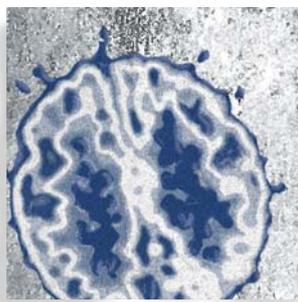


Changes in the immune system in depression and dementia: causal or coincidental effects?

Brian E Leonard, PhD, DSc; Ayemu Myint, MBBS, MMedSci



Epidemiological studies show that there is a correlation between chronic depression and the likelihood of dementia in later life. There is evidence that inflammatory changes in the brain are pathological features of both depression and dementia. This suggests that an increase in inflammation-induced apoptosis, together with a reduction in the synthesis of neurotrophic factors caused by a rise in brain glucocorticoids, may play a role in the pathology of these disorders. A reduction in the neuroprotective components of the kynurenine pathway, such as kynurenic acid, and an increase in the neurodegenerative components, 3-hydroxykynurenine and quinolinic acid, contribute to the pathological changes. Such changes are postulated to cause neuronal damage, and thereby predispose chronically depressed patients to dementia.

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Author affiliations: Department of Pharmacology, National University of Ireland, Galway, Ireland (Brian E. Leonard); Brain and Behaviour Research Institute, Department of Psychiatry and Neuropsychology, University of Maastricht, the Netherlands (Ayemu Myint)

Address for correspondence: Brian E. Leonard, Department of Pharmacology, National University of Ireland, Galway, Galway, Ireland (e-mail: belucg@iol.ie)

Epidemiological studies have implicated chronic depression as an important predisposing factor for dementia in later life. Depression has been shown to be a common antecedent of Alzheimer's disease, and may be an early manifestation of dementia before the cognitive symptoms become apparent.^{1,2} In particular, patients with depression who later develop dementia usually have a poorer baseline performance in cognitive tasks.³ Several studies have shown that depression is a risk factor for dementia, particularly Alzheimer's disease, and this may be particularly important if the depressive episode occurs within 2 years of the diagnosis of dementia.³ Indeed, it has been estimated that patients with mild cognitive impairment and depression have more than twice the risk of developing dementia than those of the same age but who do not have depression. This suggests that depression may be a prodrome of dementia.⁴ Both depression and dementia are associated with inflammatory changes in the brain. The chronic inflammatory diseases, such as rheumatoid arthritis, are frequently associated with depression,⁵ while proinflammatory cytokines, such as interferon α (IFN α), used therapeutically in the treatment of hepatitis, for example, are known to precipitate depressive episodes in psychiatrically nondepressed patients.⁶ An experimental study has also been reported in which rats treated with IFN α showed anxiety behavior in open field, and changes in cytokines in both peripheral blood and in certain brain regions.⁷ Numerous clinical studies, supported by clinical evidence, have shown that proinflammatory cytokines are raised in the blood of depressed patients.⁸ Such observations form the basis for the macrophage theory of depression.⁹ The possible link between depression, dementia, and inflammatory changes in the brain is also supported by clinical and experimental studies of acquired immune defi-

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Selected abbreviations and acronyms

AIDS	<i>acquired immune deficiency syndrome</i>
BDNF	<i>brain-derived neurotrophic factor</i>
COX2	<i>cyclo-oxygenase</i>
CRF	<i>corticotropin-releasing factor</i>
HPA axis	<i>hypothalamic-pituitary-adrenal axis</i>
IFN	<i>interferon</i>
IL	<i>interleukin</i>
NO	<i>nitrous oxide</i>
PGE₂	<i>prostaglandin E₂</i>
TGF	<i>transforming growth factor</i>

ciency syndrome (AIDS). It is well established that when human immunodeficiency virus (HIV)-infected patients develop AIDS, a substantial proportion of the patients also develop depression.¹⁰ Depression is one of the early manifestations of HIV dementia.¹¹ Antiretroviral therapy was also one of those early manifestations.¹¹ An experimental study in rodents showed that Efavirenz, the antiretroviral drug used in treatment of HIV infection, induced increased proinflammatory cytokines in the peripheral blood and was associated with anxiety behavior and impaired spatial memory.¹² Thus, both depression and dementia are associated with inflammatory changes.

As there is pathological evidence that increased apoptosis occurs in both chronic depression and dementia, resulting in atrophic changes in the hippocampus, frontal cortex, and other brain regions,¹³⁻¹⁵ it has been speculated that the increase in inflammatory mediators, such as interleukin (IL)-1, TNF α , and prostaglandin E₂ (PGE₂), play a central role in the pathology of these conditions. The results of clinical and experimental research therefore lead to the conclusion that an increase in apoptosis caused by inflammation, together with a reduction in the synthesis of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) that assists in the repair of damaged neuronal networks, provide a basis for the pathological changes that are common to depression and dementia. The following reviews the evidence in favor of this hypothesis.

