

Inflammation and its relevance to psychiatry

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Abstract Depression is increasingly recognised as a major public health problem worldwide. The heterogeneity of this condition implies that there may be several neurobiological pathways to depression. This article attempts to explore a pathway that links depression with the inflammatory response. Associations linking inflammation and chronic immune activation with depression have been noted, particularly in the context of (a) medical disorders with inflammatory pathophysiology and (b) immunotherapy for cancer and hepatitis C. Acute coronary syndrome is given as an example of how the inflammatory process might result in depression, and potential mechanisms are discussed. These include: direct action of pro-inflammatory cytokines on the serotonin system, with specific reference to the serotonin transporter; action of cytokines on the hypothalamic–pituitary–adrenal axis; and effects of pro-inflammatory cytokines on neurogenesis in the hippocampus. Reference is made to the potential anti-inflammatory effects of antidepressant drugs and antidepressant effects of anti-inflammatory treatments.

Depression is currently seen as a major problem, with the World Health Organization (2001) predicting that by 2010 depression will be the second most common cause of morbidity worldwide. Forging a greater understanding of the pathophysiology of this destructive affliction is therefore a greater priority than ever. There is an increasing recognition of the heterogeneity of depression, and a consequent realisation that there may be several neurobiological pathways leading to the disorder. This article explores one of these, namely the link between depression and inflammatory processes. We have used references sparingly, but would be happy to provide a full list on request.

This link has its origins in the analogy between sickness behaviour and depression noted and studied by Yirmiya (2000) and the macrophage theory of depression developed by Maes (1995). These two lines of enquiry stimulated research that found associations between chronic immune activation and depression, including: medical disorders with an inflammatory pathophysiology; immunotherapy for cancer and hepatitis C; and ageing.

By the same token, it has been reported more recently that other risk factors for depression, including psychosocial stress, psychological trauma, sleep disturbance and pain, all increase inflammatory processes.

Depression in the medically ill

It is estimated that depression in people with medical illnesses is 5–10 times more common than in the general population (Yirmiya, 2000). Well-recognised examples are disorders such as cardiovascular disease (see below), rheumatoid arthritis and multiple sclerosis. Studies have specifically reported a higher incidence of depression in illnesses associated with inflammatory processes than in those associated with non-inflammatory processes but equal disability. There is also evidence that in some systemic inflammatory diseases there exists a positive correlation between disease activity and depressive episodes.

Elevated levels of pro-inflammatory cytokines have been proposed as a possible physiological link between depression and a variety of serious medical conditions such as those described, where inflammation plays a key role in the disease process and which are strongly associated with depression. Pre-clinical studies have also suggested that psychological stress induces pro-inflammatory cytokine expression in regions of the brain associated with emotional regulation. Patients with depression have shown exaggerated activation of inflammatory response – specifically IL-6 and NF- κ B (see Box 1 for acronyms) – following acute psychological stress.

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Box 1 Acronyms used in immunology

CAM	Cell adhesion molecule
CRH	Corticotrophin-releasing hormone
IL	Interleukin
IFN	Interferon
JNK	c-Jun N-terminal kinase
NF	Nuclear factor
NK	Natural killer
MAPK	Mitogen-activated protein kinase
sICAM	Soluble intercellular adhesion molecule
STAT5	Signal transducer and transcriptional activator 5
TNF	Tumour necrosis factor

The evidence for a link between depression and inflammatory processes is further supported by the fact that pro-inflammatory cytokines (notably IL-2, IL-6, IL-1 β and TNF- α) are elevated not only in medically ill patients with depression but also in medically healthy but depressed patients. The degree of elevation of certain pro-inflammatory cytokines has also been shown to correlate with the severity of depressive illness. Further evidence has suggested that activation of the systemic inflammatory process (as measured by systemic C-reactive protein) may contribute to the pathophysiology of depression.

