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ORIGINAL PAPER

Inflammation, Depression and Dementia: Are they Connected?

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Abstract Chronic inflammation is now considered to be central to the pathogenesis not only of such medical disorders as cardiovascular disease, multiple sclerosis, diabetes and cancer but also of major depression. If chronic inflammatory changes are a common feature of depression, this could predispose depressed patients to neurodegenerative changes in later life. Indeed there is now clinical evidence that depression is a common antecedent of Alzheimer's disease and may be an early manifestation of dementia before the cognitive declines becomes apparent. This review summarises the evidence that links chronic low grade inflammation with changes in brain structure that could precipitate neurodegenerative changes associated with Alzheimer's disease and other dementias. For example, neuronal loss is a common feature of major depression and dementia. It is hypothesised that the progress from depression to dementia could result from the activation of macrophages in the blood, and microglia in the brain, that release pro-inflammatory cytokines. Such cytokines stimulate a cascade of inflammatory changes (such as an increase in prostaglandin E2, nitric oxide in addition to more pro-inflammatory cytokines) and a hypersecretion of cortisol. The latter steroid inhibits protein synthesis thereby reducing the synthesis of neurotrophic factors and preventing reairto damages neuronal networks. In addition, neurotoxic end products of the tryptophan-kynurenine pathway, such as quinolinic acid, accumulate in astrocytes and neurons in both depression and dementia. Thus increased neurodegeneration, reduced neuroprotection and neuronal repair are common pathological features of major depression and dementia. Such changes may help to explain why major depression is a frequent prelude to dementia in later life.

Keywords Pro-inflammatory cytokines · Cortisol · Tryptophan-kynurenine pathway · Macrophages · Microglia · Neurotoxicity

Introduction

Anecdotal accounts of psychological distress that causes physical ill health have appeared in the literature for centuries. In more recent times, epidemiological studies have confirmed that there is an increase in the prevalence of coronary heart disease, osteoporosis, diabetes and dementia associated with chronic stressful life events and major depression. In the past, emphasis has been largely placed on the role of the monoamine neurotransmitters as the cause of the pathophysiological changes that occur in depression and following chronic stress [1]. However, it is now apparent that the endocrine and immune systems play an important role in the pathology of these disorders [2].

The idea that chronic stress has a negative impact on mental health was developed by Hans Seyle in 1936 when he proposed that the hypothalamic-pituitary-adrenal (HPA) axis played a major role in co-ordinating the stress response. The damaging consequences of chronic stress

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was at first thought to be due to the hypersecretion of the glucocorticoids. This view was supported by the observation that disorders of the adrenal and pituitary glands were frequently associated with changes in the mental state of the patient. However, studies of the effects of chronic stress demonstrated that a maladaption of the immune and neurotransmitter systems occurred in addition to those associated with the HPA axis. Thus chronic inflammatory changes are known to occur in major depression and are often associated with cardiac disease, hypertension, diabetes and different types of autoimmune disease [3, 4].

It would be anticipated that chronic cortisolaemia would result in the suppression of the immune system in patients with depression. However, in the past 15 years there has been an important paradigm shift in the understanding of the role of the immune system in depression. There is evidence that activation, rather than suppression, of the innate immune system occurs [5]. The reduced impact of the glucocorticoids on the immune system has been ascribed to the development of glucocorticoid receptor resistance [6]. Chronic inflammation is now considered to be central to the pathogenesis not only of depression but also of cardiovascular disease, diabetes and cancer, conditions that are frequently comorbid with major depression [7].

If chronic inflammatory changes are a common feature of major depression, what could be the long-term outcome? Depression has 'been indicated as a common antecedent of Alzheimer's disease and may be an early manifestation of dementia before the cognitive decline becomes apparent [8]. It has been estimated that patients with mild cognitive impairment associated with depression have more than twice the risk of developing dementia than those who are not depressed. This suggests that depression may be a prodrome of dementia [9]. The purpose of this article is to review the evidence that links chronic low grade inflammation with changes in brain structure and function that could precipitate neurodegeneration associated with Alzheimer's disease and other dementias.

