Depressive symptoms following interferon-alpha therapy

Kenis, Gunter; Prickaerts, Jos; van Os, Jim; Koek, Ger H.; Robaeys, Geert; Steinbusch, Harry W. M.; Wichers, Marieke

Published in:
International Journal of Neuropsychopharmacology

DOI:
10.1017/S1461145710000830

Publication date:
2011

International Journal of Neuropsychopharmacology (2011), **14**, 247–253. © CINP 2010
doi:10.1017/S1461145710000830

ARTICLE

CINP

Depressive symptoms following interferon-α therapy: mediated by immune-induced reductions in brain-derived neurotrophic factor?

Gunter Kenis[1,2,7], Jos Prickaerts[2,7], Jim van Os[1,7], Ger H. Koek[3], Geert Robaeys[4,5,6], Harry W. M. Steinbusch[2,7] and Marieke Wichers[1,7]

[1] *Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, The Netherlands*
[2] *Department of Psychiatry and Neuropsychology, Section Cellular Neuroscience, Brain and Behaviour Institute, EURON, Maastricht University, Maastricht, The Netherlands*
[3] *Department of Internal Medicine, Division of Gastroenterology and Hepatology, Academic Hospital Maastricht, Maastricht, The Netherlands*
[4] *Department of Gastroenterology & Hepatology, Ziekenhuis Oost-Limburg, Genk, Belgium*
[5] *Department of Hepatology, UZ Leuven, Belgium*
[6] *Faculty of Medicine, Hasselt University, Belgium*
[7] *European Graduate School of Neuroscience, Maastricht, The Netherlands*

Abstract

Interferon-α (IFN-α) therapy for the treatment of hepatitis C is known to induce depressive symptoms and major depression in a substantial proportion of patients. While immune activation and disturbances in peripheral tryptophan catabolism have been implicated, the exact underlying mechanism remains unknown. A role for brain-derived neurotrophic factor (BDNF) in the pathophysiology of mood disorders has recently emerged. This study examined whether depressive symptoms over time are associated with changes in serum BDNF concentration in hepatitis C patients treated with IFN-α, and whether BDNF mediates the effects of IFN-α-induced immune activation on depressive symptoms. For this purpose, 17 hepatitis C patients received IFN-α treatment with ribavirin. Patients were assessed before and at 1, 2, 4, 8, 12 and 24 wk after start of treatment. Depressive symptoms were assessed using the Montgomery–Asberg Depression Rating Scale (MADRS). In addition, cytokine concentrations and serum BDNF levels were measured at all time-points. Serum levels of BDNF decreased during the course of treatment, and were significantly and inversely associated with total MADRS score. Furthermore, pro-inflammatory cytokine levels predicted lower subsequent BDNF levels, whereas low BDNF levels, as well as increased cytokine levels, were independently associated with the development of depressive symptoms during IFN-α treatment. These findings suggest that the effect of IFN-α-induced immune activation on depression may be explained in part by alterations in neuroprotective capacity, reflected by decreases in serum BDNF following IFN-α treatment.

Received 4 February 2010; Reviewed 18 May 2010; Accepted 22 June 2010; First published online 29 July 2010

Key words: Brain-derived neurotrophic factor, cytokine, hepatitis C, interferon-α, major depressive disorder.

Introduction

Interferon-α (IFN-α) therapy for the treatment of hepatitis C and several malignancies induces neuropsychiatric side-effects in a large proportion of patients. The occurrence of major depression has been reported in up to 45% of patients (Asnis & De La Garza, 2006). IFN-α-induced depression has been attributed to the induction of pro-inflammatory cytokines that can modulate several neurophysiological and neuroendocrine systems involved in mood regulation (Raison *et al*. 2006; Wichers & Maes, 2002).

