Mechanisms of interferon-alpha-induced depressive symptoms


M. C. Wichers, M. Maes
Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, the Netherlands

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 laminae 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.

A nother 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 depressed (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 amitriptyline (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. A 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

Interferon-alpha, serotonin and depression


