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SPECIAL SECTION

The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans

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Abstract

Administration of the cytokines interferon-α and interleukin-2 is used for the treatment of various disorders, such as hepatitis C and various forms of cancer. The most serious side-effects are symptoms associated with depression, including fatigue, increased sleepiness, irritability, loss of appetite as well as cognitive changes. However, great differences exist in the prevalence of the development of depressive symptoms across studies. Differences in doses and duration of therapy may be sources of variation as well as individual differences of patients, such as a history of psychiatric illness. In addition, sensitization effects may contribute to differential responses of patients to the administration of cytokines. In animals administration of pro-inflammatory cytokines induces a pattern of behavioural alterations called 'sickness behaviour' which resembles the vegetative symptoms of depression in humans. Changes in serotonin (5-HT) receptors and in levels of 5-HT and its precursor tryptophan in depressed people support a role for 5-HT in the development of depression. In addition, evidence exists for a dysregulation of the noradrenergic system and a hyperactive hypothalamic–pituitary–adrenal (HPA) axis in depression. Some mechanisms exist which make it possible for cytokines to cross the blood–brain barrier. Pro-inflammatory cytokines such as IL-1β, IFN-α, IFN-γ and TNF-α affect the 5-HT metabolism directly and/or indirectly by stimulating the enzyme indoleamine 2,3-dioxygenase which leads to a peripheral depletion of tryptophan. IL-1, IL-2 and TNF-α influence noradrenergic activity and IL-1, IL-6 and TNF-α are found to be potent stimulators of the HPA axis. Altogether, administration of cytokines may induce alterations in the brain resembling those found in depressed patients, which leads to the hypothesis that cytokines induce depression by their influence on the 5-HT, noradrenergic and HPA system.

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Cytokine therapy and neuropsychiatric side-effects

Cytokine therapy is used for the treatment of various disorders. The cytokine 'interferon-alpha' (IFN-α) has been used as a therapeutic agent in humans since 1976. First it was used for the treatment of chronic hepatitis B (Anonymous, 1976). Over the years it was also found to be effective in various forms of cancer such as renal cell cancer (Adams et al., 1984), metastatic melanoma (Borgstrom et al., 1982), chronic myelogenous leukaemia, AIDS-related Karposi's sarcoma and other forms of cancer. In addition, it has been used as a therapy for HIV-infected patients (Lane, 1991). IFN-α is mainly used for the treatment of patients suffering from a malignant melanoma and for chronic hepatitis C patients.

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IFN-α demonstrates major antiviral and immunomodulatory effects (Dumoulin et al., 1999). It increases the expression of MHC class I molecules and cellular adhesion molecules which is thought to facilitate the recognition of virus-infected or tumour cells by cytolytic T-lymphocytes (Herberman, 1997; Pfeffer et al., 1998). In addition it promotes the differentiation of macrophages, the production of pro-inflammatory cytokines such as IFN-γ (Bonaccorso et al., 2000), interleukin-6 (IL-6) (Corssmit et al., 1997), IL-1 and tumour necrosis factor-alpha (TNF-α) (Yoshie et al., 1982) and it may induce a 2- to 5-fold increase in surface receptors for the constant immunoglobulin region (Fc receptors) (Yoshie et al., 1982). These effects may result in increased macrophage function and an enhanced efficiency of antigen presentation (Rhodes et al., 1986). IFN-α also augments the cytotoxic activity of natural-killer (NK) cells by enhancing IL-2-dependent growth, cytokine production and antibody-dependent cellular cytotoxicity (Herberman, 1997). Finally, type I IFNs

(IFN-α, IFN-γ and IFN-ω) have variable effects on B-cell proliferation, differentiation, and antibody formation. Whether the effect is activation or inhibition depends upon the immunoglobulin isotype, the antigen dose, and the simultaneous secretion of other cytokines (Meurs and Hovanessian, 1988; Peters et al., 1986).

In hepatitis C the response rate of IFN-α monotherapy is only 10–15%. However, a combination therapy of ribavirin together with IFN-α increases the overall response rate to 40% (Collier and Chapman, 2001). In cancer, the response rate is around 20%. A meta-analysis showed a mean overall response rate of 14% (range 4–33%) for renal cell carcinoma and 24% (range 10–46%) for metastatic melanoma.

Another cytokine, IL-2, has been used as a therapeutic agent for the treatment of various forms of cancer, since 1981. IL-2 is an autocrine and paracrine growth factor that is secreted by activated T lymphocytes and promotes T-cell proliferation. IL-2-stimulated T cells exhibit enhanced cytotoxicity and produce lymphokines such as IFN-γ, TNF-β and transforming growth-factor (TGF)-β, B-cell growth factors such as IL-4 and IL-6 and haematopoietic growth factors such as IL-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF). In addition, IL-2 stimulates the cytolytic activity of NK cells and their secretion of several cytokines including IFN-γ, GM-CSF and TNF-α, it enhances the proliferation and antibody secretion by normal B cells and it stimulates the cytotoxic activities of activated macrophages and promotes their secretion of TNF-α, IL-1 and IL-6. IL-2 therapy has been shown to produce partial remission in some patients with renal cell carcinoma or metastatic melanoma (Oppenheim et al., 1994). In cancer therapy IL-2 is also used in combination with administration of IFN-α in order to increase the response rate.