Address for correspondence: Dr M. Wichers, Department of Psychiatry and Neuropsychology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands.
Tel.: +31-43-3688669 *Fax*: +31-43-3688689
Email: m.wichers@sp.unimaas.nl

Recent research on the biological pathophysiology of mood disorders, including major depression, focuses on disturbances in neurotrophic signalling pathways. In particular the role of brain-derived neurotrophic factor (BDNF) has been extensively investigated. BDNF plays an important role in neuronal survival and differentiation, and mediates synaptic plasticity. A role of BDNF in the pathophysiology of mood disorders has been proposed, based on several lines of evidence (Duman & Monteggia, 2006; Hashimoto *et al*. 2004). Stress, an important risk factor for depression, decreases BDNF expression in relevant brain areas of animals, while chronic administration of antidepressants increases BDNF expression. Infusion of BDNF in the brain produces antidepressant-like effects in several animal models of depression. Post-mortem analysis of human brains shows that BDNF is decreased in depressed patients and increased in patients receiving antidepressants (Chen *et al*. 2001). Furthermore, findings of decreased BDNF serum levels in depressed patients have consistently been replicated (Aydemir *et al*. 2005, 2006; Gervasoni *et al*. 2005; Gonul *et al*. 2005; Karege *et al*. 2002*a*, 2005; Shimizu *et al*. 2003). Serum BDNF levels are negatively correlated with symptom severity (Gervasoni *et al*. 2005; Gonul *et al*. 2005; Karege *et al*. 2002*a*; Shimizu *et al*. 2003; Zanardini *et al*. 2006) and are increased after chronic antidepressant treatment (Aydemir *et al*. 2005, 2006; Gervasoni *et al*. 2005; Gonul *et al*. 2005), electroconvulsive therapy (Bocchio-Chiavetto *et al*. 2006) and repetitive transcranial magnetic stimulation (Zanardini *et al*. 2006). Two recent systematic reviews and meta-analyses concluded that serum BDNF levels are indeed associated with depression status (Brunoni *et al*. 2008; Sen *et al*. 2008). Moreover, activation of the inflammatory immune system elicits changes in BDNF levels that are likely to impact on behavioural processes such as depression (Anisman, 2009).

Thus, while both clinical and pre-clinical evidence suggest a role of BDNF in mood disorders, BDNF levels in serum of patients treated with IFN-α have never been examined. In the present study, patients were followed before and during IFN-α therapy for the treatment of hepatitis C. It was hypothesized that serum BDNF levels would be negatively associated with the occurrence of depressive symptoms during the course of treatment.

Methods and materials

Subjects

Twenty-one patients with chronic active hepatitis C infection were recruited and assessed before and during the period that they underwent IFN-α treatment. Chronic hepatitis C was defined as: antibodies to HCV-positive, HCV-RNA-positive, and elevated transaminases at least once in the previous 6 months.

Excluded were patients currently meeting criteria for Axis I psychiatric disorders as defined by DSM-IV or patients currently on antidepressant medication. In addition, patients who had co-infections such as hepatitis B virus or human immunodeficiency virus, or patients with a diagnosis of uncontrolled neurological, cardiovascular, endocrine, haematological, hepatic or renal disease, or patients with insufficient knowledge of the Dutch language were excluded.

Patients were recruited from the Academic Hospital Maastricht (AZM) in The Netherlands and from the Hospital East Limburg (ZOL) in Belgium. All patients received some form of IFN-α treatment and ribavirin. Some patients received Intron A the first 12 d of treatment [10 million units (MU) daily for the first 6 d and 5 MU daily after day 6]. After these 12 d, they received a weekly injection of 80–180 μg PEG IFN-α-2b. Other patients directly started with weekly injections of 80–180 μg PEG IFN-α-2b and one patient received IFN-α-2b (Intron A), 3×3 MU weekly throughout the study period. In all patients, ribavirin was administered orally, 1000–1200 mg/d, depending on body weight. Six of the patients received an additional daily dose of 2×100 mg amantadine.

The study was approved by the standing Medical Ethics Committee of Maastricht University and performed in accordance with the Declaration of Helsinki (Hong Kong Modification, 1989). Written informed consent was obtained from each subject prior to participation.