Evidence for increased inflammation in depression

Patients with major depression who do not suffer from a medical condition have raised pro-inflammatory cytokines, increased acute phase proteins and an increased expression of chemokines and adhesion molecules in the plasma or serum [6, 10]. Of the pro-inflammatory cytokines that are raised, interleukin-6 (IL-6), C-reactive protein [6, 11], and to a lesser extent IL-1 and tumour necrosis factor alpha(TNF), have been shown to be raised in both the blood and cerebrospinal fluid (CSF) [12, 13]. Of the acute phase proteins, alpha-1 acid glycoprotein, alpha-1 antichymotrypsin and haptoglobulin have been reported to increase in the plasma of untreated depressed patients [10]. In this study, the concentrations of the positive acute phase proteins was found to increase while those of the negative acute phase proteins were decreased.

In addition to the changes in the pro-inflammatory cytokines, the anti-inflammatory cytokines, such as IL-4 and IL-10, decrease in the plasma of depressed patients [6]. Recent studies have also shown that some depressed patients have abnormal allelic variants of the genes for IL-1 beta and TNF. These abnormal variants are associated with an increased risk of depression and a reduced 'responsiveness to antidepressant treatments [14, 15].

While there is now a substantial body of evidence associating an increase in pro-inflammatory cytokines in major depression, there is also evidence that qualitatively similar changes also occur in milder forms of the disorder and also in patients suffering from fatigue and severe insomnia [16, 17]. A common feature of all these conditions is a reduced threshold to stress and therefore it seems likely that the stress-induced increase in corticotrophin releasing factor (CRF) plays a role in increasing the release of the cytokines from activated 'macrophages both in the periphery and in the brain (see review by Leonard and Song, 18). It must be noted that not all studies have found an association between inflammation and the pathogenesis of depression [19, 20] while in some studies the association between inflammation and the symptoms of depression is substantially reduced when factors such as the body mass index, gender and personality are factored into the correlation [21]. Some studies have also failed to find a correlation between the severity of the symptoms of depression and the increase in the inflammatory status [22].

Such inconsistencies suggest that inflammation contributes to the pathogenesis of some, but not all, depressed patients. It is also apparent that when statistically significant changes do occur, there is considerable variability in the inflammatory parameters that are determined, the significance of the difference between the patients and the control population being attributed to a subgroup of patients only [23].

In addition to the changes in the pro-inflammatory cytokines, there is also evidence that effective antidepressant treatment largely attenuates the inflammatory changes [24, 25]. Furthermore, the number of T helper, T-memory and activated T-cells, macrophages and monocytes that act as a source of the cytokines are also increased in depression. This suggests that, in depression, there is an imbalance between the inflammatory and anti-inflammatory arms of the cellular immune system, those cytokines from the Th1 lymphocytes (such as interferon alpha, IFN) being predominant over those from the anti-inflammatory Th2 cells (such as IL-10). There is also

evidence that transforming growth factor beta-1 (TGF) from Th3 lymphocytes plays a role in re-establishing the balance between the Th1 and Th2 pathways in those patients who respond effectively to antidepressant treatment [25].

Support for the macrophage theory of depression, originally suggested by Smith [26], comes from studies in patients with various types of cancer, or hepatitis, who have been treated with IFN. IFN is a potent inducer of other pro-inflammatory cytokines including IL-6, TNF and IL-1. The therapeutic treatment of patients with IFN frequently results in a depressed mood, anxiety, sleep disturbance, loss of libido, lack of motivation and deficits in short term memory. These cardinal symptoms of depression are attenuated by chronic antidepressant treatment [27]. The changes induced by IFN in otherwise psychiatrically normal patients are probably a consequence of changes in the endocrine, neurotransmitter and immune systems rather than being a reflection of the pathological condition for which IFN was being administered [28]. Depression is also frequently associated with inflammatory diseases such as multiple sclerosis [29], allergies of different types [30], and rheumatoid arthritis [31], diseases in which pro-inflammatory cytokines are over-expressed [32].

The interpretation of the effects of IFN on the mood state of cancer and hepatitis patients rests not only on the direct action of three inflammatory mediators on neural function but also on its indirect effects on tryptophan metabolism. It is now known that pro-inflammatory cytokines induce indoleamine 2,3-dioxygenase (IDO) and tryptophan dioxygenase (TDO) activity. IDO is widely distributed in the periphery and in the brain while TDO is largely confined to the liver. These enzymes metabolise tryptophan through the kynurenine pathway, the end products being the neurotoxins quinolinic acid (QA) and 3-hydroxykynurenine (3-HK). Both of these end products are N-methyl-D-aspartate (NMDA) receptor agonists and therefore likely to induce apoptosis by stimulating neuronal glutamate receptors. Tryptophan can also be metabolised to kynurenic acid which acts as an antagonist of NMDA receptors and is thus neuroprotective. Pro-inflammatory cytokines associated with depression and depressed mood states are known to enhance the pathway leading to QA and 3-HK [27, 33–35]. There is evidence that the neurotoxins cause metabolic changes in the basal ganglia [36] and affect information processing via the cingulate cortex. The changes in the cingulate cortex may represent an increased sensitivity of the patient to conflict and negative life events [37]. These observations lend further support to the hypothesis that inflammatory changes play an important role in the pathogenesis of major depression.