Changes in the hypothalamic-pituitary-adrenal axis in depression and dementia

Stressful life events trigger neurotransmitter changes in the brain via activation of the corticotropin-releasing factor (CRF) pathway that terminates not only within the hypothalamus and other parts of the central endocrine system, but also on the locus ceruleus and raphe nuclei.¹⁶

This provides a biological link between stressful stimuli and the changes in the endocrine, immune, and neurotransmitter systems that are involved in the psychopathology of depression (Figure 1).

Investigations of the role of the hypothalamic-pituitary-adrenal (HPA) axis in the psychopathology of depression commenced over 40 years ago, when it was reported that depressed patients have a higher circulating plasma cortisol concentration than those that are not depressed.^{18,19} At this time, the dexamethasone depression test (DST) was developed to provide a functional assessment of HPA axis activity. It was discovered that this synthetic glucocorticoid would normally suppress the secretion of cortisol by activating hypothalamic and pituitary glucocorticoid receptors, thereby suppressing the secretion of CRF and adrenocorticotropic hormone (ACTH) which, in turn, reduced the activation of the adrenal cortex and the release of cortisol. The mechanism whereby these changes occurred was explained in terms of a negative feedback loop whereby the raised plasma glucocorticoid

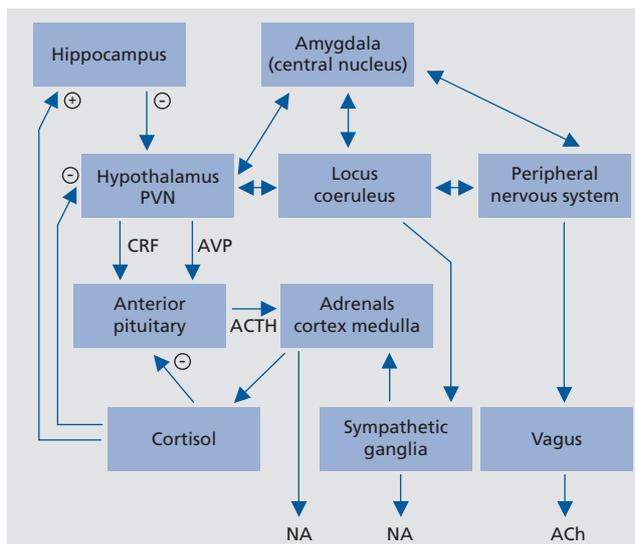


Figure 1. Relationship between stress, activation of limbic regions of the brain by CRF, and the consequent changes in the adrenal cortex and the sympathetic system. (+), activation, (-) inhibition. In chronic stress or depression, the feedback inhibitory loop malfunctions following the desensitization of the central glucocorticoid receptors in the brain and immune cells. This results in hypercortisolemia, a common feature of both major depression and Alzheimer's disease. Anxiety, a common comorbidity symptom with major depression, is associated with the increased activity of the central and peripheral sympathetic systems.¹⁷ CRF, corticotropin-releasing factor; NA, noradrenaline; AVP, arginine vasopressin; ACh, acetylcholine; ACTH, adrenocorticotropic hormone; PVN, paraventricular nucleus

concentration controls the further release of the steroid. However, it soon became apparent that in patients with major depression the negative feedback loop ceased to function due to the desensitization of the central glucocorticoid receptors. The negative DST thereby became a diagnostic marker of melancholic depression.²⁰

Nevertheless, it is now apparent that the DST lacks both specificity and sensitivity for depression,²¹ even though it may still offer reliability in the assessment of the severity of depression.²² Hypercortisolism and a negative DST are now known to occur in patients with Alzheimer's disease and alcoholism, for example.²³ Furthermore, it has been estimated that only 60% of patients with major depression demonstrate a negative DST. Nevertheless, these findings do serve to emphasize the importance of the HPA axis in psychiatric disorders.

It is frequently assumed that the synthetic glucocorticoids such as dexamethasone act on glucocorticoid receptors in an identical manner to the natural glucocorticoids such as cortisol. However, this may not be the case. Dexamethasone acts primarily on the glucocorticoid receptors in the anterior pituitary, does not readily enter the brain, and therefore differs substantially from natural glucocorticoids that activate both mineralocorticoid and glucocorticoid receptors.²⁴ There is also evidence that, while dexamethasone may reduce the release of CRF, it does not suppress the release of arginine vasopressin (AVP). There is evidence that AVP, not CRF, is the main activator of the HPA axis due to chronic stress and major depression.^{25,26} The increased action of AVP is further exacerbated by the action of IL-1 β ; chronically administered IL-1 β has been shown to cause a shift in the role of CRF to AVP in the activation of the anterior pituitary.²⁷ In addition, it has been shown that there is an age-related increase in the colocalization of AVP in CRF neurons in patients with major depression and dementia.²⁸ Thus, it seems reasonable to conclude that the hypersecretion of cortisol in patients with depression or dementia may at least be partly a consequence of an increased activation of the HPA axis by AVP. Additional evidence for the change in the functional activity of the pituitary gland is provided by the finding that the adrenals and the pituitary are enlarged in those with depression,^{29,30} these changes being associated with a hypersecretion of CRF.³¹ Furthermore, the density of the CRF receptors in the frontal cortex are reduced, presumably as a consequence of the hypersecretion of CRF.^{32,33} The hypersecretion of CRF would appear to be a state, rather than a trait, marker of depression.³⁴