Cardiovascular disease and depression

Although recognised for many years, there is a current upsurge in interest in the relationship between depression and cardiovascular disease. To date, over 100 studies have investigated the relationship between major depressive disorder and cardiovascular disease, providing evidence that major depressive disorder has a prevalence of between 20 and 35% in the year following an acute coronary syndrome (myocardial infarction or acute unstable angina) (Rumsfeld & Ho, 2005). There is compelling evidence that major depressive disorder is predictive both of development of cardiovascular disease and of adverse outcomes in those who already have the disease.

Cardiac death

The most worrying feature of all is the relationship between depression and fatal outcome in patients after an acute coronary syndrome. Most studies have found fairly consistent results, with an adjusted risk of death in the 6 months following myocardial

infarction around 4 times higher in depressed than non-depressed patients (Frasure-Smith *et al*, 1993). Indeed, it is argued that the increased mortality associated with major depressive disorder after an acute coronary syndrome is equal to or greater than any other predictor of risk (Welin *et al*, 2000). Again, hospitalisation for depression was shown to be a risk factor for myocardial infarction, after adjustments for lifestyle, lipid profile, coagulation, inflammation, prior cardiovascular events and comorbidity.

Even mild depressive symptoms are associated with greater risk of cardiac death, and the risk increases with the severity of the depression. Depressive symptoms have also been shown to be a stronger predictor of poor functional improvement than variables such as previous myocardial infarction, diabetes and left ventricular ejection fraction. The most recent data have shown that around 50% of patients with major depressive disorder after acute coronary syndrome have a history of depression apparently unrelated to their cardiovascular disease and about 50% have their first ever episode of major depressive disorder immediately following acute coronary syndrome (Glassman *et al*, 2006).

De Jonge *et al* (2006) report that only patients with an 'incident' depression, i.e. no history of depression prior to their acute coronary syndrome, have an impaired cardiovascular prognosis. These findings are similar to those reported by Grace *et al* (2005). In such incident depression the pathophysiological processes involved in the syndrome itself may be integral to the depression.

Atherosclerosis

One putative link between inflammatory cytokines and cardiovascular disease is the role of inflammation in the development of atherosclerosis. It is now well established that inflammatory phenomena at the site of atherosclerotic plaques are major determinants of the progression and clinical outcome of atherosclerotic disease. This suggests that increased activation of the immune system (including the form seen in depression) predisposes to atherosclerosis.

Moreover, inflammation is a key part of the development and progression of atherosclerosis, which have been linked to both local and systemic release of cytokines (e.g. IL-6), related acute-phase reactants (e.g. C-reactive protein) and the expression and endothelial shedding of cell adhesion molecules (Lespérance *et al*, 2004). This systemic pattern of immune activation is common in people with coronary heart disease and is especially active at the time of an acute coronary episode. These markers of inflammation predict not only the development of an acute coronary syndrome but also a worse prognosis following such an event. People with major depressive disorder show patterns of

inflammatory activation similar to those seen in cardiovascular disease (Anisman & Merali, 2002). The most consistent pattern of change observed in major depressive disorder is an elevation in the pro-inflammatory cytokines IL-1 β , IL-2, IL-6 and TNF- α (Zorrilla *et al*, 2001).

Changes in endothelial function also appear to accompany major depressive disorder and there is growing evidence that acute-phase proteins and soluble adhesion markers are raised in major depression without cardiac disease. Increases in soluble intercellular adhesion molecules such as sICAM-1 have been linked to deterioration in the blood–brain barrier, thus allowing large molecules such as cytokines access to the brain.

Results from a prospective cohort study demonstrated significant interaction between C-reactive protein and depression, such that moderately increased C-reactive protein in depressed men was predictive of a subsequent first coronary event (Ladwig *et al*, 2005). Another prospective epidemiological study (Empana *et al*, 2005) found that depression, IL-6 and sICAM-1 were associated with the incidence of cardiac events. Frasure-Smith *et al* (2007) assessed men 2 months after acute coronary syndrome and found that depression and C-reactive protein were overlapping prognostic risks.