Inflammatory changes in dementia with particular emphasis on Alzheimer's disease

The neuropathological characteristics of Alzheimer's disease include synaptic loss, neuronal cell death, reactive astrogliosis, in addition to the well established markers neurofibrillary tangles and amyloid plaques [38]. The neuritic plaques contain aggregated beta-amylaloid (Ab) that is assumed to impair neuronal function in addition to inducing the inflammatory response [39, 40]. It is also worthy of note that many of the neuropathological changes have also been found in elderly depressed patients (see below).

A variety of cytokines have been implicated in the pathophysiology of Alzheimer's disease. For example, although there is good evidence that the concentration of IL-1 is increased in the brain of the patient, the precise role of this pro-inflammatory cytokine in Alzheimer's disease is incompletely defined. It is known that IL-1induces the expression of inducible nitric oxide synthase (iNOS) by astrocytes which could indirectly potentiate NMDA induced neurotoxicity [41]. Experimental studies, in which IL-1 was administered intracerebroventricularly into rats over a period of 7 days, clearly demonstrated changes in the turnover of brain monoamines (decrease in noradrenaline and an increase in serotonin and dopamine), a rise in the plasma concentration of PGE2 and a decrease in the anti-inflammatory cytokine IL-10 [42]. The cognitive deficit and the increase in depressive and anxiety-like behaviours also suggested that IL-1 may play an important role in both depression and dementia. However, in addition to the neurotoxic changes that elevated concentrations of IL-1 may cause in the brain, it must be emphasised that the neurotoxic changes are concentration related. Thus at physiologically relevant concentrations, IL-1 has been shown to be neuroprotective [43, 44]. Similar effects have been observed for IL-6 and TNF, cytokines that are also elevated in Alzheimer's disease [45, 46]. In addition, to the increase in IL-1, there is evidence of polymorphic forms of IL-1 alpha and beta that may be risk factors not only for Alzheimer's disease but also for the age of onset of the disease [47, 48].

In the brain, the expression of IL-6 is localised in neurons, astrocytes and microglia [49, 50, 51] and occurs widely associated with both diffuse and neuritic plaques. While there is no consensus regarding the role of IL-6 in Alzheimer's disease, it is widely acknowledged that IL-6 influences the expression of other cytokines and inflammatory mediators. Thus IL-6 drives the acute phase response that contributes to neuronal injury [45]. In vitro studies have also shown that IL-6 enhances NMDA-induced neurotoxicity, possibly by promoting an increase in calcium influx [52]. This finding suggests that

combination of activated NMDA receptors and the presence of Ab and IL-6 results in a potentiation of the neurotoxic assault on the brain of the patient with Alzheimer's disease.

TNF, is also raised in the CSF of patients with Alzheimer's disease [53], although not all investigators have reported an increase in this cytokine [54]. There is evidence that Ab and IFN enhance the synthesis and release of NO and TNF from microglia [55], while a combination of TNF and IFN synergistically increase the synthesis of Ab [56] thus adding to neuronal damage. It has also been demonstrated that, in Alzheimer's disease, there are several polymorphic forms of the TNF gene that are linked to an increased risk of the APOE4 allele increasing the incidence of the disorder [57]. However, not all studies have confirmed this [58].

Other cytokines that are increased in the brain of the Alzheimer patient include the macrophage colony stimulating factor (M-CSF), a cytokine that is responsible for inducing the proliferation, migration and activation of microglia [57, 58]. Experimental studies have shown that M-CSF, in vitro, causes the augmentation of Ab induced cytokine, chemokine and NO synthesis [59]. Such observations suggest that, by activating the microglia, M-CSF promotes the inflammatory responses that enhance the neurotoxic changes.

The TGF beta family of Th3 cytokines are expressed in neurons, astrocytes and microglia [60] and have anti-inflammatory, and possible neuroprotective, properties by enhancing the synthesis of the anti-inflammatory cytokines. The increase of TGF in Alzheimer patients has been ascribed to a reaction against the increased inflammatory changes [61]. It is also possible that TGF induces the clearance of Ab plaques by microglia that could form the basis for the neuroprotective potential of this cytokine.

