Acta Neuropsychiatrica 2002: 14: 103–105
Printed in Denmark. All rights reserved

ISSN 0924-2708

EDITORIAL

Mechanisms of interferon-alpha-induced depressive symptoms

Wichers MC, Maes M. Mechanisms of interferon-alpha-induced depressive symptoms.
Acta Neuropsychiatrica 2002: 14:103–105. © Blackwell Munksgaard 2002

M. C. Wichers, M. Maes

Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, the Netherlands

Correspondence: M.C. Wichers, Department of Psychiatry and Neuropsychology, Maastricht University, PO BOX 616, 6200 MD Maastricht, the Netherlands. Tel. + 31-43-3871025; Fax: + 31-43-3871026; http://users.skynet.be/crc.mh/

Side-effects of interferon-alpha

Several studies have found a high incidence of neuropsychiatric side effects during long-term interferon-alpha (IFNα) therapy, including depressed mood, anxiety, loss of interest, slowness, severe fatigue, hypersomnia lethargy, poor appetite, irritability, short temper emotional lability, social withdrawal and lack of concentration (1). In a study from the National Institutes of Health (2) 10 of 58 patients (17%) with chronic viral hepatitis treated with a 4–12-month course of recombinant IFNα developed psychiatric side-effects. Furthermore, Bonaccorso et al. (1) found that of 30 patients, 40.7% suffered of major depression according to DSM-IV criteria after treatment with IFNα for three months. Some studies even report that treatment with IFNα may lead to suicidal thoughts and suicide attempts (3).

The mechanisms by which IFNα is able to influence brain function are not yet clear. Some mechanisms have been proposed and will be discussed below.

Influence of IFNα on serotonin, cytokine network and HPA axis

The brain is relatively isolated from the immune system due to the presence of the blood brain barrier (BBB) (4). However, it is thought that systemically administered IFNα is able to cross the BBB (5) and that it enters the brain through areas lacking the BBB, particularly the organum vasculosum lamina terminalis (6).

Serotonin (5-HT) plays an important role in mood regulation. Major depression is accompanied by disturbances in the 5-HT metabolism (7). IFNα is able to affect the central serotonergic system. It up-regulates the transcription of the central 5-HT transporter, which enhances the reuptake of 5-HT and causes a depletion of extracellular 5-HT (8). In addition, IFNα affects the low-affinity 5-HT1A receptor sites (9) and it may be able to modulate 5-HT2 receptors (10). Furthermore, IFNα is able to modulate the 5-HT system through its effect on the enzyme indoleamine 2,3 dioxygenase (IDO), which induces the catabolism of tryptophan, the precursor of 5-HT, to kynurenine. Overstimulation of IDO leads to depletion of plasma concentrations of tryptophan and perhaps to reduced synthesis of 5-HT in the brain, as the latter depends on plasma availability of tryptophan (11). While IFNγ directly affects IDO activity, IFNα has a weak direct effect and in addition an indirect effect through a 15-kDa protein, which is a product of IFNα-treated monocytes and lymphocytes and which stimulates IDO and IFNγ production (12). Thus, IFNα is able to influence the central 5-HT system directly as well as by modulating peripheral tryptophan catabolism.

Another mechanism by which IFNα may be able to produce depressive symptoms is by modulating the hypothalamic–pituitary–adrenal (HPA) axis. The main driving force behind HPA activation is

hypothalamic corticotropin-releasing factor (CRF), which enhances the release of ACTH from the pituitary, which in turn stimulates the release of corticosteroids from the adrenal glands. Overactivity of the HPA axis, experimentally induced in animals by long-term central CRF-infusion, causes symptoms such as anxiety, anhedonia, anorexia, changes in sexual behavior and changes in sleeping pattern (13).

Depressed people also have an overactive HPA axis characterized by an increased number of ACTH and cortisol secretory pulses (14), elevated levels of CRF in the CSF (13), an increased number of CRF secreting neurons in limbic brain regions (15) and a reduced number of CRF binding sites in the frontal cortex secondary to increased CRF concentration (16). Administration of dexamethasone, a synthetic glucocorticoid, reveals, in depressed patients, a relative resistance to its suppressive effect on the activity of the HPA axis (17). Therefore, the hypothesis is postulated that negative feedback mechanisms through glucocorticoid receptors are impaired in depressives (17).