Neuropsychiatric side-effects of IFN-α

In almost all patients, administration of IFN-α induces an acute influenza-like syndrome 6–8 h after the initial injection. Symptoms include fever, chills, malaise, myalgias, arthralgias and tachycardia. These symptoms gradually diminish over the first 2 wk of treatment. Other side-effects are gastrointestinal symptoms, such as anorexia, dyspepsia, nausea, diarrhoea, abdominal pain; respiratory symptoms, such as cough, dyspnoea and pharyngitis; dermatological symptoms such as hair loss, itching and rash; and haematological symptoms, such as anaemia, thrombocytopaenia and granulocytopaenia (Dieperink et al., 2000). However, the most common reason for discontinuation of IFN-α-based immunotherapy are neuropsychiatric symptoms.

The most common neuropsychiatric side-effects are symptoms associated with depression, such as fatigue, increased sleepiness and difficulty sleeping, irritability, loss of appetite, weight loss and low mood. A full-blown depressive disorder is reported in up to 36% of cases (Collier and Chapman, 2001). Other neuropsychiatric symptoms are cognitive changes involving verbal memory, cognitive speed and executive function (Pavol et al., 1995). In rare cases IFN-α may cause psychosis, delirium (Heeringa et al., 1998; Nozaki et al., 1997), persistent manic depressive illness (Monji et al., 1998) recurrence of a post-traumatic stress disorder (Maunder et al., 1998) or suicidal behaviour (Fukunishi et al., 1998; Janssen et al., 1994; Schäfer et al., 1999; Windemuth et al., 1999).

Most studies which examine the effects of IFN-α only briefly mention the occurrence of neuropsychiatric side-effects in some patients, using subjective reports. However, there are several studies which specifically examined the rate of depressive and cognitive symptoms during IFN-α therapy using instruments to measure these affective and cognitive changes (Tables 1–3). Almost all studies report an increase in depressive symptoms during IFN-α therapy (Bonaccorso et al., 2002; Hunt et al., 1997; Malaguarnera et al., 1998, 2001; Pariante et al., 1999; Pavol et al., 1995; Renault et al., 1987). One study measured depressive symptoms using the Beck Depression Inventory (BDI), but also performed PET scans before and 3 months after starting IFN-α therapy (Juengling et al., 2000). Although they reported a non-significant increase in depressive symptoms, they found that hypometabolism in the prefrontal areas covaried strongly with the BDI score ($p < 0.001$), suggesting that IFN-α changes the frontal lobe functioning. Another study (Adams et al., 1984) reported an increase in the behavioural symptoms of depression, such as decreased energy, psychomotor slowing, hypersomnia, loss of interest and decreased appetite. Paradoxically and in contrast to most studies, they found a decline in the number of patients experiencing episodic depression, which they explained as reflecting the patients' state of emotional indifference, consistent with changes in frontal lobe functioning. Only two studies found no changes at all in depressive symptoms (Mapou et al., 1996; Mulder et al., 2000).

More inconsistent results are found concerning the influence of IFN-α on symptoms of anxiety. Four studies, using the State-Trait Anxiety Inventory (STAI) (Caraceni et al., 1998), the Hamilton Anxiety Rating Scale (HAMA) (Bonaccorso et al., In Press), the non-patient version of the Structured Clinical Interview for DSM-III-R (SCID-NP) (Pariante et al., 1999) or a mental

Table 1. Studies using depression/anxiety assessments and measurements for cognitive function

Study	*n*	Measure	Condition	Findings
Pavol et al. (1995)	25	Subtests of WAIS-R, Verbal and non-verbal selective reminding test, grooved pegboard, subtest of multilingual aphasia examination, TMT-A and B, booklet category test, MMPI	IFN-α Control	In IFN-α group: worsening cognition, higher depresssion ratings, stress reactions and somatic concern
Caraceni et al. (1998)	67	UPDS, BPS, Corsi cubes spatial memory test, Digit span, STAI, TIC	IFN-α ($n=37$) Control ($n=30$)	In IFN-α group: action tremor, brief visual hallucinations, higher level of anxiety, no changes in cognitive function
Juengling et al. (2000)	11	PET scan, AVLT, verbal fluency, TMT-A, BDI, HADS and SCL-90	IFN-α	Non-significant raise in depression and decline in anxiety. Significant worsening AVLT, frontal hypometabolism which correlated strongly with BDI scores
Mapou et al. (1996)	18	Complete neuropsychological evaluation including tests of attention, response speed, motor skills, language, visuospatial skills, learning and memory. BDI, STAI	IFN-α	No significant changes
Adams et al. (1984)	10	Clinical mental status examination Bender Gestalt Test, TMT-A and B, Halstead Reitan Battery, 3 WAIS subtests	IFN-α	Increase in behavioural symptoms of depression, e.g. less energy, psychomotor slowing, hypersomnia, loss of interest and decreased appetite. However, depressed mood and anxiety decreased. Worsening executive functioning, planning

status examination (Renault et al., 1987) as assessment, showed an increase in level of anxiety. In three other studies (Adams et al., 1984; Hunt et al., 1997; Juengling et al., 2000), however, levels of anxiety appeared to be decreased. Although in one study the decline was non-significant (Juengling et al., 2000).

