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Cytokines, stress, and depressive illness

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Abstract

It has been suggested that immune activation, and particularly increased activity of several cytokines, notably interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor-α as well as their soluble receptors is characteristic of depression. Normalization of cytokine activity does not necessarily occur following successful antidepressant, suggesting that cytokines may be trait markers of depression, or simply represent bystander effects of the illness. The relationship between cytokines and depression is complicated as a variety factors could directly or indirectly influence cytokine activity. While cytokine elevations are most pronounced in severe (melancholic) depression, their activity may also be related to chronicity of illness, neurovegetative features of depression (altered sleep patterns, food intake, weight changes, fatigue or general activity), or the high stress perception characteristic of depression. Although, studies assessing cytokines in depressive populations are basically correlational in nature, patients receiving cytokine immunotherapy frequently show depressive symptoms, which may be attenuated by antidepressant medication, supporting a causal role for cytokines in depressive disorders. The processes underlying such outcomes remain to be established, but the affective changes may stem from the neuroendocrine and central neurochemical changes elicited by cytokines, as these are reminiscent of those thought to subserve depression.

Keywords: Depression; Anxiety; Stress; Neuroendocrine; Cytokine; Interleukin-1; Interleukin-2

1. Introduction

It has been suggested that stressors instigate hormonal variations, coupled with central neurochemical alterations that favor the development of depressive illness. Indeed, in many respects the effects of stressors are reminiscent of the presumed neurochemical disturbances thought to be associated with depression, including elevated hypothalamic–pituitary–adrenal (HPA) functioning and altered norepinephrine (NE), dopamine (DA), and serotonin (5-HT) activity within hypothalamic and limbic brain regions. Studies in animals have indeed shown that stressors will induce behavioral changes akin to those that characterize depression, and these behavioral disturbances are alleviated by treatments, including antidepressant agents, that attenuate the stressor-provoked amine alterations (Anisman, Zalcman, & Zacharko, 1993).

While it has been assumed that psychological (psychogenic) and physical (neurogenic) stressors are most closely aligned with depression, the

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suspicion has arisen that systemic stressors, including immune alterations, may also act in such a provocative capacity (Maes, 1999). Communication occurs between the immune, endocrine, autonomic, and central nervous systems (Blalock, 1994; Rothwell & Hopkins, 1995), such that psychological events that affect central neurochemical processes may affect immune activity. Conversely, immune activation may affect hormonal processes and the activity of central neurotransmitters. Thus, by virtue of the neurochemical effects imparted, immune activation may come to affect behavioral outputs and may even be related to behavioral pathology such as depressive illness (Licinio & Wong, 1999; Maes, 1995, 1999).

The present review will describe the presumed relationship between cytokines and depressive illness in humans, and some of the hypothesized mechanisms that may underlie this relationship. Before discussing the literature concerning depression in humans, a brief overview is presented regarding the neurochemical and hormonal concomitants of cytokine challenge. A more detailed review of this literature is presented in Anisman and Merali (1999) and in the accompanying paper (Anisman, Kokkinidis, & Merali, 2002).

2. Cytokines as immunotransmitters

While several potential routes of communication exist between the immune and central nervous systems (Watkins, Maier, & Goehler, 1995), signaling molecules of an activated immune system, namely cytokines, may also play a fundamental role in alerting the CNS of immunological challenge (Anisman & Merali, 1999; Dunn, 1995). For instance, cytokines, such as interleukin-1β (IL-1β), stimulate cytokine receptors on the dendrites of the vagal nerve at visceral locations or at the level of the nodose ganglion (Dantzer et al., 1996; Maier & Watkins, 1998), hence activating brainstem regions, including the nucleus of the solitary tract (NTS). As well, cytokines may gain access to the brain, promoting the release of various neurotransmitters. Certainly, the large size of cytokine molecules limits access to the brain, but entry may occur where the blood–brain barrier is less restrictive (e.g., the organum vasculosum laminae terminalis), or via different transport systems (Banks, 2001; Plotkin, Banks, Maness, & Kastin, 2000). Furthermore, the integrity of the blood–brain barrier may be compromised by various insults including stressors, pathological conditions (e.g., seizure), and by cytokines (Rothwell, 1999; Rothwell & Hopkins, 1995). Thus, there are conditions in which the influence of cytokines on CNS processes may be appreciably increased.