Measurements

Patients were assessed before and at 1, 2, 4, 8, 12 and 24 wk after treatment start. At each assessment, blood samples were collected and the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) was administered. The presence of major depression was determined using the Structured Clinical Interview for DSM-IV Axis I Disorders version 5.0.

Blood samples were used for the measurement of BDNF. In addition, platelet number and serum levels of interleukin-6 (IL-6), IL-8, IL-10, soluble IL-6 receptor (sIL-6R), sIL-2R, tumour necrosis factor-α (TNF-α) and IL-1 receptor antagonist (IL-1RA) were determined. Diurnal cortisol levels were determined in saliva samples that were collected the day prior to each of the seven assessment points of the longitudinal study

(baseline, 1, 2, 4, 8, 12 and 24 wk after starting IFN-α treatment) as previously described (Wichers *et al*. 2007).

Blood was collected between 08:00 and 10:00 hours after an overnight fast into (i) BD Vacutainer™ EDTA tubes for determination of platelet number and other routine clinical tests, and (ii) BD Vacutainer SST tubes for serum preparation (BD, The Netherlands). Serum was stored at $-80\ ^{\circ}$C until analysis. BDNF in serum was measured using the BDNF E_{max} Immunoassay System (Promega, The Netherlands). In accordance with the manufacturer's recommendations, samples were acid treated before being appropriately diluted for analysis. Cytokine levels in serum and cortisol in saliva were determined as previously described (Wichers *et al*. 2007).

Statistics

The data were analysed with Stata version 11.0 (StataCorp, USA). In order to improve normality of distributions, the IL-8, IL-1RA and IL-6 variables were subjected to an inverse square-root transformation.

Multilevel random regression analysis was applied using the XTREG command of Stata. This multilevel model takes into account that level-1 units (individual observations) are clustered into level-2 units (subjects). First, an analysis was performed to examine changes in BDNF serum levels during treatment. Second, total MADRS score was regressed on BDNF levels to assess the association between BDNF levels and the occurrence of depressive symptoms. Since BDNF is stored in thrombocytes and since IFN-α therapy can induce thrombocytopenia, all analyses were corrected for number of thrombocytes. Analyses were also corrected for the following *a priori* hypothesized confounders: age, gender, smoking, hospital centre, benzodiazepine medication and use of marijuana during the study. It has been suggested that endogenous corticosteroids influence BDNF expression (Prickaerts *et al*. 2006). In our data, regression analysis showed that there was no association between BDNF and either awakening cortisol response ($\beta=-0.65$, $p=0.395$) or daily average cortisol (Gunnar *et al*. 2001; Wichers *et al*. 2007) ($\beta=-0.51$, $p=0.395$) and the latter are therefore not considered as confounding factors. Third, cytokine levels were regressed on BDNF levels. Finally, BDNF and cytokine concentrations were entered in the model simultaneously in order to examine to what degree the effect of each on depressive symptoms was independent of the other.

Results

Subjects

Patient characteristics have been described previously (Wichers *et al*. 2007) and are briefly summarized. Twenty-one patients were included in the study. Four patients dropped out due to problems not associated with psychiatric side-effects. The final study group consisted of 17 patients (13 men and four women). The mean age of the group was 42 ± 7.4 yr. One subject had partial missing data on depressive symptoms. In 7/17 patients (41%), a temporary dose reduction or discontinuation of therapy was necessary due to haematological adverse events. Ten patients (59%) reported lifetime drug dependence and had acquired the virus by intravenous drug use. Six of the 17 patients (35%) received low-dosage benzodiazepines during the study and 7/17 patients were currently using some form of drugs, of which five were regular users of marijuana. Of these five individuals, one additionally used heroin on a regular basis. The other two individuals were on methadone substitution. Their drug habit was stable throughout the studied period. Five out of 16 patients (31%) fulfilled DSM-IV criteria for MDD at some point during the study period. The average baseline level of BDNF was 15.7 (S.D. = 4.9, range = 8.3–24.4) ng/ml. Average thrombocyte count per week was 227 (S.D. = 71), 169 (S.D. = 48), 196 (S.D. = 70), 190 (S.D. = 75), 179 (S.D. = 61), 182 (S.D. = 50) and 201 (S.D. = 63) for baseline and the six follow-up measurements, respectively. Mean cytokine concentrations and their standard deviations at each measurement occasion have been described in a previous publication pertaining to this sample (Wichers *et al*. 2007).