If hypercortisolemia is a common feature of major depression and some types of dementia, it would be anticipated that immunosuppression would be a common feature of these conditions. However, it is apparent that both immunosuppression (for example, of natural killer cell [NKC] activity) and immune activation (for example, macrophage activation) are common features of depression. One possible explanation is that an increased vulnerability to environmental stress, which is a common feature of both depression and dementia,³⁵ elicits a bidirectional, homeostatic interaction between the endocrine and immune systems. Thus, CRF has been associated with humoral activation that results in an increased release of proinflammatory cytokines. By activating the HPA axis, proinflammatory cytokines not only further release CRF, but also lead to glucocorticoid resistance, thereby impairing the regulatory feedback mechanism. Conversely, the increase in the concentration of plasma cortisol, together with the increased sympathetic activity that is a normal feature of the stress response, suppresses NKC and T-cell replication. There is evidence that activation of the β -adrenoceptors on the NKC membrane, and which results in the decrease in activity of the NKCs, occurs independently of the activation of the HPA axis.³⁵ Clearly the interaction between the immune system and the HPA axis is both complex and interdependent.

In the past 20 years, attention has focused on changes in the hypothalamic-pituitary-adrenal axis, together with the biogenic amine neurotransmitters noradrenaline, serotonin, and, to a lesser extent, dopamine.^{36,37} More recently, however, it has become apparent that both major depression and chronic stress result in more persistent structural changes in the brain as a consequence of the decrease in the synthesis of neurotrophic factors, such as BDNF and the antiapoptotic factor bcl-2.³⁸ These changes are attributed to the chronic increase in brain glucocorticoids that arise due to the desensitization of central glucocorticoid type 2 receptors that occur as a consequence of the reduction in the inhibitory feedback mechanism.³⁹ Such effects contribute to the failure in brain repair mechanisms which is indicated by a reduction in dendritic branching and a decrease in neurogenesis, particularly in the hippocampus and, to some extent, in the frontal cortex.^{40,41} Such changes, together with an activation of the proinflammatory cytokines by chronic stress and depression, also enhance apoptosis through their indirect excitotoxic and metabolic actions.⁴² Thus stress-induced hypercortisolemia and proinflammatory

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cytokines share a final common pathway that leads to impaired neuronal plasticity and deficits in central neurotransmission.

The possible link between hypercortisolemia and depression is further provided by the changes induced by antidepressants and glucocorticoid receptor antagonists such as mifepristone.⁴³ Thus, preliminary clinical evidence has shown that the sensitization of the central glucocorticoid receptors by such treatments, that results in the re-establishment of the feedback inhibition of cortisol release, are correlated with the attenuation of the symptoms of depression.⁴⁴

Is there a link between depression and dementia? The clinical perspective

There is overwhelming evidence that inflammatory changes are an important causative factor in the pathology of Alzheimer's disease and related dementias.⁴⁵ The increase in β amyloid (Ab) is not only a major pathological feature of such dementias, but is also responsible for stimulating inflammatory responses in the brain. These changes include an increased expression of cell adhesion molecules and proinflammatory cytokines, and the activation of microglia in the brain parenchyma.⁴⁶ In vitro studies have also demonstrated that Ab induces IL-1b and IFN γ from vascular cells, thereby inducing a cascade of inflammatory changes.^{47,48} In addition, the infiltration of macrophages together with CD4+ and CD8+ T-cells, from the periphery have been detected in Ab deposits in cerebral vessels in patients with cerebral amyloid angiopathy.⁴⁹

The combination of Ab and proinflammatory cytokines is linked to the increase in apoptosis in the brains of patients with dementia.⁵⁰ For example, there is evidence that lymphocytes show a significant increase in DNA fragmentation in Alzheimer patients when compared with aged, but normal, controls.⁵¹ This change has been linked to an increase in the intracellular concentration of calcium ions, a prerequisite for apoptosis⁵² that has not been recorded in lymphocytes from aged control subjects. Furthermore, apoptotic cell death is preceded by the expression of apoptosis-associated molecules such as p53, Fas (CD95/APO-1) and IL-1b converting enzyme. Whereas the normal brain is partly immunologically privileged, in patients with inflammatory diseases such as multiple sclerosis, stroke, Alzheimer's disease, and possibly major depression, Fas is widely expressed in the

brain.⁵³ This apoptotic protein is expressed on CD4+ and CD8+ T-cells and on NKCs. Such observations provide a further link between the inflammatory changes in the brain and increased apoptosis that precludes dementia.

Despite these convincing observations regarding the inflammatory changes in patients with Alzheimer's disease, it is somewhat surprising to find that IL-6, a major proinflammatory cytokine that is elevated in the plasma and cerebrospinal fluid (CSF) of patients with major depression, has been reported to be unchanged⁵⁴ or even decreased^{55,56} in the blood of Alzheimer's patients. Some investigators have, however, reported that IL-6 is increased in these patients.⁵⁷ Some of these differences may be accounted for by the methods used to assay IL-6. Thus the concentration of IL-6 in the serum and CSF is often at the limit of detection, while in in-vitro studies, in which stimulated lymphocytes are isolated by gradient centrifugation, the cells are stressed which may alter their phenotype.