In addition to infiltration from the periphery, cytokines are constitutively expressed in several brain sites, including circumventricular regions, hypothalamus, hippocampus, cerebellum, forebrain regions, basal ganglia, as well as brainstem nuclei. Moreover, bioactivity of cytokines within brain may be provoked by various challenges, such as systemic or central bacterial endotoxin administration, and under neuropathological conditions, including brain injury, cerebral ischemia, and seizure (Plata-Salaman & Turrin, 1999; Rothwell, 1999; Rothwell & Hopkins, 1995; Turrin et al., 2001). The functional role of central cytokine activation remains to be fully elucidated. Proinflammatory cytokines such as IL-1β, may function in a reparative capacity in neurological diseases or brain trauma, or alternatively, they actually promote neuronal damage following central insults (Plata-Salaman & Turrin, 1999; Rothwell, 1999).

3. Neurochemical consequences of cytokine challenge

3.1. Immediate effects of cytokines

Paralleling the effects of psychological or physical stressors, both central and systemic IL-1β administration increased hypothalamic neuropeptide release, including activation of neurons of the paraventricular nucleus, which contain corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) (Ericsson, Kovacs, & Sawchenko, 1994; Rivest & Rivier, 1994). The CRH and AVP synergistically stimulate pituitary adrenocorticotropic hormone (ACTH) release, which then stimulates release of adrenal corticosterone. There is reason to believe that NE may promote the IL-1β induced HPA changes, while nitric oxide restrains HPA responses to proinflammatory stimuli (Dunn, 1995; Turnbull & Rivier, 1996).

In addition to affecting neuropeptide release, systemic administration of IL-1β and TNF-α increased NE, DA, and 5-HT activities in several hypothalamic nuclei, as well as at limbic sites (Anisman & Merali, 1999; Dunn, 1995, 2001). While these cytokines elicit stressor-like effects, in some respects their actions could be distinguished from those of traditional stressors. For instance, unlike stressors (Deutch & Roth, 1990), IL-1β did

not induce marked DA changes within the prefrontal cortex and nucleus accumbens (Lacosta, Merali, & Anisman, 1998; Merali, Lacosta, & Anisman, 1997; Song, Merali, & Anisman, 1999). However, increased in vivo accumbal DA release was elicited by systemic administration of the bacterial endotoxin, lipopolysaccharide (LPS) (Borowski, Kokkinidis, Merali, & Anisman, 1998), raising the possibility that immune activation and the sequential (or concurrent) release of several cytokines are necessary to mimic the effects of stressors.

Just as cytokines affect neuroendocrine and neurochemical processes, stressors increase IL-1β mRNA expression and protein within the brain (Minami et al., 1991; Nguyen et al., 1998, 2000), and pretreatment with an IL-1 receptor antagonist (IL-1Ra) attenuated the hypothalamic monoamine and the neuroendocrine effects otherwise observed (e.g., increased pituitary ACTH and adrenal glucocorticoid release) (Shintani et al., 1995). Yet, it has been reported that in response to a psychological stressor, administered either acutely or chronically (e.g., predator exposure), mRNA expressions of IL-1β, IL-1R-I, IL-1R-II, IL-1RA, IL-1 accessory proteins, and TNF-α were not altered (Plata-Salamán et al., 2000). It may be that this stressor was simply not an effective one in promoting central cytokine variations. After all, activation of CNS cytokines in response to everyday insults may be maladaptive. Nevertheless, it is possible that in animals that are particularly vulnerable to stressors, altered CNS cytokine functioning would be realized.