BDNF levels and depressive symptoms during treatment

BDNF levels and MADRS scores during treatment are displayed in Fig. 1. Serum BDNF levels gradually decreased during treatment ($\beta=-0.789$, $p<0.001$). Compared to baseline, this decrease was significant from week 2 onwards (see Table 1). As previously reported, total MADRS score significantly increased during treatment (Wichers *et al*. 2005*a*). Regression analysis showed that BDNF levels were significantly and negatively associated with total MADRS score ($\beta=-1.064$, $p<0.001$). Sensitivity analyses including only those patients who did not experience dose reduction during the study period showed that effects in this restricted sample were slightly stronger compared to the complete sample (effect of decreases in BDNF during treatment: $\beta=-0.879$, $p<0.001$; association of

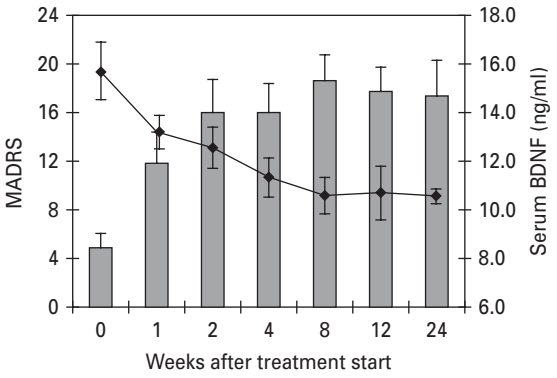

Fig. 1. Montgomery–Asberg Depression Rating Scale (MADRS) scores (▩) and brain-derived neurotrophic factor (BDNF) serum concentrations (–◆–) before and during treatment with IFN-α.

BDNF with MADRS score: $\beta = -1.259$, $p < 0.001$). Figure 2 graphically depicts the decrease in BDNF levels, stratified by development of depression.

Immune activation, BDNF and depressive symptoms

To assess whether activation of the cytokine network is involved in the decrease of BDNF during IFN-α treatment, the association between serum levels of BDNF and cytokine was examined. Soluble IL-2R ($\beta = -0.006$, $p = 0.002$), IL-1RA ($\beta = -23.94$, $p = 0.032$), IL-10 ($\beta = 0.325$, $p = 0.019$) and sIL-6R ($\beta = 0.023$, $p = 0.020$) were significantly associated with BDNF. No other cytokines were significantly associated with serum BDNF levels. Previously we showed that sIL-2R levels, but not IL-1RA, IL-10 or the SIL-6R concentrations, are related to increases in MADRS scores during IFN-α treatment (Wichers *et al*. 2007). Therefore, we examined the time-lagged associations between sIL-2R and BDNF in order to estimate the directionality of their association. Second, to examine their independent associations with depressive symptoms, BDNF and sIL-2R were added simultaneously in the regression model. The first analysis was performed using the tsset command in Stata 11.0, with time units specified as weeks. The effect of BDNF levels on later sIL-2R concentrations was not significant ($\beta - 8.141$, $p = 0.458$). However, the effect of sIL-2R levels on later BDNF was significant ($\beta - 0.0054$, $p = 0.001$). When both BDNF and sIL-2R were added simultaneously as predictors of depressive symptoms, both BDNF ($\beta - 0.658$, $p = 0.005$) and sIL-2R ($\beta = 0.0180$, $p < 0.001$) were significantly associated with depressive symptoms. This suggests that sIL-2R levels decrease later BDNF levels and that both low BDNF levels and increased sIL-2R levels independently contribute to the prediction of depressive symptoms during IFN-α treatment.