Neuropsychiatric side-effects of IL-2

Most studies evaluating IL-2 treatment report side-effects such as loss of energy, fatigue, malaise and decreased food intake (Hersch, 1989; Krigel et al., 1990; Pardo et al., 1996). Only few studies were carried out that examined the neuropsychiatric effects of IL-2 using psychiatric and/or cognitive instruments. Denicoff et al. (1987) studied 44 patients with metastatic cancer who received recombinant IL-2 alone, or IL-2 followed by treatment with combined autologous lymphokine-activated killer cells and IL-2. Cognitive tests and mood self-rating instruments were administered at the beginning and end of the IL-2 only and combined IL-2 and lymphokine-activated killer-cell treatment phases, as well as before discharge. Of the 44 patients studied, 15 showed severe behavioural changes, such as severe agitation and combative behaviour that necessitated the use of neuroleptic agents in 12 patients, physical restraints in 12, or emergency psychiatric consultation. In addition, 22 patients had severe cognitive changes, such as disorientation, delusions and hallucinations, and met the DSM-III criteria for delirium. Neuropsychological changes were mainly seen in the performance of the trail-making test (part B), in which the mean reaction time was nearly doubled. The Beck Depression rating scores were increased at the end of the combined IL-2 and lymphokine-activated killer-cell phase, but this test did not reach statistical significance when corrected for number of *t* tests done. Only one patient eventually met the DSM-III criteria for depression. One other study (Buter et al., 1993), in which neuropsychiatric toxicity was evaluated every treatment week, reports neuropsychiatric symptoms after a high dose of IL-2. Fourteen of 61 patients

Table 2. Studies using only assessments of depression/anxiety

Study	*n*	Measure	Condition	Findings
Malaguarnera et al. (1998)	96	Zung's self-rating depression scale (SDS)	Recombinant IFN-α-2a Recombinant IFN-α-2b Lymfoblastoid IFN-α Leukocyte IFN-α	In all groups a significant increase in SDS
Malaguarnera et al. (2001)	96 (same population)	HAMD	Same conditions	In all groups a significant increase in HAMD
Bonaccorso et al. (2002)	14	HAMA and MADRS	IFN-α-2a	Significant increase in HAMA and MADRS, 50% scored >15 on MADRS
Hunt et al. (1997)	38	HADS, BDI, SF-36	IFN-α-2b	BDI significantly elevated in 20–30% of the patients, HAD anxiety scores decreased in first month, HAD depression scores did not change. No change in health status
Mulder et al. (2000)	63	SCID, SCL-90	IFN-α	No changes in anxiety or depression scores
Pariante et al. (1999)	50	SCID	Natural or recombinant IFN-α	11 of 50 patients developed diagnosed major depressive disorder (MDD), MDD not otherwise specified, generalized anxiety disorder or severe dysphoria
Renault et al. (1987)	58	Psychiatric consultation and SCL-90	IFN-α	17% developed psychiatric side-effects

Table 3. Study using only assessment of cognitive function

Study	*n*	Measure	Condition	Findings
Poutiainen (1993)	21	Mental control, digit span, logical memory tests of Wechsler Memory Scale (WMS), calculation ability, naming and interference tasks of the Stroop test, copying a cube and signature writing	IFN-α ($n=16$) Control ($n=3$)	Cognitive deterioration in logical memory task of WMS, calculation ability, signature writing

experienced neuropsychiatric symptoms. One patient died of brainstem ischaemia, 1 complained about hallucinations. Computer tomography of the brain revealed brain metastases in 2 patients, 1 suffering from disorientation and depressive symptoms and 1 having headaches and concentration difficulties.

IL-2 therapy has also been combined with administration of IFN-α. Fenner et al. (1993) conducted a study in which 101 patients were evaluated for neurotoxicity during treatment with a combination of IL-2 and IFN-α. A total of 39 patients had minor or major concentration difficulties, 5 became disoriented, 37 suffered from mild paraesthesia, 4 patients had transient muscle weakness and 1 patient had hemiparesis. In addition, Capuron et al. (2000) evaluated the development of depression and anxiety in cancer patients receiving IL-2 (20 patients), IFN-α (8 patients) or a combination of IL-2 and IFN-α (6 patients), using the Montgomery–Asberg Depression Rating Scale (MADRS) and the Covi Anxiety Scale, respectively. IL-2 treatment, but not IFN-α treatment, significantly raised the depression scores. Combined treatment of IL-2 and IFN-α produced much higher depression scores than IL-2 alone. Anxiety scores were raised significantly only after the combined treatment of IFN-α and IL-2. Addition of IFN-α to IL-2 treatment seemed

to be acting synergistically in the development of anxiety and depressive symptoms and amplifies the neuropsychiatric effect of IL-2.