3.2. Sensitization of cytokine effects

In considering the impact of various stressors, it is essential to underscore that such factors not only have marked immediate repercussions but may also proactively influence the response to later challenges. Stressful events may engender the sensitization of neuronal systems so that later stressor experiences result in exaggerated neurochemical alterations. Thus, it may be that stressful events increase vulnerability to depressive illness, and the provocation of affective disturbances will be realized upon reexposure to the stressor or upon exposure to other types of insults that trigger the sensitized neurochemical response (Anisman et al., 1993). As in the case of processive stressors, IL-1β and TNF-α provoke a "sensitization-like" effect so that the neuroendocrine response to later challenges is increased (Hayley, Brebner, Merali, & Anisman, 1999; Tilders & Schmidt, 1998). In particular, these cytokines increase the co-storage of CRH and AVP within CRH terminals at the external zone of the median eminence. This effect develops with the passage of time, peaking after about 2 weeks, and in the case of IL-1β, persists as long as 2 months after the initial cytokine challenge (Hayley, Lacosta, Merali, van Rooijen, & Anisman, 2001a; Schmidt, Janszen, Wouterlood, & Tilders, 1995; Tilders & Schmidt, 1998; Tilders, Schmidt, & De Goeij, 1993). As CRH and AVP synergistically stimulate pituitary ACTH release, later exposure to a neurogenic stressor (footshock) or to the cytokine itself, augmented plasma ACTH and corticosterone secretion (Schmidt et al., 1995).

Administration of TNF-α not only affected CRH and AVP at the median eminence, but also influenced CRH-immunoreactivity (CRH-ir) at the central amygdala. However, while the hypothalamic CRH/AVP coexpression developed simply with the passage of time (irrespective of whether animals were reexposed to the cytokine), changes of CRH-ir at the central amygdala were only evident upon reexposure to the cytokine 1–7 days following initial treatment. In effect, TNF-α induced the *potential* for increased CRH-ir within the central amygdala, but an actual increase of CRH-ir was only realized upon cytokine reexposure. While detailed analyses remain to be conducted involving other stressor-sensitive aspects of the amygdala (medial, basolateral and central), these data reinforce the view that systemic challenges activate processes that have often been considered part of the circuitry associated with anxiety (Davis, Rainnie, & Cassell, 1994; LeDoux, 1995).

Paralleling the time-dependent sensitization of HPA activity, TNF-α proactively increased the utilization of NE within the PVN, and this effect progressed with the passage of time. In contrast, however, within the prefrontal cortex and the central amygdala the sensitization was only evident upon reexposure to the cytokine at the one-day interval (Hayley et al., 1999), an effect also seen following treatment with LPS (Hayley et al., 2001a,b). Taken together, it seems that cytokines instigate a series of dynamic changes involving different temporal patterns and brain regions, and may subserve different behavioral sequelae (Hayley et al., 1999).

Given the similarities between the neurochemical effects of stressors and proinflammatory cytokines, and the presumed involvement of HPA functioning and monoamines in depressive disorders, the possibility exists that like traditional

stressors, systemic insults favor the development of affective disorders. Moreover, it ought to be considered that insults that affect cytokine activity may influence the response to later challenges, and hence vulnerability to affective illness. In this respect, like early-life trauma (e.g., extended separation of rat pups from the dam) which increases vulnerability to stressor-provoked neurochemical changes encountered during adulthood (Anisman, Zaharia, Meaney, & Merali, 1998), neonatal endotoxin challenges increased stressor-provoked neuroendocrine disturbances during adulthood (Shanks et al., 2000). It has yet to be established whether such manipulations also promote increase signs of depressive-like behaviors.

4. Cytokines and depressive illness

Animals treated with cytokines, such as IL-1β or TNF-α exhibit a constellation of symptoms referred to as sickness behaviors. These include soporific effects, reduced locomotor activity, piloerection, ptosis, diminished social interactions, and diminished consumatory behaviors, all of which are manifestations of the malaise associated with illness (Dantzer et al., 1999). To be sure, these symptoms are not akin to those of depression; however, it has been shown that IL-2 administration, as well as that of LPS, which initiates activation of several macrophage derived cytokines, may induce an anhedonic response (reduced pleasure obtained from otherwise rewarding stimuli), which is a key symptom of depression (Anisman, Merali, & Kokkinidis, 1996; Anisman & Merali, 1999; Borowski et al., 1998). Likewise, endotoxin administration reduces consumption of a palatable substance (again possibly reflecting anhedonia), and this effect was modifiable by antidepressant administration (Yirmiya, 1996; Yirmiya et al., 1999). Of particular relevance is that the behavioral changes exerted by cytokines are not simply a reflection of malaise engendered by the treatments, but are thought to arise owing to alterations of a centrally mediated motivational state (Dantzer et al., 1999).