Taken together, these findings point to an association between inflammation and major depressive disorder (Box 2). Although correlation does not mean causation, such systemic inflammation at the time of and following an acute coronary event might conceivably facilitate the onset of major depressive disorder.

Immunotherapy and depression

The example of interferon treatment for hepatitis C

It has been noted that administration of alpha interferon commonly causes depressive symptoms as a side-effect, and in 30–45% of patients it causes a diagnosable depressive illness (Raison *et al*, 2006). A higher rate of psychiatric illness exists in patients with hepatitis C than in the general population, but development of neuropsychiatric symptoms on initiation of interferon treatment in those with no psychiatric history has been documented. Alternative mechanisms have been postulated, including interferon's side-effects mimicking the symptoms of depression, and direct neurotoxicity of the hepatitis C virus. However, interferon treatment is used for other diseases, including malignant melanoma, and similar neuropsychiatric side-effects are observed.

Box 2 Cardiovascular disease and depression

- Increased mortality is associated with major depressive disorder which has onset after an acute coronary event
- Depression is associated with increased risk of coronary death
- Inflammatory action and changes in endothelial action in major depressive disorder seem to be similar to those in cardiovascular disease

Thus, where a pro-inflammatory cytokine is administered to treat a disease it appears to directly cause a depressive illness in a significant proportion of those treated.

Mechanisms underpinning inflammation and depression

A number of mechanisms have been suggested to explain the link between inflammation and depression (Box 3).

Direct action of cytokines on the brain

The neuropsychiatric side-effects experienced when cytokines are exogenously administered to treat illnesses such as hepatitis C provide evidence that cytokines can directly affect the brain (Raison *et al*, 2006). The raised pro-inflammatory cytokine

Box 3 Potential mechanisms underpinning inflammation and depression

- Raised pro-inflammatory cytokine levels in depression act directly on the hypothalamus and amygdala
- Depression induces immunosuppression through raised corticotrophin-releasing hormone in the central nervous system and reduced natural killer cell response
- Pro-inflammatory cytokines can activate the HPA axis, and persistently high levels result in raised cortisol levels
- In treatment with alpha interferon, reduced serotonin synthesis may reduce synaptic serotonin levels
- Serotonin transporter activity is increased by certain pro-inflammatory cytokines thus reducing overall serotonergic tone

profile observed in depression suggests that the raised cytokine levels may be producing depressive symptoms by exerting a direct effect on the brain.

Pro-inflammatory cytokines have been shown to exert multiple behavioural effects, including depressed appetite and weight loss, sleep disturbance, motor retardation, cognitive impairment and anhedonia. It is hypothesised that these are mediated by the direct actions of cytokines on the hypothalamus. Similarly, treatments involving administration of pro-inflammatory cytokines (e.g. IL-2, IFN- α and TNF- α) are also associated with anhedonia and cognitive impairment (Schiepers *et al*, 2005).

More recently, pre-clinical work has identified that following myocardial infarction, rats showed increased apoptosis in the amygdala. Further experiments demonstrated that this increase did not occur if a cytokine synthesis inhibitor was administered after the infarction was induced. This lends support to the hypothesis that changes in the brain due to physical illness are mediated by pro-inflammatory cytokines (Wann *et al*, 2007).

Effects on the immune system

Usually, inhibitory elements such as glucocorticoids and anti-inflammatory cytokines limit the activation of the immune system to levels that are appropriate for clearing the initial antigenic stimulus. However, in certain conditions these inhibitory feedback loops become impaired, allowing chronic immune activation and persistence of sickness symptoms. Depression may correspond to one of these conditions where inhibitory loops are altered and neuroendocrine and immune systems become persistently activated.