Interpretation of differences across studies

Although many studies agree that depression and cognition scores worsen during immunotherapy, there are many differences in the prevalences of these side-effects, ranging from no significant differences in depressive symptoms (Mulder et al., 2000) to a prevalence of 45% of patients who suffer from a full-blown depressive disorder after 12 wk of IFN-α treatment (Musselman et al., 2001). Some explanations for this discrepancy may be postulated. In the first place, the neuropsychiatric side-effects appear to be dose-related (Dusheiko, 1997). Denicoff et al. (1987) found that patients who were receiving low doses were more likely to have only mild cognitive effects or no neuropsychiatric effects than were those receiving high doses (68% compared with 29%). In addition, the duration of therapy may influence the occurrence of psychiatric symptoms. After 24 wk, 25% of a total of 231 patients receiving IFN-α therapy showed depressive symptoms, while after 48 wk of treatment the percentage was 37% of a total of 225 patients (McHutchison et al., 1998). For anxiety, 9 and 13% of all patients experienced symptoms of anxiety after 24 and 48 wk, respectively. The incidence of irritability also increased as a function of duration of therapy, with 19% experiencing irritability after 24 wk and 27% after 48 wk of therapy. Furthermore, in some studies patients receive additional medication that may affect the incidence of psychiatric side-effects. Another issue is the method used to measure the psychiatric symptoms. Most studies base their incidence rate on subjective reports, other studies, however, summarized in Tables 1 and 2, use more reliable objective measurements to assess the amount of psychiatric problems of patients. This of course may also be a source of variation in the percentage of patients reporting that they have experienced some kind of neuropsychiatric side-effect.

Predictors of psychiatric symptoms

Others sources of variation are the individual differences between patients. In psychiatric risk groups, the incidence of neuropsychiatric side-effects may be higher and a history of psychiatric illness is seen as a contraindication for treatment with IFN-α. It is thought that patients with pre-existing psychiatric conditions have more risk of developing develop psychiatric side-effects. Ho et al. (2001) found that 32% of patients with a psychiatric history and only 14% of patients without a psychiatric history developed neuropsychiatric symptoms. In addition, delirium tended to occur in patients with previous evidence of organic brain injury or dysfunction, or previous drug and alcohol abuse (Renault et al., 1987). Furthermore, Hensley et al. (2000) found severe neuropsychiatric toxicity in 12 of 19 patients (63%) with a pre-existing neurological or psychiatric diagnosis compared to 10 of 72 patients (14%) without diagnosis. However, other studies showed no evidence of this increased risk for neuropsychiatric side-effects for at-risk patients (Mulder et al., 2000; Pariante et al., 1999).

There is also some evidence that biological measurements may function as a predictor for the risk of neuropsychiatric side-effects. Lowered activity of peptidases, such as prolylendopeptidase (PEP) and dipeptidyl peptidase IV (DPP IV) may occur in major depression. Patients who had a lowered PEP or DPP IV activity before starting IFN-α therapy had significantly higher MADRS and HAMA scores at both baseline and during immunotherapy than patients with normal baseline PEP or DPP IV activity. Furthermore, patients with lowered serum DPP IV activity also had significantly higher increases in MADRS ratings following IFN-α therapy than those with normal serum DPP IV activity (Maes et al., 2001).

Sensitization and cross-sensitization

Other sources of variability across patients are time-dependent sensitization (TDS) and cross-sensitization. TDS is the phenomenon that a drug, administered once or twice, triggers a biological process which then progresses entirely as a function of the passage of time (Antelman et al., 2000). For example, an acute exposure to either the tricyclic antidepressant, imipramine, or one very brief electroconvulsive shock (ECS), followed by 7–10 d without treatment, induced a change in the responsivity of dopamine autoreceptors, which grew, i.e, sensitized or strengthened, with the passage of time, resulting in changes that were approx. 30% greater than those seen in control groups examined at the same time, but exposed to daily drug or ECS (Chiodo and Antelman, 1980a,b). A drug represents a foreign substance which is a potential threat to the organism. TDS is a non-specific process with adaptive value which ensures that if the organism survives the initial threatening episode it would have a sensitized defensive response, enabling it to react faster and/or more strongly, should it ever re-encounter the same or a similar stimulus (Antelman et al., 2000). Because of the existence of this phenomenon it is possible that patients react differently to a specific drug, because of different

previous experiences. Furthermore, long-lasting cross-sensitization of behavioural responses have been described for drugs and stressors, i.e the phenomenon that sensitization may also lead to exaggerated responses to stimuli of a different nature (Antelman et al., 1980). For example, it has been found that single administration of IL-1 to adult rats not only enhanced adrenocorticotropin (ACTH) and corticosterone responses to IL-1, but also to electric foot shocks (Schmidt et al., 1995) and amphetamine (Schmidt et al., In Press). Similarly, electric foot shocks induce long-lasting sensitization of the ACTH response to a novel environment (van Dijken et al., 1993) and cross-sensitization of the hypothalamic–pituitary–adrenal (HPA) response to amphetamines (Schmidt et al., In Press). Thus, because of the fact that patients may differ in the extent to which they have experienced specific stressors, or intake of drugs or other foreign substances, they may differ in reaction to the administration of IFN-α or IL-2.