It has also been argued that the decrease in proinflammatory cytokines in Alzheimer's disease is a consequence of the hypercortisolemia⁵⁵ although this would not explain why cytokines such as IL-6 remain elevated in depressed patients where hypercortisolemia also commonly occurs.

The cognitive changes and dysphoria that are common symptoms in the early stages of Alzheimer's disease have been correlated with the increase in proinflammatory cytokines such as IFN α .⁶ Despite the equivocal evidence regarding the rise in plasma IL-6 concentration in Alzheimer patients, there are reports that the IL-6 concentration correlates with the severity of dementia.⁵⁸ From the numerous studies of the changes in the immune system of patients with dementias, it would appear that the inflammatory changes can trigger an increased synthesis and accumulation of Ab.⁵⁹ The accumulation of Ab then initiates a further cascade of inflammatory changes in the brain involving proinflammatory cytokines and neurotoxic free radicals such as nitric oxide (NO)⁶⁰; this involves the activation of the NF κ B pathway and the complement system. Neuronal COX 2 expression is also increased in Alzheimer's disease, and the resulting increase in PGE₂ contributes to the subsequent deterioration in the clinical state of the patient.⁶¹ In addition, the rise in IL-1 β may also indirectly contribute to the cognitive deficit by inhibiting cholinergic function⁶²; a deficit in acetylcholine is generally accepted as the primary neurotransmitter that is causally involved in the cognitive and memory deficits in the dementias.⁴⁴

The question arises as to whether the increase in Ab is a reflection of the rise in proinflammatory cytokines, an important consideration if major depression predisposes to dementia. In support of this connection, there is evidence that severe head trauma in young persons can result in a large number of amyloid plaques shortly after the traumatic event.⁶³ The accumulation of Ab was shown to occur secondarily to the stress induced activation of the microglia that precipitate the release of IL-1; the Ab formed then stimulated the “cytokine cascade,” a key element in the pathogenesis of dementia.⁶⁴

Further evidence in support of the hypothesis linking the outcome of chronic depression with dementia comes from studies on the progression of an HIV infection to AIDS. It is well known that severe life stress, and bereavement of a partner with AIDS, is associated with a rapid progression of HIV to AIDS and a consequent increase in mortality.⁶⁵ For example, it has been reported that changes in immune function, such as a reduction in NK cells, correlates with the incidence of depression and the progressive deterioration in the clinical status of the patients with HIV/AIDS^{10,66,67} although not all investigators have found such an association.⁶⁸ Nevertheless, such studies do provide possible support for the hypothesis that impaired immune function associated with the symptoms of depression may act not only in the progression of an AIDS infection but also to the onset of AIDS dementia in those patients who do not die as a consequence of secondary infections or cancer.

Changes in proinflammatory cytokines in depression and dementia

Evidence implicating a role for the proinflammatory cytokines in the etiology of depression has been provided by studies on the changes in IL-1, IL-6, and TNF α in depressed patients and also by the effects of IFN α on psychiatrically normal individuals being treated for hepatitis or a malignancy. Such studies have implicated these cytokines as causative factors in the symptoms of major depression. These symptoms include depressed mood, anxiety, cognitive impairment, lack of motivation, loss of libido, sleep disturbance, and deficits in short-term memory. Such symptoms usually disappear once the plasma cytokine concentrations return to normal.⁶⁹ These changes appear to be a consequence of the neurotransmitter and endocrine changes induced by the cytokines, rather than the pathological condition for which the treatment has

been administered.^{70,71} It is perhaps not surprising therefore to find that the symptoms of depression frequently occur in patients recovering from a chronic infection, those with multiple sclerosis,⁷² allergies,⁷³ and rheumatoid arthritis.⁷⁴ In all these situations, proinflammatory cytokines are known to be overexpressed⁷⁵ The initial studies linking depression with an abnormality of the immune system,⁷⁶ impaired mitogen-stimulated lymphocyte proliferation,⁷⁷ and reduced NK cell activity⁷⁸ in untreated depressed patients, showed changes that largely returned to normal once the patient recovered from the depressive episode. Recent research into the immune changes occurring in depression has concentrated on cytokines, soluble cytokine receptors, and plasma acute-phase proteins. For example, positive acute-phase proteins have been shown to increase while the negative acute-phase proteins decreased in depression, changes that are known to be a consequence of the action of IL-6 on liver function.⁷⁹ In addition, complement proteins (C3,C4) and immunoglobulin M are increased in depressed patients. Such changes are evidence of immune activation involving both the inflammatory cytokines and B-cells that are activated by the proinflammatory cytokines. Further evidence of immune activation in depressed patients is provided by the studies showing that the plasma concentration of IL-1, IL-6, IFN γ , soluble IL-6 and IL-2 receptors, and the IL-1 receptor antagonist, are raised. These changes are correlated with a rise in plasma acute-phase proteins.⁸⁰ Effective antidepressant treatments largely attenuate such immune changes. In addition to the increases in proinflammatory cytokines, 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 the plasma cytokines.⁸¹⁻⁸³ From these changes, it would appear that in depression there is an imbalance between the inflammatory and the anti-inflammatory arms of the immune system, the cytokines from the T1 pathway (such as IFN γ) becoming predominant over those of the anti-inflammatory T2 (for example, IL-4) pathway. A recent study has shown that the T3 cytokine, transforming growth factor b1 (TGF β 1) whose function is to re-establish the balance between the T1 and T2 pathways, is increased in depressed patients following effective antidepressant treatment.⁸⁴ Though TGF β 1 is reported as a regulatory cytokine that keeps the balance between Th1 and Th2 cytokines,⁸⁵ precisely how the increases in the proinflammatory cytokines are attenuated by TGF β 1 in depressed patients is unclear.