Commensurate with animal studies showing a relationship between stress, depression, and immunity (Herbert & Cohen, 1993), major depression in humans is associated with alterations of various aspects of the immune response, including a reduction of mitogen-stimulated lymphocyte proliferation, as well as reduced natural killer (NK) cell activity (Herbert & Cohen, 1993; Irwin, 1999; Maes, 1995, 1999). These effects are most pronounced in severely depressed patients (i.e., those exhibiting melancholia) (Maes, 1995), and the altered immunity may be attenuated with symptom remission (Irwin, Smith, & Gillin, 1992). In contrast to the assumption that depression was associated with the suppression of nonspecific immunity, it has been argued that affective disturbances may actually be secondary to an initial immune *activation* (Licinio & Wong, 1999; Maes, 1995, 1999), possibly due to the altered HPA functioning and central monoamine activity. Indeed, depressed patients were found to display signs of immune activation, reminiscent of an acute phase response, including increased plasma concentrations of complement proteins, C3 and C4, and IgM, as well as positive acute phase proteins, haptoglobin, α-antitrypsin, α1 and α2 macroglobulin, coupled with reduced levels of negative acute phase proteins (Maes, 1999; Sluzewska, 1999). Major depressive illness was also accompanied by an increased number of activated T cells ($CD25^+$ and $HLA\text{-}DR^+$), secretion of neopterin, prostaglandin E2, and thromboxane (Maes, 1995, 1999).

In addition to these factors, it has been reported that depression was accompanied by increased levels of circulating cytokines or their soluble receptors, including IL-2, soluble IL-2 receptors (sIL-2R), IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-6, soluble IL-6 receptor (sIL-6R), and γ-interferon (IFN) (Berk, Wadee, Kuschke, & ONeill-Kerr, 1997; Frommberger et al., 1997; Maes, 1995, 1999; Maes et al., 1991, 1992, 1997; Maes, Bosmans, Meltzer, Scharpe, & Suy, 1993a, 1995; Mullar & Ackenheil, 1998; Nassberger & Traskman-Bendz, 1993; Sluzewska et al., 1995; Smith, 1991; Song, Dinan, & Leonard, 1994) as well as increased mitogen-elicited production of the proinflammatory cytokines, IL-1β, IL-6, and TNF-α (Anisman, Ravindran, Griffiths, & Merali, 1999a,b; Maes, 1995, 1999; Maes et al., 1991, 1993a,b, 1995, 1997; Seidel et al., 1995). While the elevated levels of IL-1β, IL-6, and α1-acid glycoprotein normalized with antidepressant medication (Frommberger et al., 1997; Sluzewska et al., 1995), such treatment did not affect the upregulated production of sIL-2R, IL-6, and sIL-6R in major depression (Maes, 1999) or that of IL-1 in patients suffering from chronic low grade depression (dysthymia) (Anisman et al., 1999a). Likewise, serum levels of IL-6, as well as the anti-inflammatory cytokines, IL-10 and IL-1 receptor antagonist (IL-1Ra) were

moderately elevated in depressed patients, but once again successful pharmacotherapy was not associated with normalization of these cytokines (Kubera et al., 2000). Thus, these cytokines may be trait markers of the illness, but do not play an etiological role in depression (Anisman et al., 1999b; Maes, 1999).

The data presently available concerning cytokine elevations in depressive illness are largely correlational. Thus, it is unclear whether the cytokine elevations are secondary to the illness (i.e., being directly or indirectly brought on by the depression), or contribute to the provocation of the disorder. Yet, high doses of IL-2, IFNα, and TNF-α in humans undergoing immunotherapy induce neuropsychiatric symptoms, including depression, and these effects were related to the cytokine treatment rather than to the primary illness (Capuron, Ravaud, & Dantzer, 2000, 2001; Caraceni et al., 1992; Denicoff et al., 1987; Meyers & Valentine, 1995; Miyaoka et al., 1999; Musselman et al., 2001). Interestingly, it was reported (Maes et al., 2001) that IL-2, alone or in combination with IFNα, induced a decrease of serum dipepridyl peptidase IV (DPP IV), a membrane bound serine protease which acts to catalyze the cleavage of at least some cytokines and peptides, hence affecting cytokine production and immune activity. At 3–5 days after treatment, depression scores were elevated in patients being treated for metastatic cancer, and the extent of the increase was inversely related to DPP IV levels. In addition, the treatment resulted in elevated levels of IL-6 and IL-2R, which were inversely related to DPP IV levels. Thus, these data were taken to suggest that cytokines contributed to the provocation of depressive symptoms. In a more recent report (Musselman et al., 2001) it was observed that depressive symptoms were provoked in humans treated with IFNα, and that these symptoms could be attenuated by treatment with the selective serotonin reuptake inhibitor, paroxetine. Interestingly, by attenuating the side effects of the immunotherapy, the positive effects of the treatment were also maximized. In effect, while the bulk of the data concerning the cytokine-depression relationship is essentially correlational, there is certainly good reason to suspect an etiological role for cytokines in depressive illness. At the same time, however, it needs to be remembered that the populations being assessed in studies where cytokines are being administered are relatively unique, and that the participants are undergoing considerable strain. Thus, the effects of the cytokine treatments may well represent the interactive effects of a number of factors beyond simply that of immune activation.