Cytokine-induced sickness behaviour

Peripheral or central administration of pro-inflammatory cytokines in rats, such as IL-1β, IL-6 and TNF-α, induces a behavioural pattern referred to as 'sickness behaviour' (Kent et al., 1992). IL-1β and TNF-α provoked increased sleep (Krueger et al., 1995), reduced locomotor activity (Bianchi et al., 1992; Lacosta et al., 1998) and also produced a decrease in chocolate milk consumption in mice (Brebner et al., 2000). Furthermore, it was found that these two cytokines act synergistically in doing this (Brebner et al., 2000). In addition, decreased social exploration and decreased body weight was found in response to administration of IL-1 and TNF-α (Bluthe et al., 1994). Pretreatment with IL-1 receptor antagonist (IL-1Ra) antagonized the depressive effect of TNF-α on behaviour, but not on body weight. These results suggest that behavioural alterations of TNF-α, but not metabolic changes, are mediated by IL-1. Bluthe et al. (2000) did not find direct effects of IL-6 on social exploration, immobility or body weight and no effects of IL-6 were found in the consumption of chocolate milk (Brebner et al., 2000). However, when IL-6-deficient mice (IL-6$-/-$) were compared with IL-6$+/+$ mice, a weakened effect of lipopolysaccharides (LPS) and IL-1 on social interaction and body weight was found in the IL-6-deficient mice, suggesting a supporting, but not essential role for IL-6 in the development of sickness behaviour (Bluthe et al., 2000).

These symptoms, induced by administration of pro-inflammatory cytokines, resemble the vegetative symptoms of depression in humans, such as anorexia, weight loss, psychomotor retardation, sleep disorders and anergy (Maes, 1993). Charlton (2000) describes sickness behaviour as an evolutionary-evolved physiological and psychological adaptation to acute infective and inflammatory illness in many mammalian species, which is nearly identical to major depressive disorder in humans. Charlton (2000) proposes that malaise, the symptoms of feeling ill, is the core emotion of depression and that low mood is the product of malaise.

The serotonin (5-HT) hypothesis of depression

Major evidence exists that disturbances in the serotonergic functioning play a causal role in the pathophysiology of depression. The serotonergic system evolved very early in evolution and is widely distributed throughout the brain. Output innervates virtually all regions of the central nervous system, particularly the cerebral cortex, limbic regions, basal ganglia and hypothalamus (Tork, 1990). This extremely wide distribution probably explains why alterations in 5-HT function can modify so many behaviours, including motor output, learning, sleep, circadian pattern, food intake and sexual activity (Smith and Cowen, 1997).

Several neurochemical changes in the 5-HT system are seen in depressed people. Tryptophan (Trp), the precursor of 5-HT has to compete with other competing amino acids (CAA) for entrance through the blood–brain barrier. Lower plasma Trp levels and a lower Trp/CAA ratio are found in depression (Maes et al., 1993). This depletion of plasma concentrations of Trp is likely to lead to a reduced synthesis of 5-HT in the brain since the latter depends on the plasma availability of Trp. Furthermore, studies have consistently found that acute Trp depletion, experimentally induced by giving a Trp-free amino-acid diet, can transiently reverse the therapeutic effect of antidepressant medications (Dursun et al., 2001) and that it produces a deterioration in mood in subjects who are at a greater risk for depression (Dursun et al., 2001).

In addition, central changes in 5-HT metabolism have been shown. Changes are found in the 5-HT transporter (5-HTT) function. The 5-HTT is located on the presynaptic membrane 5-HT cell bodies in the raphe nuclei (RN) where it regulates 5-HT levels in the synaptic cleft by modulating the reuptake of 5-HT into the presynaptic cell (Staley et al., 1998). Evidence exists that 5-HT uptake is genetically controlled. Transcriptional activity of the human 5-HTT gene is modulated by a polymorphic repetitive element (5-HTTLPR). Having the long variant of the 5-HTTLPR genotype leads to more 5-HTT mRNA, 5-HTT protein and 5-HT uptake than having the short variant (Lesch et al., 1996).

Moreover, this polymorphism is associated with anxiety-, depression- and aggression-related personality traits and it may influence the risk of affective disorders such as depression (Lesch and Mossner, 1998).

Other central changes of the 5-HT system in depression include changes in 5-HT_2 and 5-HT_{1A} brain receptors (Maes and Meltzer, 1995). Increased 5-HT_2 receptor binding in the frontal cortex was found in depressed patients compared to controls using single photon emission tomography (PET) (Yatham et al., 2000). Another PET study showed a reduction in 5-HT_{1A} receptor binding in many regions of the brain, including the frontal, temporal and limbic cortex, in both medicated and unmedicated depressed patients compared to control subjects (Sargent et al., 2000).