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The role of the microglia in inflammatory changes in the brain

Localized inflammatory responses in the brain parenchyma have been associated with the pathogenesis of a number of neurological disorders including Alzheimer's disease and Parkinson's disease.^{86,87} At these lesion sites, activated microglia release such inflammatory mediators as TNF α and PGE₂.⁸⁸ It is well-known that PGE₂ is an important mediator of inflammation. In-vitro evidence shows that PGE₂ secretion from lymphocytes of depressed patients is increased,⁸⁹ as is the PGE₂ content of the saliva, serum, and CSF of such patients.^{90,91} Of the proinflammatory cytokines, IL-6 appears to play a key role in the synthesis of this prostaglandin both in vitro and in vivo.^{92,93} Conversely, different types of antidepressants have been shown to inhibit the secretion of proinflammatory cytokines and to reduce the synthesis of PGE₂.⁹⁴⁻⁹⁶ This raises the interesting possibility that the reduction in proinflammatory cytokines and inflammatory mediators such as PGE₂ in the brain may be associated with the therapeutic actions of antidepressants.¹⁷ As it appears that the proinflammatory cytokines increase the inducible form of cyclo-oxygenase (COX2) in the brain, it would be expected that COX2 inhibitors would not only attenuate the central inflammatory changes but also exert an antidepressant effect. There is some clinical evidence to support this view. Thus, rofecoxib, when administered to a large group of patients suffering from osteoarthritis, was found to reduce the symptoms of those who were suffering from comorbid depression; 15% of the patients had depression at the start of the study, which decreased to 3% at the end of the period of treatment.⁹⁷ Other clinical studies have suggested that the COX2 inhibitor celecoxib has positive effects on cognitive function in depressed patients.⁹⁷ It should be noted that celecoxib has also been shown to have beneficial effects as an "add-on" component to clozapine in the treatment of schizophrenia in patients who are only partially responding to the antipsychotic medication.^{98,99} There are several mechanisms that are postulated to be involved in the etiology of depression. It is commonly assumed that a decrease in both the noradrenergic and serotonergic functions are causally related to the changes in the mood, motivation, and cognitive changes associated with the disorder. There is now experimental evidence to show that the inhibition of COX2 is associated with a rise in the synthesis of serotonin in the cortex of the rat brain.¹⁰⁰ In addition, PGE₂ has been

shown to reduce the release of noradrenaline from central noradrenergic neurons, an effect that would be blocked by the COX2 inhibitors. Thus inhibition of COX2 activity in the brain contributes not only to the reduction in inflammatory changes but also to an enhancement of biogenic amine function. PGE₂ is probably one of the most potent inflammatory mediators in terms of the initiation and propagation of inflammation within the brain.¹⁰¹ Both clinical^{90,102} and experimental studies have shown that there is an increase in the tissue concentrations of PGE₂ in depression and in an animal model of depression.⁸⁹ In the brain, the microglia act as macrophages. On activation, they release proinflammatory cytokines, PGE₂, and neurotoxic metabolites of the kynurenine pathway.¹⁰³ Recent experimental evidence has shown that lipopolysaccharide (LPS), an activator of macrophage activity and a cause of brain inflammation, induces mitochondrial PGE₂ synthase and COX2 activity in activated microglia, thereby increasing the synthesis of PGE₂ at sites of inflammation in the brain.¹⁰⁴ This provides a possible mechanism to explain the inflammatory changes in patients with depression or dementia; changes that contribute to neurodegeneration. Nitric oxide (NO) can also act as an inflammatory mediator that contributes to neurodegeneration,¹⁰⁵ and is raised in the plasma of depressed patients.¹⁰⁶ NO is produced by both the constitutive and inducible forms of NO synthase (NOS) that are associated with neurons and microglia.¹⁰⁷⁻¹⁰⁹ Recent evidence suggests that proinflammatory cytokines activate inducible NOS, thereby increasing NO; apoptosis results from the nitrosylation of deoxyribonucleic acid (DNA).¹¹⁰ The increase in peripheral and central macrophage activity associated with the inflammatory changes initiate, via the activated microglia, increases in PGE₂ and NO that further potentiate the inflammatory changes (*Figure 2*). Thus in both depression and dementia, PGE₂, NO, and neurotoxic metabolites from the kynurenine pathway appear to play an important role central inflammatory processes that contribute to neurodegeneration.