Table 1. Multilevel regression analysis indicating difference in BDNF levels to baseline at each measurement occasion

Week no.	β	p
1	−1.67	0.012
2	−2.74	0.003
4	−3.68	<0.001
8	−3.93	<0.001
12	−4.32	<0.001
24	−5.11	<0.001

β, Regression coefficient; p, level of significance.

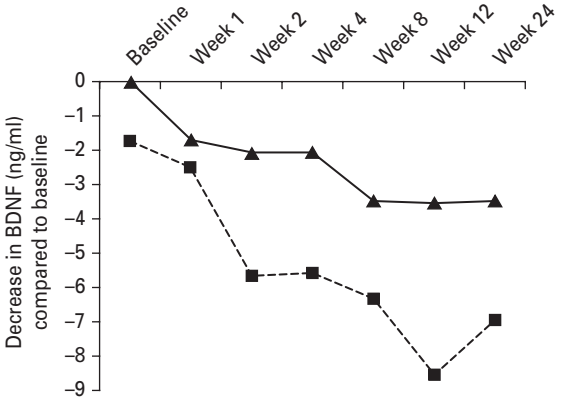

Fig. 2. Differential decline in brain-derived neurotrophic factor (BDNF) levels during the course of IFN-α treatment for those patients who develop depression (- -■- -, $n = 5$) compared to those who do not (–▲–, $n = 11$). The effect size of BDNF compared to baseline is shown.

Discussion

This longitudinal study examined, for the first time, the association between development of depressive symptoms during IFN-α therapy and changes in serum levels of BDNF. The data showed that depressive symptoms were significantly associated with decreases in serum BDNF levels. Two markers of immune activation – sIL-2R reflecting T-cell activation, and IL1-RA reflecting monocyte activation – were also inversely associated with BDNF, while other markers reflecting anti-inflammatory activity (IL-10 and sIL-6R) were positively associated with BDNF.

A previous study using the same sample showed that of these markers only sIL-2R was significantly associated with depressive symptoms (Wichers *et al*. 2007). Given the present study design (experimental

administration of IFN-α) and the results (that increased sIL-2R predicts a later decrease in BDNF) the findings support the hypothesis that immune activation reduces BDNF levels. The association of BDNF with depressive symptoms could theoretically be explained on the basis of a third, confounding, variable (i.e. immune activation), without a causal role for BDNF in the development of depressive symptoms. However, the fact that both BDNF and sIL-2R were associated with depressive symptoms, each independently of the other, appears to exclude that possibility. Thus, the results support the hypothesis that the changes in BDNF may not be a non-causal by-product of biochemical changes during IFN-α treatment, but rather that BDNF may be on the causal pathway of IFN-α-induced immune activation to depressive symptoms. These data provide insight into the mechanism underlying the depressogenic effects of IFN-α and add further evidence to the conception that alterations in neurotrophic factors underlie the pathophysiology of mood disorders. Previous studies have suggested that development of depressive symptoms during IFN-α therapy is associated with increases in pro-inflammatory cytokines (Bonaccorso *et al*. 2001; Wichers *et al*. 2007), which are known to elicit depressive-like behaviour (Raison *et al*. 2006; Schiepers *et al*. 2005). Other proposed mechanisms of IFN-α-induced depressive symptoms are alterations in peripheral tryptophan metabolism, disturbances in central neurotransmitter turnover and dysfunction of the hypothalamic–pituitary–adrenal axis (Bonaccorso *et al*. 2002; Capuron *et al*. 2002*a*, *b*, 2003*a*, *b*; De La Garza & Asnis, 2003; Kitagami *et al*. 2003; Wichers *et al*. 2005*b*). Our findings suggest a role for neurotrophic factors in IFN-α-induced depression. Duman and Monteggia (2006) have recently proposed a model for the involvement of BDNF and other neurotrophic factors in stress-related mood disorders. In animals, stress reduces BDNF expression in relevant brain regions, which can lead to reduced neuronal protection and cell survival. Similarly, a role of BDNF in cytokine-induced depression can be suggested. First, some of the effects of stress on hippocampal BDNF expression are mediated, at least in part, by the pro-inflammatory cytokine IL-1β (Barrientos *et al*. 2003). Second, IFN-α is able to penetrate the brain parenchyma (Pan *et al*. 1997) and can induce local production of IL-1β. In addition, IFN-α-induced IL-1β expression in the hippocampus decreases cell proliferation in the dentate gyrus (Kaneko *et al*. 2006), a phenomenon that is dependent on BDNF expression and associated with hippocampal neurogenesis (Lee *et al*. 2002). In addition, peripheral immune activation also lowers BDNF levels in the brain (Guan & Fang, 2006). Taken together, it is suggested that IFN-α-induced depression and development of depressive symptoms are associated with decreased BDNF expression in relevant brain regions, thereby compromising neuronal plasticity, including neuroprotection and neuronal survival.