The noradrenergic hypothesis of depression

The first catecholamine hypothesis of depression posited that depression was associated with a decrease in noradrenergic neurotransmission (Bunney and Davis, 1965; Schildkraut, 1965). It was thought that supersensitivity of the inhibitory, presynaptic α_2-adrenoreceptors (α_2-ARs) may explain decreased catecholaminergic neurotransmission with resultant postsynaptic β-receptor up-regulation (Garcia-Sevilla et al., 1981). Recently, this catecholamine-depletion hypothesis has been reformulated into the 'dysregulation hypothesis' which proposes that an impaired negative feedback on the presynaptic neuron causes an exaggerated noradrenaline (NE) release. The following findings support this hypothesis. First, depressed patients showed significantly higher plasma NE levels than controls (Maes et al., 1990, 1991; Potter et al., 1985; Roy et al., 1988). Several studies showed increased levels of NE in urine, blood and cerebrospinal fluid (Maes et al., 1999).

Furthermore, studies have been performed that show evidence for a subsensitivity of the presynaptic α_2-ARs (Kafka and Paul, 1986; Maes et al., 1999; Mitrius et al., 1983; Roy and Kafka, 1989). This subsensitivity of central α_2-ARs may be the cause of an impaired negative feedback on the presynaptic catecholaminergic neuron, which in turn may induce a disinhibition of noradrenergic output in response to any activation (Maes et al., 1999). Thus, dysregulation of the NE system may also contribute to the pathophysiology of depression.

The HPA axis and depression

Corticotropin-releasing factor (CRF) mediates endocrine, autonomic and behavioural responses to stress. During stress the synthesis of CRF in the paraventricular nucleus (PVN) increases and is released from terminals, stimulating the anterior pituitary gland, which releases ACTH, which in turn induces the release of glucocorticoids from the adrenal cortex (Arborelius et al., 1999). Besides mediating the endocrine response to stress it plays a role in autonomic responses, by increasing heart rate and mean arterial pressure, and in behavioural responses to stress, by suppression of exploratory behaviour, decreasing food intake and sexual behaviour and increasing conflict behaviour and grooming in animals (Dunn and Berridge, 1990; Koob et al., 1993; Owens and Nemeroff, 1991). There is some evidence that a hyperactive HPA axis may play a role in the pathophysiology of depression (Arborelius et al., 1999). Elevated cerebrospinal fluid CRF concentrations and plasma cortisol levels have been observed in drug-free patients with major depression compared with patients with other psychiatric disorders and healthy controls (Nemeroff et al., 1984). In addition, post-mortem studies revealed elevated CRF concentrations and CRF mRNA in the hypothalamic PVN of depressed patients (Raadsheer et al., 1994, 1995). Further, normalization of these levels occurs after successful antidepressant treatment with electroconvulsive therapy (Nemeroff et al., 1991) or with fluoxetine (De Bellis et al., 1993).

In addition to a hyperactive HPA axis, evidence exists for an impaired negative feedback control of the HPA axis exerted by corticosteroids. Endogenous glucocorticoids serve as potent negative regulators of the synthesis and release CRF through binding to glucocorticoid receptors (GR) in the hypothalamus and hippocampus. An abnormality in this feedback function in depressed patients is supported by their abnormal responses to the dexamethasone suppression test (DST) (Carroll et al., 1976). Depressed patients demonstrate non-suppression of cortisol secretion following administration of the synthetic glucocorticoid, dexamethasone (Gold et al., 1988; Nemeroff, 1996; Owens and Nemeroff, 1993). A reduction in the number of GRs in depressed patients relative to healthy controls has been reported (Gormley et al., 1985; Sallee et al., 1995; Whalley et al., 1986). Furthermore, Gormley et al. (1985) and Lowy et al. (1988) reported that only depressed DST suppressors showed a decrease in GR binding after dexamethasone administration.

Interactions between neurotransmitter systems and HPA axis with implications for depression

There is a significant interconnectivity (Mongeau et al., 1997) between the locus coeruleus (LC), where most

cell bodies containing NE are found, and the raphe nuclei, the primary location of serotonergic neurons. Their actions appear to be mutually inhibitory. The dorsal raphe nucleus (DRN) is able to mediate activation of the LC by its effect on the two principal neural inputs that modulate LC activity, the nucleus paragigantocellularis (PGI) with an excitatory and the nucleus prepositus hypogloss (PrH) with an inhibitory influence on LC activity. The DRN inhibits LC activity by activating the PrH via 5-HT_2 receptors and by inhibiting the PGI via inhibitory 5-HT_{1A} receptors. In return, the LC exerts an inhibitory influence on the median raphe nucleus (MRN) via the inhibitory α_2 receptors and both excitatory and inhibitory effects on the DRN via α_1 and α_2 receptors, respectively. In addition, inhibitory α_2 receptors have been localized on 5-HT terminals and excitatory 5-HT_3 receptors on NE terminals. This suggests a negative feedback loop in which increasing extracellular 5-HT concentrations lead to increased inhibition of 5-HT via the activation of the presynaptic α_2 receptors of the noradrenergic system (Mongeau et al., 1997; Ressler and Nemeroff, 2000).