IFNα may affect the HPA axis by its effect on the cytokine network. It stimulates the production of other proinflammatory cytokines such as interleukin (IL)-1 and IL-6 (18). These cytokines are known to exert potent enhancing effects on the HPA axis by stimulating CRF, ACTH and the production of corticosteroids (19). A logical candidate pathway for IL-1 to influence the brain is via the vagus nerve (10th cranial nerve). First, the vagus innervates tissues known to participate in immune functions and branches of the vagus are often associated with lymph nodes that drain regions in which immune activation occurs. Secondly, the injection of IL-1β into the hepatoportal vein increases vagal electrical activity. In addition, subdiaphragmatic vagotomy blocks the neural, physiological and behavioral effects of IL-1β (20).

Prevention of side-effects with antidepressants

Antidepressant pharmacotherapy may be useful to prevent the depressive side-effects of administration of IFNα.

First, antidepressive agents exert an influence on the serotonergic system. Antidepressant drugs may act via their long-term ability to modulate pre- and postsynaptic serotonergic function. Furthermore, tricyclic antidepressants such as clomipramine and imipramine, selective serotonin reuptake inhibitors (SSRIs) such as sertraline, heterocyclic antidepressants such as trazodone and 5-HTP, the direct precursor of 5-HT, are found to have a significant suppressive effect on the proinflammatory cytokine IFNγ and/or a stimulatory effect on IL-10 secretion, an anti-inflammatory cytokine whole blood stimulated with polyclonal activators (21). Another study (22) showed that the antidepressants imipramine, clomipramine and citalopram caused an inhibition of IL-2 and IFNγ release from activated T cells after polyclonal activation and a similar inhibitory pattern was seen for IL-1β, TNF-α and IL-6 release from monocytes. Thus, antidepressants may counteract the effects of IFNα on the cytokine network by its negative immunoregulatory effects.

Finally, antidepressant drugs such as desipramine, imipramine and amytriptyline (23) are able to decrease HPA activity. The fact that patients who do not respond to antidepressant treatment continue to have HPA dysregulation (24) supports a causal relationship between normalization of stress hormone regulation and clinical recovery. Antidepressants may be able to down-regulate HPA activity by decreasing CRH gene expression in the paraventricular nucleus of the hypothalamus (25) and by increasing corticosteroid receptor sites in brain regions known to mediate the inhibitory effects of glucocorticoids on subsequent HPA activity, thereby increasing the feedback inhibition over the HPA axis (26).

In addition it has been shown that they are able to reduce IFNα-induced depression. Administration of paroxetine (27) and imipramine (28) have proven to be effective in alleviating IFNα-induced depressive symptoms in hepatitis C patients. Thus, antidepressants might be useful to prevent the development of depression in IFNα therapy.

References

1. Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Major depression induced by interferon-alpha in patients affected by hepatitis C virus. J Affect Disord 2000, in press.
2. Renault PF, Hoofnagle JH, Park Y et al. Psychiatric complications of long-term interferon alfa therapy. Arch Intern Med 1987;147:1577–1580.
3. Schafer M, Messer T, Wegner U, Schmid-Wendtner Mh, Volkenandt M. [Psychiatric side effects during adjuvant therapy with interferon-alpha in patients with malignant melanoma. Clinical evaluation as well as diagnostic and therapeutic possibilities]. Hautarzt 1999;50:654–658.
4. Darling JJ, Hoyle NR, Thomas DGT. Self and non-self in the brain. Immunol Today 1981;2:176–181.
5. Pan W, Banks WA, Kastin AJ. Permeability of the blood–brain and blood–spinal cord barriers to interferons. J Neuroimmunol 1997;76:105–111.
6. Shibata M, Blatteis CM. Human recombinant tumor necrosis factor and interferon affect the activity of neurons in the organum vasculosum laminae terminalis. Brain Res 1991;562:323–326.

https://doi.org/10.1034/j.1601-5215.2002.140301.x Published online by Cambridge University Press