Neurodegeneration and the role of neurotoxic metabolites of the tryptophan pathway

The depletion of tryptophan from the diet results in a reduction in serotonin in the brain that correlates with the onset of a depressed mood state.¹¹¹ Tryptophan is metabolized by two main pathways, by tryptophan

hydroxylase leading to the synthesis of serotonin in the brain and by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) resulting in the formation of kynurenine.^{112,113} It has been hypothesized that in depression the metabolism of tryptophan by IDO and TDO is increased, thereby reducing the availability of the amino acid to synthesize serotonin.¹⁰³ TDO is located in the liver, while IDO is found in the lungs, placenta, blood and brain.^{72,114} The activity of TDO is increased by tryptophan and by cortisol. As hypercortisolemia frequently occurs in both depression and dementia, it would be anticipated that TDO is overactive in patients with these disorders. By contrast, IDO activity is increased by proinflammatory cytokines such as IL-6 and IFN γ , and inhibited by anti-inflammatory cytokines such as IL-4.^{115,116} Thus the activities of both TDO and IDO are likely to be increased in depression and dementia as a consequence of the rise in circulating cortisol and the proinflammatory cytokines. There are two main stages in the metabolism of tryptophan following the actions of the dioxygenases.¹¹⁷ Following the conversion of tryptophan to kynurenine by IDO or TDO, kynurenine is metabolized by kynurenine hydroxylase to the neurotoxic metabolites 3-hydroxykynurenine, 3-hydroxy-anthranilic acid, and quinolinic acid. An alternative pathway involves the conversion of

kynurenine to 3-hydroxyanthranilic acid by kynureninase. These form the neurodegenerative arm of the tryptophan-kynurenine pathway.

Alternatively, kynurenine may be metabolized by kynurenine aminotransferase to the neuroprotective end product kynurenic acid.¹¹⁸ The mechanisms whereby quinolinic and kynurenic acids act as neurotoxic and neuroprotective agents respectively is related to their activation or inhibition of the *N*-methyl-D-aspartate (NMDA) receptor, quinolinic acid and 3-hydroxyanthranilic acids being agonists of the NMDA receptor while kynurenic acid is an antagonist.^{119,120} It has also been hypothesized that the imbalance between those NMDA receptor antagonist and agonist are involved in the pathophysiology of chronic or treatment-resistant depression.¹⁰⁴ In the brain, the metabolism of tryptophan by the enzymes of the kynurenine pathway occurs in both astrocytes and microglia^{121,122} the former producing mainly kynurenic acid while the latter produces the neurotoxic end products 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid.¹²³ Astrocytes have been shown to metabolize quinolinic acid and thereby reduce the neurotoxic impact that may arise following microglia activation. From the foregoing evidence, it can be hypothesized that inflammatory changes in both depression and dementia involve the activation of microglia and an increase in the inflammatory challenge to the brain. Such changes also occur in patients with hepatitis who have been treated with the proinflammatory cytokine IFN α and who developed depressive symptoms as a side effect of the treatment. In these patients, it has been shown that the plasma kynurenic acid concentration was reduced, thereby suggesting that the neurodegenerative metabolites were increased.¹²⁴ More recently we have shown that similar changes occur in the blood of patients with major depression.¹²⁵ The results of this study also showed that therapeutically effective antidepressant treatment increased the neuroprotective kynurenic acid in the blood in those patients suffering from an acute episode of depression, but not in those with chronic depression. These changes occurred irrespective of the clinical improvement in the symptoms of the patients. This suggests that the progress to dementia may increase as the depression becomes more chronic. In patients with major depression, shrinkage of the hippocampus,^{126,127} a decrease in the number of astrocytes and a neuronal loss from the prefrontal cortex,^{41,128,129} and the striatum¹³⁰ have been reported. Such findings support the view that neurodegenerative changes

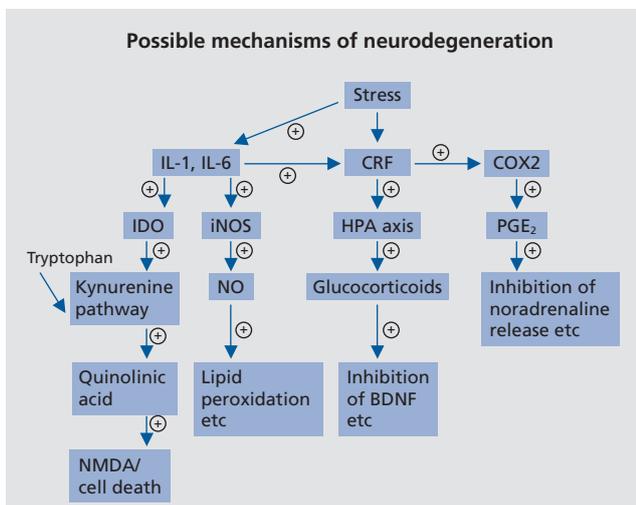


Figure 2. Relationship between the main neurodegenerative pathways in the brain and depression. (+) Pathways that are increased in depression, and probably dementia.^{89,101,103,105,107} IDO, indoleamine 2,3-dioxygenase; iNOS, inducible nitric oxide synthase; CRF, corticotropin-releasing factor; COX 2, inducible cyclo-oxygenase 2; PGE₂, prostaglandin E₂; HPA, hypothalamic-pituitary-adrenal; NO, nitrous oxide; IL, interleukin; NOS, nitrous oxide synthase; BDNF, brain-derived neurotrophic factor

