450.

Holsboer F. 1999. The rationale for CRF receptor antagonists to treat depression and anxiety. *J Psychiatr Res* **33**: 181–214.

Leonard BE. 2008. Does psychoneuroimmunology have a future? In Vivo 21, 925–927, 2007.

Leonard BE, Myint A-M. 2006. Inflammation an depression: is there a causal connection with dementia? *Neurotox Res* **10**: 149–160.

DOI: 10.1002/hup

Leonard BE, Song C. 1999. Stress, depression and the role of cytokines. In *Cytokines, Stress and Depression*, Dantzer R (ed.). Academic Plenum: New York, Kluwer; 251–265.

Leonard BE. 2001. Brain cytokines and the psychopathology of depression. In *Antidepressants*, Leonard BE (ed.). Birkhauser Verlag: Basel; 109–120.

Leonard BE. 2007. Inflammation, depression and dementia:are they connected? *Neurochem Res* (in press). DOI 10.1007/S 11064- 007-9385-y

Lesch KP, Bengal D, Heils A. 1996. Association of anxiety related traits with a polymorphism in the 5HT transporter gene regulating region. *Science* **274**: 1527–1531.

Little KY, McLauglin DF, Ranc J. 1997. Serotonin transporter binding sites with mRNA levels in depressed persons committing suicide. *Biol Psychiatry* **41**: 1156–1164.

Lovenberg TW, Liaw CW, Grigoriadia DE, Clevenger W, Chalmers DT, de Souza EB. 1995. Cloning and characterization of a functionally distinct CRF receptor subtype from rat brain. *Proc Natl Acad Sci USA* **92**: 836–840.

Maes M, Planken VD, Stevens WJ, *et al*. 1992. Leucocytosis, monocytosis and neutrophilia:hallmarks of severe depression. *J Psychiatr Res* **26**: 125–134.

Maes M, Planken VD, Stevens WJ. 1992. Leucocytosis, monocytosis and neutrophilia in severe depression. *J Psychiatr Res* **261**: 125–134.

Mason JW. 1971. A re-evaluation of the concept of non specificity in stress theory. *J Psychiatr Res* **8**: 123–140.

Mazzanti CM, Lappalainen J, Long JC. 1998. Role of serotonin transporter promoter polymorphism in anxiety-related traits. *Arch Gen Psychiatry* **55**: 936–940.

McEwen BS, Stellar E. 1993. Stress and the individual mechanisms leading to disease. *Arch Int Med* **153**: 2093–2101.

McKittrick CR, Blanchard DC, Blanchard RJ, McEwen RJ, Sakai RR. 1995. Serotonin receptor binding in a colony model of chronic social stress. *Biol Psychiatry* **37**: 383–393.

Meijer OC, De Kloet ER. 1998. Corticosterone and serotonergic neurotransmission in hippocampus: functional implications of central corticosteroid receptor diversity. *Crit Rev Neurobiol* **12**: 1–20.

Musso T, Gusella GL, Brooks A, Longo DL, Varesio L. 1994. Interleukin-4 inhibits IDO expression in human monocytes. *Blood* **83**: 1408–1411.

Myint A-M, Kim Y-K, Verkerk R, Scharpe S, Steinbusch H, Leonard BE. 2007. Kynurenine pathway in major depression; evidence of impaired neuroprotection. *J Affect Disord* **98**: 143–151.

Myint A-M, Kim Y-K. 2003. Cytokine-serotonin interactions through indoleamine 2,3 dioxygenase: a neurodegenerative hypothesis of depression. *Med Hypotheses* **61**: 519–525.

Myint A-M, Leonard BE, Steinbusch H, Kim Y-K. 2005. Th1, Th2 and Th3 cytokine alterations in major depression. *J Affect Disord* **88**: 169–173.

Neumaier JC, Petty F, Kramer GL, Szot P, Hamblin MW. 1997. Learned helplessness increase 5HT1B receptor mRNA levels in the rat dorsal raphe nucleus. *Biol Psychiatry* **41**: 668–674.

Nibuya M, Takahashi M, Russell DS, Duman RS. 1999. Regulation of BDNF and trkB mRNA in rat brain by chronic electroshock seizures in rat hippocampus. *Neurosci Lett* **267**: 81–84.

Nitsch RM, Deng M, Growdon JH, Wurtman RJ. 1996. Serotonin 5HT2A and 5HT2C receptors stimulate amygdaloid precursor protein ectodomain secretion. *J Biol Chem* **271**: 4188–4194.