In summary, the available evidence suggests that the changes in pro-inflammatory cytokines are qualitatively, and possibly quantitatively, similar in both major depression and Alzheimer's disease. This does not explain why there are important differences in the extent of the brain damage in these disorders; in Alzheimers disease multiple brain regions are affected while in major depression the neurodegenerative changes are largely restricted to the hippocampus, frontal cortex, temporal lobes and the amygdala. Nevertheless, there is also evidence that, in Alzheimer's disease, there is a profound atrophy of the hippocampus, frontal and parietal cortices [62] and that the incidence of depression is reported to occur in approximately 50% of patients with this disorder [63]. Other clinical studies have also reported that depressed patients with significant cognitive impairment have more than a three-fold greater risk of developing dementia than those who do not show a significant cognitive impairment.

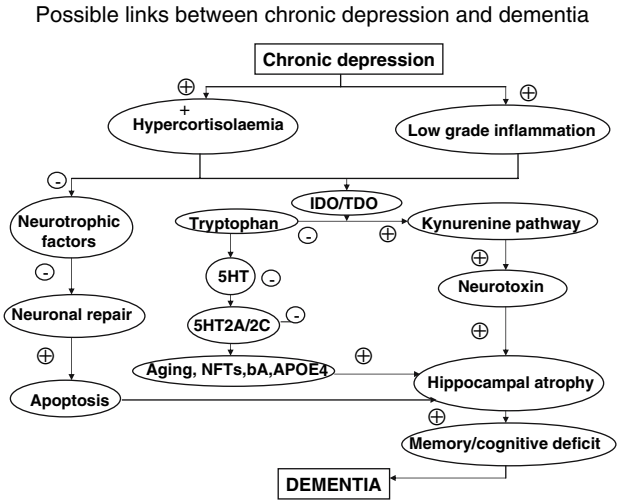

Fig. 1 Possible links between chronic depression and dementia.NFT's = neurofibrillary tangles, bA = beta amyloid, APOE 4 = apolipoprotein E4 (+) = increase; (−) = decrease

Finally, there is clinical evidence that patients with a history of major depression before the onset of Alzheimer's disease have a higher density of Ab plaques and NFTs in the hippocampus than those who develop the late onset form of Alzheimer's and who had ever suffered from depression earlier in life [64].

Increase in endogenous neurotoxins in depression and dementia

In addition to the damaging impact of the various inflammatory mediators, the glucocorticoids and the reduction in neuronal repair due to the decrease in neurotrophic factors, it is also evident that endogenous neurotoxins produced as end products of the trypytophan-kynurenine pathway may contribute to the brain damage seen in depression and dementia. As has already been mentioned, the kynurenine pathway is stimulated by the pro-inflammatory cytokines [65, 66]; both tryptophan 2,3 dioxygenase in the liver and indoleamine 2,3 dioxygenase (IDO), that is more widely distributed, being activated by these cytokines. In depression and Alzheimer's disease, activation of TDO and IDO not only lead to an increase in the synthesis of the neurotoxins 3-hydroxykynurenine (3-OHK) and quinolinic acid (QA) but also a reduction in serotonin synthesis. The main steps in the metabolism of tryptophan through the kynurenine pathway are summarised in Fig. 1.

The neurotoxic effects of QA and 3-OHK reside in their ability to stimulate NMDA receptors in contrast to kynurenine, that is reduced in depression and dementia, that acts as an antagonist of NMDA receptors and therefore confers some neuroprotective effects [67, 68]. Activated microglia

that occur in both depression and dementia as a consequence of the inflammatory changes, act as a local source of QA and 3-OHK [65] whereas astrocytes metabolise these neurotoxins [69] and also act as a major source of kynurenic acid, the neuroprotective component of the kynurenine pathway. As QA and 3-OHK are toxic to astrocytes in the range of concentrations that are associated with depression and dementia, the ratio of astrocytes to microglia decreases in both of these disorders. This further exposes neurons to the effects of the neurotoxins.