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occur in several discrete regions of the brain in patients suffering from chronic depression. Furthermore, as the astrocytes are a major source of kynurenic acid, apoptosis of these cells would result in a reduction in the neuroprotective effect of kynurenic acid. There is evidence that in the astrocytes the kynurenine pathway is limited due to the absence of kynurenine hydroxylase. As a consequence, astrocytes only produce a very low concentration of the neurotoxin quinolinic acid and a relatively high concentration of the neuroprotective agent kynurenic acid.¹¹³ Furthermore, in astrocytes IDO is preferentially induced by IFN γ , a cytokine that also induces the catabolism of quinolinic acid.¹¹³ However, it is also apparent that the increase in the synthesis of kynurenine by the astrocytes can indirectly contribute to the formation of quinolinic acid by the microglia. This situation would be compounded by the increased activation of the microglia by the proinflammatory cytokines with the consequent rise in the concentration of the inflammatory mediators PGE₂ and NO. *Figure 3* summarizes the pathways involved in the metabolism of tryptophan by the kynurenine pathway and the relationship with inflammatory cytokines in depression.

The inhibition of neuronal repair mechanisms resulting from the reduction in neurotrophic factors that follow the rise in blood and tissue cortisol,¹³¹ apoptosis of astrocytes which are the sources of several neurotrophic factors,¹³² and the possible disruption of the phospholipase

D pathway that has antiapoptotic properties and is involved in neurite formation and repair,¹³³ further contribute to the neuronal loss. Another association between depression and dementia is through this IDO initiated kynurenine pathway related neurotoxicity. An immunohistochemical study has proven that the immunoreactivity of IDO and quinolinic acid are high in the hippocampus of Alzheimer's disease patients.¹³⁴

So far, emphasis has been placed on the role of inflammatory mediators and neurotoxins produced by the kynurenine pathway on the possible causes of the neurodegenerative changes in the brain that eventually develops into dementia. Recently, experimental evidence has shown that transgenic mice that overexpress human tau protein (a prominent feature of different types of dementia) show depressive-like behavior in the Forced Swim Test. This test is widely used to predict antidepressant activity, and is based on the observation that when rodents are placed in a container of warm water from which they cannot escape, they soon adopt an immobile posture. This is assumed to reflect a state of "learned helplessness" that reflects a depressive-like state.¹³⁵ This behavioral state was reversed by the administration of the selective serotonin reuptake inhibitor antidepressant fluvoxamine. In-vivo microdialysis studies showed that the release of serotonin from the prefrontal cortex was reduced in the transgenic mice, an effect that was reversed by the fluvoxamine treatment. The results of this study suggest that transgenic mice overexpressing human tau protein show symptoms of depressive-like behavior that are associated with a reduction in serotonergic function. As the behavioral and neurotransmitter changes are reversed by a selective serotonin reuptake inhibitor (SSRI) antidepressant, it would appear that serotonin may provide a link between the pathological effects of tau protein and the subsequent depressive-like state. It would be incautious to extrapolate from this subchronic study in a transgenic mouse to the complex clinical situation in which multiple pathological changes contribute to the onset of dementia. Nevertheless, the experimental studies do provide evidence in support of the hypothesis that the long-term outcome of chronic depression is often dementia. Further evidence for this hypothesis comes from the study by Steffens et al⁴ who demonstrated a link between late-onset depression and the rise in plasma apolipoprotein E4 which is widely considered to be a risk factor for late-onset Alzheimer's disease. *Figure 4* summarizes the possible pathways leading from depression to dementia.

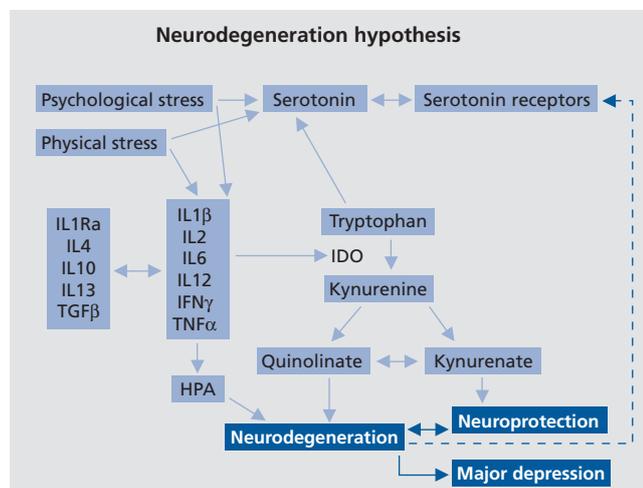


Figure 3. Outline of the kynurenine pathway, and its induction by proinflammatory cytokines, that results in the accumulation of the major neurotoxic metabolite, quinolinic acid.^{103,107,113} IL, interleukin; TGF, transforming growth factor; IFN, interferon; IDO, indoleamine 2,3 dioxxygenase; HPA, hypothalamic-pituitary-adrenal