Stress or activating stimuli cause an initial activation of the LC–NE system via the release of CRF from the amygdala in the limbic system and from the PVN in the hypothalamus. This activation is opposed by the inhibition of these circuits by 5-HT release which promotes tolerance to aversion and decreases the stress response (Mongeau et al., 1997; Ressler and Nemeroff, 2000).

In depression, as described previously, the interaction between NE and 5-HT may be out of balance: the NE system is hyperactive causing an enhanced response to stress/fear related stimuli, while the 5-HT system has been found to be hypoactive, thus causing decreased inhibition of stress reactivity and decreased tolerance to aversion. These neurotransmitter alterations hereby contribute to an abnormally activated amygdala which leads to increased release of CRF and adrenal steroids, which in turn further activate vigilance and stress/fear responsiveness (Ressler and Nemeroff, 2000).

Influence of cytokines on depression-modulating systems

Cytokines and blood–brain barrier

The presence of a blood–brain barrier (BBB) effectively restricts the free exchange of most solutes between plasma and the extracellular fluid of the brain. Nevertheless, peripherally circulating cytokines are able to affect central brain function. Passive transport across the BBB is not likely, because cytokines are relatively large protein molecules and their hydrophilic nature does not allow them to cross the BBB (Maier and Watkins, 1998). However, four possible ways have been proposed for cytokines to communicate with the brain. First, cytokines may be transported into the brain by specific active transport mechanisms (Maier and Watkins, 1998). Secondly, specific uptake mechanisms for various peptides, including IL-1α and IL-1β, have been demonstrated at the luminal surface of the BBB (Begley, 1992; Ermisch et al., 1993). In addition, cytokines may enter the brain at the sites where the BBB is deficient, for example at the organum vasculosum of the lamina terminalis (OVLT), with the consequent stimulation of other messengers, such as prostaglandins in this location, which can diffuse to neighbouring regions (Blatteis, 1990; Stitt, 1992). Thirdly, cytokines may affect the BBB by the induction of adhesion molecules, such as ICAM-1 and VCAM-1 in the brain endothelium, which increases the potential for circulating T lymphocytes, especially CD4+ T lymphocytes, to cross the BBB (Brown, 2001). Fourthly, cytokines may be able to activate ascendant peripheral nerves. The vagus nerve innervates regions of the body in which immune responses occur (the gut, spleen, thymus, lymph nodes etc.) and provides afferent input to the brain from these regions. IL-1 receptors are found on structures that surround vagal terminals called paraganglia. These paraganglia synapse onto the vagal fibres where they release a number of different neurotransmitters. Thus, IL-1 released by activated immune cells binds to IL-1 receptors, which causes the paraganglia to release a transmitter onto the vagal terminals, thereby activating afferent vagal fibres. These fibres terminate in the nucleus tractus solitarius (NTS) and the area postrema. The NTS projects to the hippocampus and the hypothalamus, acting on central IL-1 receptors. This allows peripheral IL-1 to induce central IL-1 production (Ek et al., 1998; Maier and Watkins, 1998). Thus, although passing the BBB is difficult for cytokines, they do have the potential to influence brain function.

Influence of cytokines on 5-HT

Several cytokines have profound effects on the serotonergic systems in the brain and in the periphery. Peripheral and central administration of IL-1β, IFN-γ, and TNF-α significantly increase extracellular 5-HT concentrations in rats in several brain areas such as the hypothalamus, the hippocampus and the cortex (Clement et al., 1997). Intraperitoneal injection of LPS and IL-1 increased mouse brain concentrations of the 5-HT catabolite, 5-hydroxyindoleacetic acid (5-HIAA), and Trp in all brain areas examined (Dunn, 1992a). No changes were found after IL-6 injection. However,

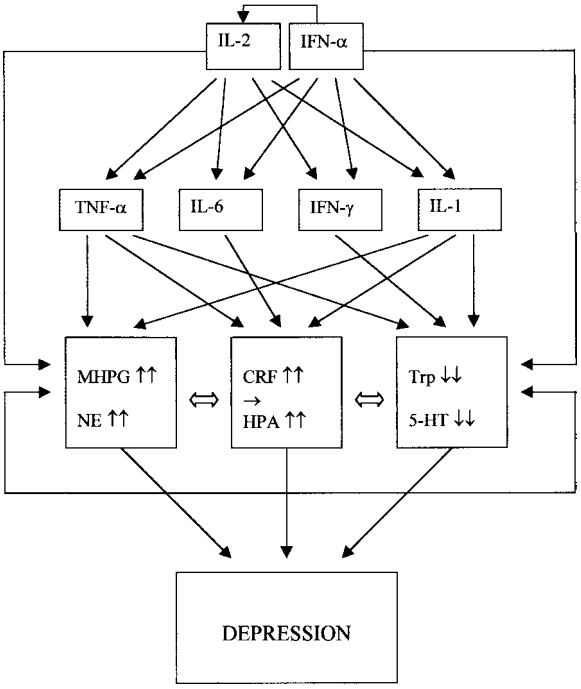

Figure 1. Possible ways for pro-inflammatory cytokines to induce depression.