7. Maes M, Meltzer H. The serotonin hypothesis of major depression. In: Bloom F, Kupfer D, eds. Psychopharmacology: the fourth generation of progress. New York: Raven Press, 1995, 933–944.
8. Morikawa O, Sakai N, Obara H, Saito N. Effects of interferon-alpha, interferon-gamma and cAMP on the transcriptional regulation of the serotonin transporter. Eur J Pharmacol 1998;349:317–324.
9. Abe S, Hori T, Suzuki T, Baba A, Shiraishi H, Yamamoto T. Effects of chronic administration of interferon alpha A/D on serotonergic receptors in rat brain. Neurochem Res 1999;24:359–363.
10. Kugaya A, Kagaya A, Uchitomi Y, Yokota N, Yamawaki S. Effect of interferon-alpha on DOI-induced wet-dog shakes in rats. J Neural Transm 1996;103:947–955.
11. Heyes MP, Saito K, Crowley JS et al. Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. Brain 1992;115: 1249–1273.
12. Recht M, Borden EC, Knight E Jr. A human 15-kDa IFN-induced protein induces the secretion of IFN-gamma. J Immunol 1991;147:2617–2623.
13. Nemeroff CB, Widerlov E, Bissette G et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 1984;226: 1342–1344.
14. Rubin RT, Poland RE, Lesser IM, Winston RA, Blodgett AL. Neuroendocrine aspects of primary endogenous depression. I. Cortisol secretory dynamics in patients and matched controls. Arch General Psychiatry 1987;44:328–336.
15. Raadsheer FC, Hoogendijk WJ, Stam FC, Tilders FJ, Swaab DF. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology 1994;60:436–444.
16. Nemeroff CB, Owens MJ, Bissette G, Andorn AC, Stanley M. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. Arch Gen Psychiatry 1988;45:577–579.
17. Carroll BJ. Clinical applications of the dexamethasone suppression test for endogenous depression. Pharmacopsychiatria 1982;15:19–25.
18. Maes M, Capuron L, Ravaud A et al. Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2-based immunotherapy. Neuropsychopharmacology 2001;24:130–140.
19. Navarra P, Tsagarakis S, Faria MS, Rees LH, Besser GM, Grossman AB. Interleukins-1 and -6 stimulate the release of corticotropin-releasing hormone-41 from rat hypothalamus *in vitro* via the eicosanoid cyclooxygenase pathway. Endocrinology 1991;128:37–44.
20. Maier SF, Goehler LE, Fleshner M, Watkins LR. The role of the vagus nerve in cytokine-to-brain communication. Ann NY Acad Sci 1998;840:289–300.
21. Kubera M, Kenis G, Bosmans E, Scharpe S, Maes M. Effects of serotonin and serotonergic agonists and antagonists on the production of interferon-gamma and interleukin-10. Neuropsychopharmacology 2000;23:89–98.
22. Xia Z, Depierre JW, Nassberger L. Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. Immunopharmacology 1996;34:27–37.
23. Duncan GE, Knapp DJ, Carson SW, Breese GR. Differential effects of chronic antidepressant treatment on swim stress- and fluoxetine-induced secretion of corticosterone and progesterone. J Pharmacol Exp Ther 1998;285:579–587.
24. Maes M, De Ruyter M, Hobin P, Suy E. Repeated dexamethasone suppression test in depressed patients. J Affect Disord 1986;11:165–172.
25. Brady LS, Whitfield HJ Jr, Fox RJ, Gold PW, Herkenham M. Antidepressant drugs regulate corticotropin-releasing factor and tyrosine hydroxylase messenger RNAs in rat brain. J Clin Invest 1991;87:831–837.
26. Rowe W, Steverman A, Walker M et al. Antidepressants restore hypothalamic-pituitary-adrenal feedback function in aged, cognitively-impaired rats. Neurobiol Aging 1997;18:527–533.
27. Musselman DL, Lawson DH, Gumnick JF et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 2001;344:961–966.
28. Gleason OC, Yates WR. Five cases of interferon-alpha-induced depression treated with antidepressant therapy. Psychosomatics 1999;40:510–512.

https://doi.org/10.1034/j.1601-5215.2002.140301.x Published online by Cambridge University Press