5. Characteristics of the depression–cytokine relationship

In evaluating the depression–cytokine relationship, several factors ought to be considered relating to the characteristics of depressive illness, or factors comorbid with or secondary to the depression. Irwin (1999) has described many of these direct or interactive effects and their implications for depression and hence only a cursory overview is presented here.

5.1. Severity and chronicity of illness

There is little question that the neuroendocrine correlates of depression are related to severity of illness, and there is evidence that this factor impacts on immune and cytokine activity. For instance, NK cell disturbances, as well as the elevations of cytokines and their soluble receptors, were marked in melancholic (severely depressed) patients, but were less notable in moderately depressed patients (Maes, 1995, 1999). As the symptoms of depression and the HPA alterations are more profound in melancholic than in typical major depression, particular attention ought to be devoted to the possible contribution of neurovegetative features and hormonal dysregulation to altered cytokine levels. Additionally, as severe depression often requires hospitalization, it has been considered that this (and related factors such as change of diet, diurnal factors, social buffering, etc) may be responsible for the altered immune and cytokine functioning (Herbert & Cohen, 1993).

Limited attention has been devoted to the relationship between illness chronicity and cytokine activity, and the cytokine changes associated with chronic stressors. In animals, some of the neurochemical and neuroendocrine effects of acute stressors are attenuated following a chronic stressor regimen. For instance, in response to chronic stressors compensatory increases of central NE may be induced, hence preventing the amine reductions that would otherwise ensue (e.g., Anisman et al., 1993). This does not mean, however, that "adaptation" has occurred, but only that the animal has, at least for the moment, the necessary amine stores needed to contend with

the stressor. Indeed, the sustained increase of synthesis and utilization of the transmitter may not be without cost. The wear and tear on the system associated with a chronic stressor (referred to as allostatic load) may have particularly adverse consequences (McEwen, 1998). In a like fashion, it may be important to distinguish between the effects of acute and chronic depressive illness. In fact, chronic depression of a relatively mild nature (dysthymia) may be associated with particularly poignant effects in that mitogen-stimulated production of IL-1β was increased to a greater extent than in major depression of moderate severity (Anisman et al., 1999a). The magnitude of the increase was related to the duration of the illness, as well as the age of illness onset. Thus, even in the absence of a severe episode, altered cytokine activity may occur, provided that the depressive illness was sufficiently long-lasting. Interestingly, in dysthymic patients normalization of IL-1β production did not accompany the alleviation of symptoms associated with antidepressant treatment (Anisman et al., 1999b). These findings are consistent with those reported by Maes (1999), and provisionally support the notion that cytokine production might be a trait marker of the illness. Yet, it is worth considering that since dysthymia is a chronic condition, a longer period of treatment may be required to alter the neurochemical (including cytokine) correlates of the illness, even though behavioral symptoms may abate within 12 weeks. In effect it is possible that more sustained treatment is necessary to realize normalization of the cytokine levels or activity (Griffiths, Ravindran, Merali, & Anisman, 2000; Ravindran, Griffiths, Merali, & Anisman, 1995).