Zalcman et al. (1994) also reported elevated 5-HIAA levels in the hippocampus and prefrontal cortex after intraperitoneal injection with IL-6 into mice.

Cytokines, such as IL-1, IFN-γ and TNF-α not only acutely stimulate 5-HT neurotransmission, but also reduce the production of 5-HT by stimulating an enzyme called indoleamine 2,3-dioxygenase (IDO), which converts Trp, the precursor of 5-HT, into kynurenine. Overstimulation of IDO leads to depletion of plasma concentrations of Trp and, therefore, to reduced synthesis of 5-HT in the brain (Heyes et al., 1992).

Furthermore, the pro-inflammatory cytokines IL-1, IFN-α, IFN-γ and TNF-α also have been shown to upregulate the 5-HTT, causing a depletion of extracellular 5-HT (Morikawa et al., 1998; Mossner et al., 1998; Ramamoorthy et al., 1995), while the anti-inflammatory cytokine IL-4 was shown to induce a reduction of 5-HT uptake (Mossner et al., 2001).

Finally, evidence exists for modulation of 5-HT_{1A} (Abe et al., 1999) and 5-HT_2 (Kugaya et al., 1996) receptors by IFN-α.

Influence of cytokines on NE

Effects of cytokines on the noradrenergic system have also been described. IL-1 has been shown to stimulate hypothalamic and preoptic noradrenergic neurotransmission in rats (Kabiersch et al., 1988) and mice (Dunn, 1988). In addition, Zalcman et al. (1994) also observed IL-1-induced increases in the 3-methoxy-4-hydroxyphenylglycol (MHPG)/NE ratio in the prefrontal cortex and hippocampus in mice. All these effects of IL-1 are characteristic of various forms of IL-1 administered by various routes (Dunn et al., 1999).

Other cytokines also show some influence on NE. Intraperitoneal injection of IL-2 in mice increased MHPG concentrations and the MHPG/NE ratio in the hypothalamus (Zalcman et al., 1994). For TNF-α inconsistent results have been found. It has been reported to increase brain MHPG, but only at the higher doses (1 μg or more) (Ando and Dunn, 1999). In contrast, other studies reported that TNF-α inhibited NE release from the median eminence (Elenkov et al., 1992) and from the myenteric plexus (Hurst and Collins, 1994).

Influence of cytokines on HPA axis

IL-1 has been shown to be a potent stimulator of the HPA axis (Besedovsky et al., 1986). IL-1 administration to mice markedly increased HPA activation, indicated by elevation of plasma corticosterone, in parallel with its effect on NE (Dunn and Swiergiel, 1998). In addition, many researchers have reported that IL-6 administration activates the HPA axis as indicated by elevations of ACTH and corticosterone. Wang and Dunn (Dunn, 1992b; Wang and Dunn, 1998) found that injection of murine IL-6, injected either intravenously or intraperitoneally, elicted modest increases in plasma ACTH and corticosterone. However, maximal concentrations were much lower than observed with IL-1 (Wang and Dunn, 1998). TNF-α also enhances HPA activation, but was found to be significantly less potent than IL-1 (Besedovsky et al., 1991; Del Rey and Besedovsky, 1992; Dunn, 1992b).

Furthermore, pro-inflammatory cytokines may induce a mechanism which leads to the generation of glucocorticoid resistance. The human glucocorticoid receptor (hGR) gene encodes two protein isoforms: GRα which binds hormone, translocates to the nucleus, and regulates gene transcription, and GRβ which does not bind known ligands and attenuates GRα action. TNF-α and IL-1β induce a disproportionate increase in GRβ over GRα. By causing this accumulation of GRβ isoform levels, which leads to increased inhibition of GRα action, pro-inflammatory cytokines may trigger glucocorticoid resistance (Webster et al., 2001).

Hypothesis of the mechanism of cytokine-induced depression

In short, IFN-α and IL-2 have been shown to cause several depressive and other neuropsychiatric symptoms

in a high percentage of patients. Mechanisms by which these symptoms are produced are unknown, however, a possible model of the way in which pro-inflammatory cytokines may induce depression may be proposed (Figure 1). IFN-α stimulates the production of pro-inflammatory cytokines. The latter, in turn, affect the central NE and 5-HT neurotransmitter systems and the activity of the HPA axis. Also, these systems themselves show extensive interconnectivity, allowing for mutual interactions between them. Therefore, we may postulate that a disturbance in one these systems also affects the other systems. Changes in these systems, such as increased NE activity, increased HPA activity and decreased 5-HT brain availability, caused by pro-inflammatory cytokines, are exactly the changes also seen in patients with depression, suggesting that cytokines may induce depression by their effect on the 5-HT system, NE system, and the HPA axis.

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