Indeed, our findings of reductions in circulating levels of BDNF during IFN-α treatment may reflect altered BDNF synthesis in the brain. In the circulation system, BDNF is taken up by and stored in platelets, which do not synthesize BDNF (Fujimura *et al*. 2002). The source of BDNF remains as yet undetermined, but it is thought that BDNF is mainly produced in the brain (Karege *et al*. 2002*b*) and enters the circulation through reabsorption of cerebrospinal fluid (Pan *et al*. 1998). Other potential sources of serum BDNF are vascular endothelial cells (Nakahashi *et al*. 2000) and activated lymphocytes and monocytes (Kerschensteiner *et al*. 1999). However, it is unlikely that the latter are involved in IFN-α-related decreases in serum BDNF, since IFN-α is known to activate immune cells (Brassard *et al*. 2002), that would result in elevated circulating BDNF concentrations. It is therefore suggested that IFN-α-mediated immune activation, both peripherally and centrally, decreases BDNF synthesis in the brain, resulting in lower levels of BDNF in serum. The decreases in central BDNF production compromises neuroprotective capacity of the brain micro-environment.

Occurrence of depression during IFN-α therapy often requires cessation of treatment or adjustment of dose regimen, thereby compromising treatment outcome (Asnis & De La Garza, 2006). Fortunately, IFN-α-induced depression can be successfully treated and prevented with antidepressants (Asnis & De La Garza, 2005; Maddock *et al*. 2004; Schramm *et al*. 2000). It is well known that antidepressants enhance BDNF expression in several brain areas (Duman & Monteggia, 2006), and that treatment with antidepressants increases serum BDNF levels (Aydemir *et al*. 2005, 2006; Gervasoni *et al*. 2005; Gonul *et al*. 2005). Thus, antidepressants may normalize IFN-α-related decreases in BDNF, thereby preventing depression or alleviating depressive symptoms.

Limitations

The present study concerns IFN-α-induced depression, and caution should be exercised in generalizing the findings to depressive disorders of different aetiology. However, the involvement of BDNF in stress-related mood disorders has already been shown, and, together with the current data, it suggests

that BDNF is a key molecule in the pathophysiology of mood disorders in general.

The total number of patients included in this study was low and although all patients varied in depressive symptoms on a continuous scale, only five patients fulfilled DSM-IV criteria for depression over the course of treatment. Moreover, some patients had a history of drug addiction and some were given anxiolytic medication during the course of treatment. Although regression analyses were controlled for these variables, they may have produced some additional error variation. The results should therefore be replicated in a larger sample and in populations other than hepatitis C patients.

Acknowledgements

The work of G.K., J.P. and H.S. is partly supported by the EU Framework 6 Integrated Project NEWMOOD (LSHM-CT-2003-503474).

Statement of Interest

None.