Depression is associated with elevated levels of corticotrophin-releasing hormone (CRH) in the central nervous system (CNS). It has been shown that raised levels can decrease natural killer cell activity. This appears to be due to central, as opposed to adrenal, CRH receptor mechanisms. *In vitro* studies have suggested that central doses of CRH can decrease both cellular and humoral immune responses. This therefore illustrates one possible mechanism by which depression can induce the immunosuppression.

Other findings have shown increased levels of circulating catecholamines and neuropeptide Y in people with depression. This seems to have a strong predictive value regarding decline of natural killer cell response.

More recent research in this field was performed in the context of depression induced by alpha interferon. It was shown that mood and cognitive symptoms were highly responsive to pre-treatment with paroxetine, whereas the neurovegetative syndrome

(depressed appetite, sleep disturbance, motor retardation) did not respond to antidepressants (Capuron *et al*, 2002a). This suggests that there may be different pathophysiological mechanisms causing the affective and cognitive symptoms compared with the effects on the immune system.

Cytokines and the HPA axis

Some patients with depression exhibit hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, characterised by hypercortisolaemia. Pro-inflammatory cytokines are activators of the HPA axis, and there is evidence that persistently raised pro-inflammatory cytokine levels counteract the normal negative feedback loop whereby raised corticosteroid levels would reduce HPA axis activity. Raised cortisol levels are also associated with increased anxiety and fear behaviour, and with decreased ability to manage social stress (Burke *et al*, 2005).

A consistent finding is the capacity of cytokines that mediate innate immune responses (e.g. IFN- α , IL-1, IL-6, TNF- α) to increase the release of CRH.

Increased CRH is a reliable finding in major depressive disorder, as evidenced by increased cerebrospinal fluid concentrations of the hormone and increased CRH mRNA and protein in post-mortem studies of the hypothalamus of individuals who had had major depression.

It has further been suggested that cytokine-induced activation of the HPA axis may represent a risk factor for depression.

Lastly, inflammatory cytokines have been shown to alter nearly all aspects of glucocorticoid receptor functioning, and the signal transduction pathways by which cytokines affect glucocorticoid receptors include NF- κ B, p38-MAPK, JNK and STAT5.

Effect on tryptophan metabolism

Recent research suggests that alpha interferon may exert its effects by altering tryptophan metabolism (Wichers *et al*, 2005). Alpha interferon induces indoleamine 2,3-dioxygenase (IDO), an enzyme involved in tryptophan (TRP) metabolism. This is the rate-limiting enzyme in the L-TRP–kynurenine pathway that converts L-TRP (a precursor of tryptophan) to N-formylkynurenine. Thus, induction of IDO results in a diminished central synthesis of 5-HT (serotonin). Decreased 5-HT synthesis has been linked to reduced synaptic serotonin levels, providing a possible mechanism by which alpha interferon produces its neuropsychiatric side-effects.

Further, significant decreases in serum concentrations of tryptophan, the primary precursor of 5-HT, have been reported in patients undergoing IL-12 and/or IFN- α treatment.

Effect on serotonin transport

In the brain, the availability, and hence signalling potential, of released serotonin is regulated solely through the action of the serotonin transporter (SERT). The SERT captures serotonin molecules and transports them back into the nerve terminal, making them available for recycling into new synaptic vesicles. The strength of serotonin activity at serotonin receptors is inversely proportional to the number of functional SERT molecules present at the presynaptic membrane. Selective serotonin reuptake inhibitors (SSRIs) and related antidepressants exploit this by blocking the reuptake of serotonin through SERT, thus increasing serotonin signalling overall.

In cases of established depression there is evidence of a decrease in the availability of SERT, reflecting a loss of serotonergic neurons and a chronic decrease in the amount of serotonin available for transmission, leading to compensatory downregulation of SERT. It has been suggested that antidepressant drugs may reverse this effect. Of relevance to this suggestion are data from pre-clinical studies that indicate that SERT activity is increased by pro-inflammatory cytokines TNF- α , IL- β and IFN- γ .