5.2. Typical vs atypical depressive features

Subtypes of depression exist that differ with respect to etiology, neurochemical concomitants, course, symptoms, and treatment. Accordingly, the possibility was considered that these depressive subtypes might also differ with respect to the potential involvement of cytokine processes. In "typical" major depression the symptoms comprise either depressed mood or loss of interest or pleasure in otherwise rewarding stimuli or events (anhedonia), coupled with four of the following: feelings of worthlessness/guilt, diminished ability to think or concentrate, recurrent thoughts of death or suicidal ideation, and neurovegetative features such as weight loss, insomnia, psychomotor agitation/retardation, fatigue, or loss of energy. In a variant of the illness, namely that of "atypical depression," symptoms may be very similar except that neurovegetative symptoms predominate (hyperphagia, significant weight gain, hypersomnia), coupled with extreme fatigue, mood reactivity, and persistent rejection sensitivity. There is reason to believe that these illness subtypes also differ with respect to their neurochemical concomitants. In particular, hypersecretion of CRH may be less prominent in atypical than in typical major depression (Nemeroff, 1996), and plasma corticosterone levels may be lower as well (Anisman et al., 1999a,b). Further, desipramine-elicited plasma cortisol secretion was greater in atypical patients, suggesting a less dysfunctional norepinephrine system (McGinn, Asnis, & Rubinson, 1996). Finally, atypical patients responded preferentially to monoamine oxidase inhibitors relative to tricyclic agents, particularly among females (McGrath et al., 1992). Parenthetically, similarities exist between atypical depression and other illnesses with atypical features (chronic fatigue syndrome, bulimia, or seasonal affective disorder), including reduced basal plasma cortisol, increased basal ACTH, and reduced ACTH release following CRH challenge (Demitrack et al., 1991; Gold, Licinio, Wong, & Chrousos, 1995; Joseph-Vanderpool et al., 1991; Levitan et al., 1997). As HPA activity may influence cytokine functioning, these neuroendocrine differences raise the suspicion that cytokine and immune differences might be expected in differing subtypes of depression.

It is certainly possible that the neurovegetative characteristics of depression, quite apart from the mood disturbances, may be responsible for the altered cytokine functioning. In fact, it has been reported that sleep disturbance alone may precipitate altered cytokine activity (Moldofsky, 1995), and it is conceivable that reduced food intake and weight loss in typical major depression may come to provoke cytokine alterations. In this respect, Cover and Irwin (1994) reported that the altered NK cell activity in major depressive illness was correlated with two symptom clusters, namely that of motor retardation and sleep disturbance. Parenthetically, it is known that depressive illness may be associated with altered circadian rhythms (coupled with early morning awakening in typical depression, or conversely the increased fatigue and sleep in atypical depression), and it is possible that these factors contribute to the altered cytokine activity observed. The circadian variations of neuroendocrine functioning have

been well documented, and it appears that cytokine activity also varies with time of day. The peak production of IFN-γ, TNF-α, IL-1, and IL-12 occurs at night and early morning, corresponding to the nadir of cortisol production (Petrovsky & Harrison, 1997). These findings have implications not only for the variations seen with respect to symptoms of inflammatory disorders, but raise the possibility that the cytokine elevations in depressive illness may be related to diurnal alterations.

With respect to the atypical symptoms of depression, experiments conducted in our laboratory, revealed that while IL-1β production was increased in depressive and dysthymic patients, this effect was present irrespective of whether patients exhibited typical or atypical features (Anisman et al., 1999a,b). Yet, in this study the severity of illness was moderate, and the possibility cannot be excluded that with more severe illness (where reduced eating and sleep would have been commensurately more pronounced), neurovegetative features might have played a greater role in determining cytokine variations. Further, in this particular experiment IL-1β production was measured in mitogen-stimulated lymphocytes. This does not imply, however, that neurovegetative factors are unrelated to circulating cytokine levels. In fact, we recently observed that although IL-1β ordinarily appears in only trace amounts in serum, circulating levels of this cytokine were elevated among atypical depressive patients, but not in typical major depressive patients (Griffiths, Ravindran, Merali, & Anisman, 1996). To be sure, considerable variability existed among the atypical patients with about half showing levels indistinguishable from that of typical major depressive or nondepressed subjects. However, alleviation of symptoms following pharmacotherapy, was accompanied by decline of circulating IL-1β levels. Inasmuch as typical and atypical depression were associated with comparable increases of stressor perception (relative to a nondepressed group), and both conditions were associated with excessive use of emotion focused coping strategies, the elevated IL-1β levels unique to atypical depressives cannot be attributed to such factors.