References

Anisman H (2009). Cascading effects of stressors and inflammatory immune system activation: implications for major depressive disorder. *Journal of Psychiatry and Neuroscience* **34**, 4–20.

Asnis GM, De La Garza II R (2005). Interferon-induced depression: strategies in treatment. *Progress in Neuropsychopharmacology and Biological Psychiatry* **29**, 808–818.

Asnis GM, De La Garza R (2006). Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology, and treatment approaches. *Journal of Clinical Gastroenterology* **40**, 322–335.

Aydemir C, Yalcin ES, Aksaray S, Kisa C, *et al.* (2006). Brain-derived neurotrophic factor (BDNF) changes in the serum of depressed women. *Progress in Neuropsychopharmacology and Biological Psychiatry* **30**, 1256–1260.

Aydemir O, Deveci A, Taneli F (2005). The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. *Progress in Neuropsychopharmacology and Biological Psychiatry* **29**, 261–265.

Barrientos RM, Sprunger DB, Campeau S, Higgins EA, *et al.* (2003). Brain-derived neurotrophic factor mRNA downregulation produced by social isolation is blocked by intrahippocampal interleukin-1 receptor antagonist. *Neuroscience* **121**, 847–853.

Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, *et al.* (2006). Electroconvulsive therapy (ECT) increases serum brain derived neurotrophic factor (BDNF) in drug resistant depressed patients. *European Neuropsychopharmacology* **16**, 620–624.

Bonaccorso S, Marino V, Puzella A, Pasquini M, *et al.* (2002). Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *Journal of Clinical Psychopharmacology* **22**, 86–90.

Bonaccorso S, Puzella A, Marino V, Pasquini M, *et al.* (2001). Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Research* **105**, 45–55.

Brassard DL, Grace MJ, Bordens RW (2002). Interferon-alpha as an immunotherapeutic protein. *Journal of Leukocyte Biology* **71**, 565–581.

Brunoni AR, Lopes M, Fregni F (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *International Journal of Neuropsychopharmacology* **11**, 1169–1180.

Capuron L, Hauser P, Hinze-Selch D, Miller AH, *et al.* (2002*a*). Treatment of cytokine-induced depression. *Brain Behavior and Immunity* **16**, 575–580.

Capuron L, Neurauter G, Musselman DL, Lawson DH, *et al.* (2003*a*). Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. *Biological Psychiatry* **54**, 906–914.

Capuron L, Raison CL, Musselman DL, Lawson DH, *et al.* (2003*b*). Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *American Journal of Psychiatry* **160**, 1342–1345.

Capuron L, Ravaud A, Neveu PJ, Miller AH, *et al.* (2002*b*). Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Molecular Psychiatry* **7**, 468–473.

Chen B, Dowlatshahi D, MacQueen GM, Wang JF, *et al.* (2001). Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biological Psychiatry* **50**, 260–265.

De La Garza IIR, Asnis GM (2003). The non-steroidal anti-inflammatory drug diclofenac sodium attenuates IFN-alpha induced alterations to monoamine turnover in prefrontal cortex and hippocampus. *Brain Research* **977**, 70–79.

Duman RS, Monteggia LM (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry* **59**, 1116–1127.

Fujimura H, Altar CA, Chen R, Nakamura T, *et al.* (2002). Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thrombosis and Haemostasis* **87**, 728–734.

Gervasoni N, Aubry JM, Bondolfi G, Osiek C, *et al.* (2005). Partial normalization of serum brain-derived neurotrophic

factor in remitted patients after a major depressive episode. *Neuropsychobiology* **51**, 234–238.

Gonul AS, Akdeniz F, Taneli F, Donat O, *et al.* (2005). Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *European Archives of Psychiatry and Clinical Neuroscience* **255**, 381–386.

Guan Z, Fang J (2006). Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. *Brain Behavior and Immunity* **20**, 64–71.