Although most attention has been directed towards the neurotoxic effects of Ab and NFT in Alzheimer's disease, there is evidence that the kynurenine pathway also plays a pathological role, together with oxidative stress and lipid peroxidation of the neuronal membranes [70]. A decrease in the concentration of kynurenic acid has been detected in the CSF of patients with Alzheimer's [71]. In addition, the activity of IDO was found to increase in Alzheimer's, a change that is correlated with an altered immune and oxidative stress response [71, 72]. Recently it has also been shown that the concentration of kynurenic acid in the red blood cells of patients with Alzheimer's was significantly decreased while those of kynurenine, the precursor of 3-OHK and QA, was unchanged [73]. This suggests that the neurodegenerative arm of the kynurenine pathway is increased in dementia, thereby representing a qualitatively similar change to that occurring in patients with major depression.

A comment on the effects of antidepressants on neurodegeneration

In recent years there has been a major paradigm shift in explaining the mode of action of antidepressants from the modulation of monoamine neurotransmitters (the Amine Theory) to the repair of damaged neuronal networks (see Leonard and Myint, 74). Thus there is both clinical and experimental evidence that exposure to severe stress during critical periods of brain development (for example, early childhood trauma) have lasting effects on brain structure and function [75]. This suggests that depression is associated with compromised information processing involving the formation of neuronal networks. If dysfunctional networks form the pathological basis of depression, how do antidepressants counteract such changes? Malberg et al. [76] have provided an explanation by demonstrating that antidepressants increase the number of new hippocampal neurons in the rat brain, changes that are correlated with improved behavioural function [77]. These results suggest that the chronic effects of antidepressants are associated with the repair, and possible construction, of new neuronal networks [78]. Such a process requires both the elimination of redundant parts of the neuronal network by apoptosis as well as the repair of damaged portions of the network by the increase in neurotrophic factors such as brain derived neurotrophic factor [79] and the synthesis of new neurons. Antidepressants are known to enhance axonal and dendritic sprouting [80, 81], changes that are initiated by the synthesis of neurotrophic factors that are vital for the selection and stabilisation of synaptic contacts [82].

From this brief summary, it is hypothesised that effective antidepressant treatments, irrespective of their nature, may improve neurotransmitter function secondarily to their effects in repairing damaged neuronal networks. However, the efficacy of antidepressant treatments appear to depend on the phase of development of depression. As is apparent in Alzheimer's disease, in depression once neuronal damage has reached a stage at which the functional integrity of specific brain regions cannot be reversed, antidepressant treatment becomes minimally effective. This has been the subject of a recent review [74].

Table 1 Summary of the cytokine related immune changes in depression and dementia

Immune parameter	Depression	Dementia
Pro-inflammatory cytokine	IL-1 (+)	IL-1 (+)
	IL-6 (+)	IL-6 (+)
	TNF (+)	TNF (+)
	IFN (+)	IFN (+)
Anti-inflammatory cytokine	IL-4 (−)	IL-4 (?−)
	IL-10 (−)	IL-10 (?−)
	IL-13 (−)	IL-13 (?−)
	TGF beta (−)	TGF beta (+)
Other inflammatory mediators	PGE2 (+)	PGE2 (+)
	NO (+)	NO (+)
	M-CSF (?+)	M-CSF (+)
	MCP 1 (+)	MCP 1 (?)
Ab and NFT's	(?+)	(+++)
Neurodegenerative branch:		
Kynurenine pathway*	(++)	(++)
Cortisol	(+)	(+)

M-CSF = macrophage colony stimulating factor, MCP 1 = macrophage chemoattractant protein, (+) increased, (-) decreased, (?) insufficient published data, Ab = beta amyloid, NFT's = neurofibrillary tangles. References cited in text

Conclusion

Table 1 summarises some of the inflammatory changes that have been shown to occur in depression and dementia, particularly Alzheimer's disease. Such changes may help to explain why chronic major depression is frequently a prelude to the onset of different forms of dementia in later life.

From the evidence presented in this review, it is apparent that neuronal loss is a common feature of major depression and dementia. It is hypothetised that the progress of depression to dementia could result from the chronic inflammatory changes that are linked to the activation of macrophages in the blood and microglia in the brain. The neurodegenerative changes in both depression and dementia are associated with the increase in the pro-inflammatory cytokines and other inflammatory mediators such as PGE2 and NO, hypercortosolaemia and the accumulation of such neurotoxins as quinolinic acid and 3-hydroxykynurenine, the end products of the cytokine activated tryptophan-kynurenine pathway. The activation of the microglia by the pro-inflammatory cytokines, and the apoptosis of the astrocytes that leads to a reduction in the synthesis of the neuroprotective agent kynurenic acid, further adds to the neurodegenerative changes. Thus increased neurodegeneration, reduced neuroprotection and neuronal repair are common pathological features of both chronic major depression, Alzheimer's disease and possibly other forms of dementia. Such changes may help to explain why major depression is often a prelude to dementia in later life.