5.3. Recurrent depression and treatment-resistant depression

It has been suggested that the recurrence of depression (approximately 50% of patients suffer recurrence within 1 year) may involve sensitization of stressor-induced release of certain peptides, such as CRH and thyroid releasing hormone (Post & Weiss, 1995). It was argued that the initial episode of depression may stem from a potent stressor provoking peptidergic alterations. However, with each subsequent stressor experience, or with each episode of depression, the peptidergic systems become more reactive so that less intense psychosocial stressors will effectively provoke the onset of a depressive episode. Ultimately, these episodes may occur even in response to minor stressors (Post, 1992). Given the relationships between neuropeptide and cytokine functioning, it ought to be considered that cytokine-induced neurochemical alterations might likewise vary with first vs. subsequent depressive episodes. It was further suggested (Griffiths et al., 2000) that recurrence of depression and chronic depression (one is also tempted to add treatment-resistant depression) might involve chronic cytokine activation that promotes neuroendocrine and neurotransmitter alterations. If a treatment alters neurotransmitter or neuroendocrine functioning, then symptoms will be alleviated (or incomplete remission established). However, if the source for the neurochemical disturbances, and hence the depression itself, involves persistent cytokine dysregulation, the neurochemical disturbances will reappear thus again favoring depression. In effect, antidepressants suppress (mask) the behavioral/cognitive symptoms of depression, without necessarily influencing the etiological processes. In those patients in whom cytokine disturbances promote depression, persistent immune activation will serve to increase the probability of relapse or recurrence (Griffiths et al., 2000).

6. Concluding remarks

The available data are consistent with the proposition that cytokine variations may be related to depressive illness. However, we reiterate once again that in the main these data were obtained in studies that assessed cytokine levels in already depressed populations, and hence they do not suggest a causal relationship. The studies involving immunotherapy lend credence to the cytokine-depression position, but it must be remembered that the doses of cytokine administered are in excess of the circulating levels of the cytokine, and hence may not be representative of what happens in the individual under other

conditions. Besides, as these patients are already ill, and certainly experiencing considerable strain, the possibility exists that the cytokine effects on affective state reflect the interactive effects with stressors, and a comparable outcome would not have evolved in otherwise healthy individuals.

A further consideration with respect to the cytokine-depression hypothesis concerns the impact of stressors on cytokine activity. Inasmuch as stressors influence cytokine functioning (Herbert & Cohen, 1993), it is possible that the altered cytokine activity seen in depression may actually be secondary to the increased stressor perception (or actual experiences). For instance, all subtypes of depression that we have examined are associated with increased stressor perception, the use of excessive emotionally focused coping strategies, reduced perception of uplifting events, diminished quality of life, and increased feelings of loneliness (Ravindran et al., 1995, 1999). As well, psychosocial and financial stresses may evolve secondary to the depression, interpersonal skills may be greatly impaired, and hence social buffering of stresses may be limited. Potentially, cytokine changes may not be related to the mood disturbance per se, but may be secondary to the real or perceived stress associated with the illness.

In addition to considering a role for stressors in affecting immunity, numerous comorbid features are often present among depressed individuals, any of which could impact on cytokine functioning. This includes high levels of anxiety and the presence personality disturbances, and even deterioration of personal hygiene (neglect). As well, as indicated by Irwin (1999) depressive illness may be associated with increased drug use (including nicotine, alcohol, as well as illicit drugs) which could directly or indirectly impact on immune and cytokine activity.

The relationship between cytokines and the features of depression remain to be identified; however, it is possible that the elevated cytokine levels (e.g., IL-1β) contributed to some aspects of the atypical symptomatology, including increased sleep and muscle fatigue which are well documented effects of proinflammatory cytokines. However, these cytokines would also be expected to reduce eating (Dantzer et al., 1996), a characteristic not seen in atypical patients. Likewise, at this juncture there are insufficient data available concerning the relationship between cytokines and duration of illness, covariance with age or age of illness onset, and it is unclear whether normalization of cytokine treatment eventually occurs with alleviation of symptoms. Clearly, the analyses of the stress-depression topography require more extensive cytokine and neuroendocrine analyses; however, these biological analyses need to be met by equally sophisticated characterizations of the depressive disorders and their comorbid features.

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