Gunnar MR, Morison SJ, Chisholm K, Schuder M (2001). Salivary cortisol levels in children adopted from romanian orphanages. *Development and Psychopathology* **13**, 611–628.

Hashimoto K, Shimizu E, Iyo M (2004). Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Research. Brain Research Reviews* **45**, 104–114.

Kaneko N, Kudo K, Mabuchi T, Takemoto K, *et al.* (2006). Suppression of cell proliferation by interferon-Alpha through interleukin-1 production in adult rat dentate gyrus. *Neuropsychopharmacology* **31**, 2619–2626.

Karege F, Bondolfi G, Gervasoni N, Schwald M, *et al.* (2005). Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. *Biological Psychiatry* **57**, 1068–1072.

Karege F, Perret G, Bondolfi G, Schwald M, *et al.* (2002*a*). Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Research* **109**, 143–148.

Karege F, Schwald M, Cisse M (2002*b*). Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neuroscience Letters* **328**, 261–264.

Kerschensteiner M, Gallmeier E, Behrens L, Leal VV, *et al.* (1999). Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? *Journal of Experimental Medicine* **189**, 865–870.

Kitagami T, Yamada K, Miura H, Hashimoto R, *et al.* (2003). Mechanism of systemically injected interferon-alpha impeding monoamine biosynthesis in rats: role of nitric oxide as a signal crossing the blood-brain barrier. *Brain Research* **978**, 104–114.

Lee J, Duan W, Mattson MP (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *Journal of Neurochemistry* **82**, 1367–1375.

Maddock C, Baita A, Orru MG, Sitzia R, *et al.* (2004). Psychopharmacological treatment of depression, anxiety, irritability and insomnia in patients receiving interferon-alpha: a prospective case series and a discussion of biological mechanisms. *Journal of Psychopharmacology* **18**, 41–46.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Nakahashi T, Fujimura H, Altar CA, Li J, *et al.* (2000). Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Letters* **470**, 113–117.

Pan W, Banks WA, Fasold MB, Bluth J, *et al.* (1998). Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* **37**, 1553–1561.

Pan W, Banks WA, Kastin AJ (1997). Permeability of the blood-brain and blood-spinal cord barriers to interferons. *Journal of Neuroimmunology* **76**, 105–111.

Prickaerts J, van den Hove DL, Fierens FL, Kia HK, *et al.* (2006). Chronic corticosterone manipulations in mice affect brain cell proliferation rates, but only partly affect BDNF protein levels. *Neuroscience Letters* **396**, 12–16.

Raison CL, Capuron L, Miller AH (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology* **27**, 24–31.

Schiepers OJ, Wichers MC, Maes M (2005). Cytokines and major depression. *Progress in Neuropsychopharmacology and Biological Psychiatry* **29**, 201–217.

Schramm TM, Lawford BR, Macdonald GA, Cooksley WG (2000). Sertraline treatment of interferon-alfa-induced depressive disorder. *Medical Journal of Australia* **173**, 359–361.

Sen S, Duman R, Sanacora G (2008). Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biological Psychiatry* **64**, 527–532.

Shimizu E, Hashimoto K, Okamura N, Koike K, *et al.* (2003). Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biological Psychiatry* **54**, 70–75.

Wichers M, Maes M (2002). The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. *International Journal of Neuropsychopharmacology* **5**, 375–388.

Wichers MC, Kenis G, Koek GH, Robaeys G, *et al.* (2007). Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol. *Journal of Psychosomatic Research* **62**, 207–214.

Wichers MC, Koek GH, Robaeys G, Praamstra AJ, *et al.* (2005*a*). Early increase in vegetative symptoms predicts IFN-alpha-induced cognitive-depressive changes. *Psychological Medicine* **35**, 433–441.

Wichers MC, Koek GH, Robaeys G, Verkerk R, *et al.* (2005*b*). IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Molecular Psychiatry* **10**, 538–544.

Zanardini R, Gazzoli A, Ventriglia M, Perez J, *et al.* (2006). Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *Journal of Affective Disorders* **91**, 83–86.