At the experimental level, the cytokines TNF- α , IL-2 and IFN- α have been found to significantly upregulate the expression and activity of SERT (Mossner *et al*, 1998). These findings have advanced recently with the confirmation that IL-1 β and TNF- α acutely regulate neuronal SERT activity via p38-MAPK-linked pathways (Zhu *et al*, 2005).

Effect of inflammation on neurogenesis

It was confirmed in the late 1990s that neurogenesis occurs in the adult human brain, in the dentate gyrus of the hippocampus and in the subventricular zone. It is thought that neurogenesis in the dentate gyrus is linked to hippocampal functions, particularly learning. There is evidence that hippocampal volume is reduced in depression and that hippocampal functions, including recall, are impaired in major depression. Pre-clinical studies suggest that IL-1 β can impair neurogenesis. The hippocampus contains a high concentration of receptors for IL-1 β , and studies suggest that IFN- α can impair neurogenesis, acting through an IL-1 β -mediated mechanism (Kaneko *et al*, 2006). There is also evidence that increased TNF- α can impair hippocampal neurogenesis. Monje *et al* (2003) reported that neuro-inflammation inhibits neurogenesis and that inflammatory blockage with a non-steroidal anti-inflammatory drug restores neurogenesis. In exploring a potential mechanism underlying the depression induced by alpha interferon treatment, Kaneko *et al* (2006) found that the drug suppressed neurogenesis in the

Box 4 How do cytokines reach the brain?

- Cytokines act at sites where the blood–brain barrier is weak or non-existent
- Active transport into the brain
- Peripheral cytokines trigger the central production or release of cytokines
- Peripheral cytokines act on the brain via neural pathways

dentate and that IL-1 β played an essential role in that suppression.

How do cytokines reach the brain?

Cytokines are large molecules that are generally unable to penetrate the blood–brain barrier. Several mechanisms have been proposed by which elevated cytokine levels can act on the brain (Box 4).

Entry at compromised sites in the blood–brain barrier

There are points in the CNS where the blood–brain barrier is more permeable than others. Experiments have suggested that peripheral cytokines act on the organum vasculosum of the lamina terminalis. The assumption is that cytokines diffuse through fenestrated capillaries and exert their effect via secondary mediators. There are, however, several problems with this hypothesis. First, peripheral immune challenges are associated with a delayed rise in brain cytokines. Other work has shown that the main source of IL-1 β in the brain appears to be microglial cells, and perivascular and meningeal macrophages. Later work has suggested that microglial cells can produce IL-1 without specific activation in response to peripheral cytokines.

Active transport into the brain

It has been suggested for several years that an active transport mechanism exists to transport pro-inflammatory cytokines across the blood–brain barrier. There has recently been a small but growing body of evidence to support this. Murine models of the decreased ability to produce fever in response to infection indicated that IL-1 β crosses the blood–brain barrier by active transport, and that this ability decreases with age. More recent work has suggested that this is more widespread, and that endothelial proteins at the blood–brain barrier may respond to stimuli at one side of the barrier to release compounds (including cytokines) into the cerebral circulation.

Peripheral trigger of central production

Pre-clinical studies show how systemic infusion of pro-inflammatory cytokines can produce sickness behaviour. Kent *et al*'s (1996) work also showed that the timescale of central and peripheral effects of IL-1 differed, suggesting two processes at work. It has been noted that significantly lower doses of IL-1 are needed to produce effects in the CNS than in the periphery. This ratio can be 100 or 1000 to 1. It has been hypothesised that peripheral cytokines trigger perivascular macrophage-like cells in the circumventricular organs to produce pro-inflammatory cytokines. These cytokines in turn would act directly or indirectly on neurons projecting to other brain structures.