References

1. Leonard BE (1989) The amine hypothesis of depression: a reassessment. In: TiptonK F, Youdim MBH (eds) Biochemical and pharmacological aspects of depression. Taylor and Francis, London, pp 25–49
2. Brambilla F (2000) Psychoneuroendocriniligy: research on the pituitary-adrenal-cortical system. Psychosomat Med 62:576–607
3. Jonas BS, Laudo JF (2000) Negative affect as a prospective risk factor of hypertension. Psychosomat Med 62:188–196
4. Leonard BE (2006) Physical consequences of depression. Quart J mental Health 1:33–38
5. Herbert TB, Cohen S (1993) Depression and immunity: a meta-analytic view. Psychol Bull 113:472–486
6. Maes M (1999) Major depression and activation of the inflammatory response. Adv Exp Biol Med 461:25–46
7. Evans DL (2005) Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiat 58:175–189
8. Geerlings MI, Schoevers RA, Beckman AT et al (2000) Depression and risk of cognitive decline and Alzheimer's disease. Results of 2 prospective community based studies in the Netherlands. Br J Psychiat 176:568–575
9. Steffens DC, Plassman BL, Helms MJ et al (1997) A twin study of late onset depression and apolipoprotein E4 as risk factors for Alzheimer's disease. Biol Psychiat 41:851–856
10. Song C, Dinan TG, Leonard BE (1994) Changes in immunoglobulins, complement and acute phase proteins in depressed patients and normal controls. J Affect Dis 30:283–288
11. Ford DE, Erlinger TP (2004) Depression and C-reactive protein in U.S. adults. Arch Intern Med 164:1010–1014
12. Lanquillon S (2000) Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology 22: 370–379
13. Levine J (2000) Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology 40:171–176
14. Yu YW (2003) Association study of the IL-1 beta (C-511T) genetic polymorphism with major depressive disorder, associated symptomatology and antidepressant response. Neuropsychopharmacology 28:1182–1185
15. Jun TY (2003) Possible association between -G308A TNF alpha gene polymorphism and major depressive disorder in a Korean population. Psychiat Genet 13:179–181
16. Suarez EC (2004) Enhanced expression of cytokines and chemokines by blood monocytes to in vitro lipopolysaccharide stimulation is associated with hostility and severity of depressive symptoms in healthy women. Psychoneuroendocrinology 29:1119–1128
17. van der Ven A (2003) Herpes viruses,cytokines and altered haemostsis in vital exhaustion. Psychosomat Med 65:194–200
18. Leonard BE, Song C (2007) Stress, the immune system and depression. In: Encyclopedia of stress. Elsevier North Holland Press. (in press)
19. Haack M (1999) Plasma levels of cytokines and soluble cytokine receptors in psychiatric patients upon hospital admission: effects of confounding factors and depression. J Pdsychiat Res 33:407–418
20. Steptoe A (2003) Lack of association between depressive symptoms and markers of immune and vascular inflammation in middle aged men and women. Psychol Med 33:667–674
21. Miller GE (2003) Pathways linking depression, adiposity and inflammatory markers in healthy young adults. Brain Behav Immun 17:276–285
22. Owen BM (2001) Raised levels of plasma IL-1 beta in major and post viral depression. Acta Psychiat Scand 103:226–228
23. Tiermeier H (2003) Inflammatory proteins and depression in the elderly. Epidemiology 14:103–107
24. Sluzewska A, Rybakowski J, Bosmans E. et al (1996) Indicators of immune activation in major depression. Psychiat Res 64:162–167
25. Myint A-M, Leonard BE, Steinbusch HW, Kim Y-K (2005) Thi, Th2 and Th3 cytokine alteratikons in major depression. J Affect Dis 88:169–173
26. Smith R (1991) The macrophage theory of depression. Med Hypoth 35:298–306
27. Wichers MC,Koek GH,Robaeys G et al (2005) IDO and interferon alpha induced'depressive symptoms: a shift in hypothesis from tryptophan depletion. Mol Psychiat 10:538–544
28. Meyers CA, Valentine AD (1995) Neurologic and psychiatric adverse effects of immunological therapy. CNS Drugs 3:56–68
29. Minden SL, Schiffer RB (1990) Affective disorder in multiple sclerosis. Gen Hosp Psychiatry 9:426–434
30. Marshall PS (1993) Allergy and depression: a neurochemical threshold model of the relation between the illnesses. Psychol Bull 113:23–43
31. Katon W, Sullivan MD (1990) Depression and chronic medical illness. J Clin Psychiatry 51:3–11
32. Schrott LM, Crnic LS (1996) Anxiety behavior, exploratory behavior and activitZBx and NZB F1 hybrid mice: role of genotype and autoimmune disease progression. Brain Behav Immun 10:260–274
33. Myint A-M, Kim Y-K (2003) Cytokine-serotonin interactions through indoleamine 2,3-dioxygenase: a neurodegenerative hypothesis of depression. Med Hypoth 61:519–525
34. Capuron L (2002) Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoin cytokine therapy. Mol Psychiat 7:468–473
35. Capuron L (2003) Association of exaggerated HPA axis response to the initial injection of IFN alpha with development of