O'Keane V, Dinan TG. 1991. Prolactin and cortisol responses to d-fenfluramine in major depression: evidence for diminished responsivity of central serotonergic function. *Am J Psychiatry* **148**: 1009–1015.

Ogilvie AD, Bettersby S, Robb VJ. 1996. Polymorphs in 5HT transporter gene associated with susceptibility to major depression. *Lancet* **347**: 731–733.

Ongur D, Katz IR, Meyers BS, Schneider LS, Lebowitz BD. 1998. Glia reduction in subgenual pre-frontal cortex in mood disorders. *Proc Natl Acad Sci USA* **95**: 13290–13295.

Owens MJ, Edwards E, Nemeroff CB. 1990. Effects of 5HT1A receptor agonists on HPA activity and CRF containing neurons in rat brain. *Eur J Pharmacol* **190**: 113–120.

Perkins MN, Stone TW. 1982. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with endogenous quinolinic acid. *Brain Res* **247**: 184–187.

Porter R, McAllister-Williams RH, Lunn B, Young A. 1998. 5HT receptor function in man is reduced with susceptibility to major depression. *Psychopharmacology* **139**: 243–250.

Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY. 1999. Morphometric evidence for neuronal and glia pre-frontal cell pathology in major depression. *Biol Psychiatry* **45**: 1085–1098.

Rapp MA, Dahlman K, Sano M, Grossman HT, Haroutunian V, Gorman JM. 2005. Neuropsychological differences between late onset and recurrent geriatric major depression. *Am J Psychiatry* **162**: 691–698.

Renyi L, Evenden JL, Fowler CJ. 2001. The pharmacological profile of (R) 3,4-dihydro-N-isopropyl-3-(N-isopropyl-N-propylamino)-2H-1-benzopyran-5-carboxamide, a selective 5HT1A receptor agonist. *J Pharmacol Exp Ther* **299**: 883–893.

Sachar E, Hellman L, Fukushima DK, Gallagher TF. 1970. Cortisol production in depressive illness. *Arch Gen Psychiatry* **23**: 289–298.

Saphier D Ovadia H. 1987. Selective facilitation of putative CRF-secreting neurons by IL-1. *Neurosci Lett* **114**: 283–288.

Seyle H. 1936. A syndrome produced by diverse nocuous agents. *Nature* **138**: 32.

Sheline YI, Sanghavi MA, Mintum M, Gado MH. 1999. Depression duration, but not age, predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* **19**: 5034–5043.

Sheline YI, Wang PW, Gado MH, *et al*. 1996. Hippocampal atrophy in recurrent major depression. *Proc Acad Sci USA* **93**: 3908–3913.

Sluzewska A, Rybakowski JK, Sobieska M, Wiktorowicz K. 1996. Concentrations and microheterogeneity of glycophorms of alpha-1-acid glycoproteins in major depression. *J Affect Disord* **39**: 149–155.

Song C, Dinan TG, Leonard BE. 1994. Changes in immunoglobulin, complement and acute phase proteins concentrations in depressed patients and normal controls. *J Affect Disord* **30**: 283–288.

Song C, Horrobin DF, Leonard BE. 2006. The comparison of changes in behaviour,neurochemistry, endocrine and immune functions after different routes, doses and durations of administration of IL1 beta in rats. *Pharmacopsychiatry* **39**: 88–99.

Steffens DC, Payne ME, Greenberg DL, Byrum KA. 2002. Hippocampal volume and incident dementia in geriatric depression. *Am J Geriatr Psychiatry* **10**: 62–71.

Stone TW, Darlington LG. 2002. Endogenous kynurenins as targets for drug discovery and development. *Nat Rev Drug Discov* **1**: 609–620.

van Praag HM. 1996. Faulty cortisol/serotonin interplay, psychopathology and biological characterization of a new hypothetical depression subtype. *Psychiatr Res* **65**: 143–157.

Wichers MC, Koek GH, Robays G, *et al*. 2005. IDO and interferon alpha induced depressive symptoms: a shift in hypothesis from tryptophan depletion. *Mol Psychiatry* **10**: 538–544.

Wichers MC, Koek GH, Robaeys R, Verkerk R, Scharpe S, Maes M. 2005. IDO and interferon alpha induced depressive symptoms: a shift in hypothesis from tryptophan depletion. *Mol Psychiatry* **10**: 538–544.

Young SN, Smith PE, Pihl RO, Ervin FR. 1985. Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology* **87**: 175–177.