Further evidence for the brain possessing its own cytokine system is the high degree of cytokine regulation in the brain. There is evidence that both neurons in the healthy mouse brain and endothelial cells in the rat brain can produce IL-1. Following brain injury, IL-1 is expressed by microglia or astrocytes, and this has also been proposed as a mechanism in neurodegenerative and psychiatric illness (Rothwell & Luheshi, 2000). There is a suggestion that stress can directly induce brain IL-1 production. Cells that respond to IL-1 in the case of raised peripheral cytokine levels also express specific IL-1 receptor antagonist. There is also evidence from *in vivo* pre-clinical trials to suggest a negative feedback mechanism between IL-1 and TNF- α (pro-inflammatory cytokines) and IL-10 (an anti-inflammatory cytokine). The effects of other anti-inflammatory cytokines seem to be more complex.

Action via neural pathways

There is evidence linking the vagus nerve to cytokine effects (Bret-Dibat *et al*, 1995). There is also evidence that vagotomy can block central cytokine-related immune responses. However, further work suggests that vagotomy can block effects of intraperitoneal IL-1 β , although not if it is administered systemically or directly into cerebral ventricles. This provides evidence for several afferent pathways from the periphery to the brain, and suggests that vagal transmission cannot entirely explain the relationship between peripheral and central cytokine effects. There is also evidence that peripheral cytokines act via neural transmission to sensitise brain target areas to them (Dantzer *et al*, 2000). This may explain the lower levels of circulating cytokines needed to produce CNS effects.

It has been noted that intraperitoneal infusion of IL-1 in rats can activate the HPA axis, elevating circulating glucocorticoid levels. Additionally, IL-1

infusion has been shown to activate noradrenaline metabolism in the brain. This provides another mechanism by which raised levels of circulating pro-inflammatory cytokines can affect brain function.

The anti-inflammatory activity of antidepressants

There is a growing body of evidence to suggest that commonly used antidepressant drugs also show anti-inflammatory properties. Pre-clinical studies have shown anti-inflammatory actions in desipramine and fluoxetine, venlafaxine, bupropion, amitriptyline and duloxetine. One *in vivo* animal study suggests that antidepressants (reboxetine, desipramine, fluoxetine and clomipramine) are able to suppress production of IFN- γ independent of their effects on monoamine blockade. Other studies have suggested similar effects regarding other pro-inflammatory cytokines, including TNF- α . This strongly suggests that antidepressants can act to normalise the mechanisms responsible for increased cytokine production.

A second hypothesis is that in depression it is the interplay between the HPA axis and the cytokine system that is disturbed. It is suggested that elevated HPA axis activity in acute depression suppresses cytokine regulatory mechanisms, and that successful antidepressant treatment normalises this relationship (Himmerich *et al*, 2006).

There is also evidence that non-pharmaceutical treatments for depression exert an effect on the immune system. One such is exercise, which has been shown to have an anti-cytokine effect (Kohut *et al*, 2005). Omega-3 fatty acids can lower levels of pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-6 and TNF- α) and raise levels of IL-10 (an anti-inflammatory cytokine), and there is also some evidence for their efficacy at treating depression. St John's Wort also shares antidepressant and anti-inflammatory properties.

The 'antidepressant' effect of anti-cytokine treatments

There exists a long-recognised association between adverse emotional states and rheumatoid arthritis, and research suggests a significantly raised prevalence of depression in a population of patients with the disease (Patten *et al*, 2006). Etanercept is an anti-TNF- α treatment used in the management of rheumatoid arthritis and psoriasis. The drug has been shown to relieve both the symptoms of psoriasis and the depression and fatigue associated with it (Tyring *et al*, 2006). This is in contrast to a

study that alternative treatment involving psoralen administration and exposure to ultraviolet light produced a marked improvement in the clinical severity of psoriasis, but no significant effect on symptoms of depression or anxiety.