Conclusion

Neuronal loss is a common feature of major depression and dementia. The progress of major depression to dementia could result from the chronic inflammatory changes that are linked to the activation of the microglia. The activation of inducible COX2 and NOS by the proinflammatory cytokines further increases the inflammatory challenge to the brain. As there is evidence that the kynurenine pathway is also activated by proinflammatory cytokines, it seems likely that the concentrations of the neurotoxins 3-hydroxykynurenine, 3-hydroxyanthranilic acids, and quinolinic acid will also increase as a result of the activation of the microglia. The increased apoptosis of the astrocytes, with a reduction in the availability of the neuroprotective agent kynurenic acid, further adds to the impact of the neurodegenerative changes. Hypercortisolemia, a common feature of both dementia and major depression, and apoptosis of astrocytes decreases the synthesis of neurotrophic factors thereby reducing neuronal repair. This process may be further enhanced by the disruption of the phospholipase D pathway that normally plays an important role in neurite formation and neuronal repair. This hypothesis may assist in explaining the degenerative changes in the hippocampus and other brain regions that are the features of chronic major depression. It may also explain why chronic depression is frequently a prelude to dementia in the elderly patient. □

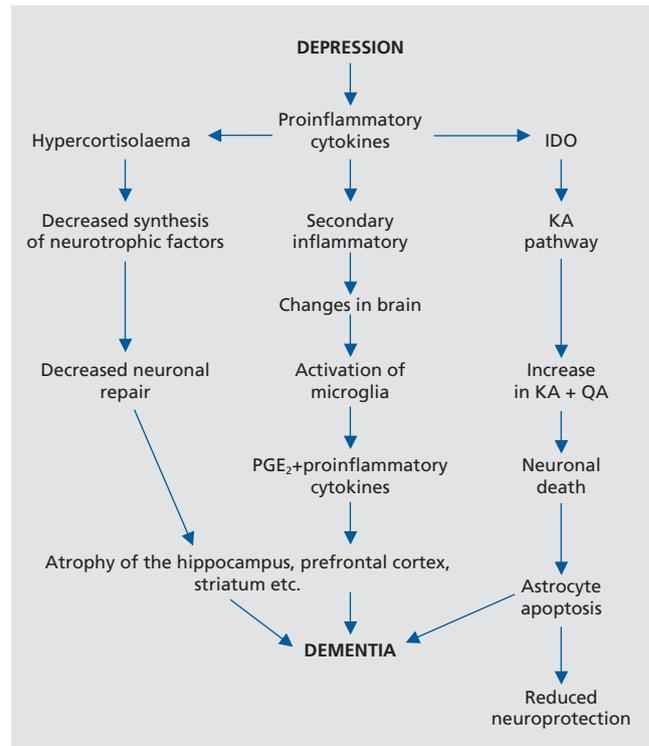


Figure 4. Theoretical pathway linking chronic depression to dementia. PGE₂, prostaglandin E₂; IDO, indoleamine 2,3 dioxigenase; KA, kynurenic acid; QA, quinolinic acid

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Basic research

Cambios del sistema inmune en la depresión y la demencia: ¿efectos causales o coincidencias?

Los estudios epidemiológicos demuestran que existe una correlación entre la depresión crónica y la probabilidad de desarrollar una demencia. Hay evidencias que los cambios inflamatorios en el cerebro constituyen características patológicas tanto de la depresión como de la demencia. Esto sugiere que un aumento en la apoptosis inducida por la inflamación, junto con una reducción en la síntesis de factores neurotróficos causada por un aumento en los glucocorticoides cerebrales, puede tener un papel en la patología de estos trastornos. Una reducción en los componentes neuroprotectores de la vía de la kinurenina, como es el ácido kinurénico, y un aumento en los componentes neurodegenerativos, el ácido quinolínico y la 3-hidroxikinurenina, contribuyen a los cambios patológicos. Se postula que tales cambios causan daño neuronal y de esa manera predisponen a los pacientes con depresiones crónicas a la demencia.

Modifications du système immunitaire dans la dépression et la démence : cause ou coïncidence ?

Des études épidémiologiques montrent qu'il existe une corrélation entre la dépression chronique et la probabilité d'une démence ultérieure. Il est prouvé que certaines modifications cérébrales de type inflammatoire sont des manifestations pathologiques à la fois de dépression et de démence. Ce qui suggère qu'une augmentation de l'apoptose provoquée par l'inflammation, accompagnée d'une réduction de la synthèse de facteurs neurotrophiques causée par une élévation des glucocorticoides cérébraux, puisse jouer un rôle dans la pathologie de ces troubles. Les modifications pathologiques sont dues à une réduction des composés neuroprotecteurs de la voie de la kynurénine, tels que l'acide kynurénique, et à une augmentation des composés neurodégénératifs, les acides 3-hydroxykynurénine et quinolinique. De tels changements sont pressentis comme étant la cause d'altérations neuronales, et prédisposent donc les déprimés chroniques à la démence.

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