depression during IFN alpha therapy. Am J Psychiat 160:1342–1345
36. Juenling FD (2000) Prefrontal cortical hypometabolism during low dose IFN alpha treatment. Psychopharmacology 152:383–389
37. Capuron L (2005) Anterior cingulate activation and error processing during IFN alpha treatment. Biol Psychiatry 58:190–196
38. Cummings JL (2004) Alzheimer's disease. N Engl J Med 351:565–567
39. Selkoe DJ (2004) Alzheimer's disease: mechanistic understanding predictors novel therapies. Ann Intern Med 140:627–638
40. Mattson MP (2004) Pathways towards and away from Alzheimer's disease. Nature 430:631–639
41. Hewett SJ, Csernansky CA, Choi DW (1994) Selective potentiation of NMDA induced neural injury following induction of astrocytic iNOS. Neuron 13:487–494
42. 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 IL-1 beta in rats. Pharmacopsychiatry 39:88–99
43. Herx LM, Rivest S, Young VW (2000) CNS initiated inflammation and neurotrophism in trauma: IL-1 beta is required for the production of ciliary neurotrophic factor. J Immunol 165:2232–2239
44. Strjbos P, Rothwell N (1995) IL-1 beta attenuates excitatory amino acid neurodegeneration in vitro: involement of NGF. J Neurosci 15:3468–3474
45. Vandenabecle P, Fiers W (1991) Is amyloidogenesis during Alzheimer's disease due to an IL-1/IL-6 mediated acute phase reaction in the brain? Immunol Today 12:217–219
46. Grimaldi LM, Casadrei VM, Ferri C et al (2000) Association of early onset Alzheimer's disease with IL-1 alpha gene polymorphism. Ann Neurol 47:361–365
47. Meda L, Cassatella MA, Szendrei GI et al (1995) Activation of microglial cells bt beta amyloid protein and IFN gamma. Nature 374:647–650
48. Sciacca FL, Ferri C, Licastro F et al (2003) IL-1beta polymorphism is associated with age at onset of Alzheimer's disease. Neurobiol Aging 24:927–931
49. Norris JG, Benveniste EN (1993) IL-6 production by astrocytes: induction by norepinephrine. J Neuroimmunol 45:137–145
50. Ye SM, Johnson RW (1999) Increased IL-6 expression by microglia from brain of aged mice. J Neuroimmunol 93:139–148
51. Gradient RA, Otten V (1993) Differential expression of IL-6 and IL-6 receptor on RNA's in rat hypothalamus. Neurosci Lett 153:13–16
52. Qui Z, Sweeney DD, Netzeband JG, Grud DL (1998) Chronic IL-6 alters NMDA receptor mediated membrane responses and enhances neurotoxicity in developing CNS neurons. J Neurosci 18:10445–10456
53. Tarkowski E, Blennow K, Wallin A, Tarkowski A (1999) Intracerebral production of TNF alpha, a local neuroprotective agent, in Alzheimer's disease and vascular dementia. J Clin Immunol 19:223–230
54. Lanzem AS, Johnston CM, Perry VH et al (1998) Longitudinal study of inflammatory factors in serum, CSF and brain tissue in Alzheimer's disease: IL-1 beta, IL-6,IL-1 receptor antagonist, TNF alpha, soluble TNF receptors and alpha-chymotrypsin. Alzheim Dis Assoc Disord 12:215–227
55. Knezevic-Cuca J, Stansberry KB, Johnston G et al (2000) Neurotrophic role of IL-6 and soluble IL-6 receptor in NIE-115 neuroblastoma cells. J Neuroimmunol 102:8–16
56. Blasko I, Marx F, Steiner E et al (1999) TNF alpha plus IFN gamma induce production oif Alzheimer beta amyloid peptides and decrease secretion of amyloid precursor proteins. FASEB J 13:63–68
57. McCusker SM, Curran MD, Dynan KB et al (2001) Association between polymorphism in regulating region of gene encoding TNF alpha and risk of Alzheimer's disease and vascular dementia: a case controlled study. Lancet 357:436–439