Antidepressants have been found to reverse major depression induced by cytokine therapy (Capuron *et al.*, 2002b). One small study showed that the antidepressants exhibit a more rapid onset of action if augmented with aspirin (Mendlewicz *et al.*, 2006).

Conclusions

Regardless of whether activation of the cytokine pathway is the core pathological process or a consequence that drives some symptoms, it is not unreasonable to examine the potential for reversing the process as an effective treatment for depression. Although there is little evidence that anti-inflammatories are effective as monotherapy for depression, there is evidence that etanercept (an anti-TNF drug) has a hedonic effect. Pre-clinical work implies that other anti-cytokine treatments may reduce the effects of psychosocial stressors, but the evidence is not conclusive (Raison *et al.*, 2005).

There is much stronger evidence that existing antidepressant drugs also possess anti-inflammatory properties. Both clinical and pre-clinical studies have shown that antidepressants can reduce levels of pro-inflammatory cytokines.

Understanding the relationship between depression and somatic disease can be useful in patient care. Simply realising that depression is far more likely to occur if a patient is physically unwell, especially in the context of certain diseases, can aid early identification and management. It has been proposed that depression affects prognosis both directly (as described for cardiac disease) and indirectly in terms of participation in treatment and rehabilitation programmes (Lauzon *et al.*, 2003).

From the above there is strong evidence that there exists a link between inflammation and depression. At present there is insufficient evidence to determine which is the true causative process: whether increased pro-inflammatory cytokine levels are the core pathological change in depression or whether it is an effect of another core process. The role of inflammation in various pathologies, from cardiovascular disease to cancer, is being better understood with time, and the role of inflammation in depression may explain the striking comorbidity between depression and these illnesses. This research also provides new opportunities to understand the pathophysiology of depression and to expand our paradigms for investigating new treatments.

Declaration of interest

None.

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MCQs

- 1 The following have been found consistently in depression:**
- a raised pro-inflammatory cytokines
 - b raised alanine aminotransferase
 - c high rheumatoid factor
 - d raised cholesterol
 - e raised troponin 1.

- 2 Regarding cardiovascular disease and depression:**
- a depression has a prevalence of >50% in the year following acute coronary syndrome
 - b there is no consistent association between depression and mortality after acute coronary syndrome
 - c depression as a risk factor for acute coronary syndrome disappears when lifestyle factors, lipid profile and similar variables are factored in
 - d there is little association between the inflammatory profile of acute coronary syndrome and depression
 - e after acute coronary syndrome incident depression is more strongly associated with mortality than is depression that has a previous history.
- 3 As regards immunotherapy and depression:**
- a treatment with alpha interferon produces high levels of neuropsychiatric side-effects
 - b over 50% of patients treated with alpha interferon become depressed
 - c interferon treatment for diseases other than hepatitis C does not result in neuropsychiatric side-effects
 - d people with hepatitis C who do not receive alpha interferon do not exhibit psychiatric symptoms
 - e there is little evidence that alpha interferon causes depression.
- 4 Inflammation and the brain:**
- a depression is associated with lower CRH in the CNS
 - b increased CRH in the CNS leads to decreased levels of natural killer cells
 - c neurovegetative symptoms induced by alpha interferon are responsive to antidepressants
 - d TNF- α decreases the release of CRH
 - e pro-inflammatory cytokines have limited effects on glucocorticoid receptor function.
- 5 Possible mechanisms linking depression and inflammation:**
- a alpha interferon inhibits IDO
 - b increase in tryptophan has been associated with alpha interferon treatment
 - c the serotonin transporter is activated by pro-inflammatory cytokines
 - d the serotonin transporter is downregulated by IL-6
 - e the principal protein kinase system relating the serotonin system with inflammation is JNK.

MCQ answers

1	2	3	4	5
a T	a F	a T	a F	a F
b F	b F	b F	b T	b F
c F	c F	c F	c F	c T
d F	d F	d F	d F	d F
e F	e T	e F	e F	e F