58. Infante J, Llorca J, Berciano J, Combarros O (2002) No synergistic effect between 850 TNF alpha promoter polymorphism and APOE epsilon 4 allele in Alzheimer's disease. Neurosci Lett 328:71–73
59. Mitrasinovic OM, Perez GV, Zhao F et al (2001) Overexpression of macrophage colony stimulating factor receptor on microglial cells induces an inflammatory response. J biol Chem 276:30142–30149
60. Finch CE, Laping NJ, Morgan TE et al (1993) TGF beta 1 is an organiser of responses to neurodegeneration. J cell Biochem 53:314–322
61. Flanders KC, Ren RF, Lippa VCF (1998) TGF betas in neurodegenerative disease. Prog Neurobiol Biol Psychiatry 54:71–85
62. Kanne SM, Balota DA, Storandt M et al (1998) Relating anatomy to function in Alzheimer's disease: neuropsychological profiles predict regional neuropathology 5 years later. Neurol 50:979–985
63. Lyketos CG, Olin J (2002) Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry 52:243–252
64. Rapp MA, Dahlman K, Sano M et al (2005) Neuropsychological differences between late onset and recurrent geriatric major depression. Am J Psychiatry 162:691–698
65. Guillemin GJ, Kerr SJ, Smythe GA et al (2001) The kynurenine pathway metabolism in human astrocytes: pathway for neuroprotection. J Neurochem 78:842–853
66. Hayaishi O Biochemical and medical aspects of tryptophan metabolism Elsevier: Amsterdam/North Holland Biomed (Press)
67. Kim JP, Choi DW (1987) Quinolinate neurotoxicity in cortical cell cultures. Neurosci 23:423–432
68. Stone TW, Darlington LG (2002) Endogenous kynurenines as targets for drug discovery and development. Nat Rev Drug Discov 1:609–620
69. Heyes MP, Achim CL, Wiley CA et al (1996) Human microglia convert l-tryptophan into neurotoxic quiolinic acid. Biochem J 320(pt.2):595–597
70. Butterfield DA, Casegna A, Lauderback CM, Drake J (2002) Evidence that amyloid beta peptide induced lipid peroxidation and its sequelae in Alzheimer's brain contribute to neural death. Neurobiol Aging 23:655–664
71. Heyes MP, Saito K, Major EO et al (1993) A mechanism of quinolinic acid formation by brain in inflammatory neurological disease. Brain 16:1425–1450
72. Markesberry WR (1997) Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med 23:134–147
73. Hartai Z, Juhasz A, Rimanoczy A et al Decreased serum and red blood cell kynurenic acid levels in Alzheimer's disease.Neurochem.Int.doi:10.1016/j.neuint.2006.08.012
74. Leonard BE, Myint A-M (2006) Inflammation and depression: is there a causal connection with dementia? Neurotox Res 10:149–160
75. Vythingham M (2002) Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiat 159:2072–2080
76. Malberg JE, Eisch AJ, Nessler EJ, Duman RS (2000) Chronic antidepressant treatment imcreases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110
77. Santarelli L (2003) Requirement of hippocampal neurogenesis for the behavioural effects of antidepressants. Science 301:805–809
78. Saivanen M, Lucas G, Emfors P et al (2005) BDNF and antidepressants have different but co-ordinated effects on neural turnoiver, proliferation and survival in the adult dendate gyrus. J Neurosci 25:1089–1094

79. Nibuya M, Takahashi M, Russell DS, Duman RS (1999) Chronic stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci Lett 267:81–84
80. Vaidya VA, Siuciak JA, Du F, Duman RS (1999) Hippocampal mossy fibre sprouting induced by chronic ECS. Neurosci 898:157–166
81. Fujioka T, Fujioka A, Duman RS (2004) Activation of cAMP signalling facilitates the morphological maturation of new born neurons in adult hippocampus. J Neurosci 24:319–328
82. Song H, Poo M (2001) The cell biology of neuronal navigation. Nat Cell Biol 3:E81–E88