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Neurochemical and behavioral responses to inflammatory immune stressors

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1. ABSTRACT

Activation of the inflammatory immune system has been associated with the development of psychological disorders such as major depressive disorder (MDD). In this regard, the release of pro-inflammatory cytokines (signaling molecules of the immune system) provokes a constellation of neurochemical and behavioral alterations, reminiscent of the effects of traditional stressors, which if sustained could influence psychological functioning. In animal models, exogenously administered cytokines, as well as bacterial endotoxins and viral analogues, induce a variety of behavioral disturbances collectively known as sickness behavior. Although it is difficult to differentiate the general malaise of sickness engendered by cytokines from the depressogenic effects, clinical studies have revealed increased levels of circulating cytokines and acute phase proteins in patients diagnosed with MDD. Furthermore, the incidence of MDD is increased in patients suffering from chronic inflammatory conditions, and immunotherapy used to treat chronic illnesses such as Hepatitis C was related to high levels of depression that could be attenuated by antidepressant treatment. Together, these findings indicate that activation of the inflammatory immune system may favor the evolution of psychological disturbances.

2. INTRODUCTION

Stressful experiences may favor the development of anxiety and of major depressive disorder (MDD). It is thought that these pathological outcomes stem, at least in part, from several neurochemical changes, including alterations of monoamine and corticotrophin-releasing hormone (CRH) functioning, as well as disturbances of growth factors such as brain-derived neurotrophic factor (BDNF) (1, 2). Of course, the impact of stressors varies appreciably among both humans and rodents, and several organismic (age, gender, genetic) and experiential factors are responsible for the diverse effects observed (e.g., 3).

It has been argued that activation of the inflammatory immune system engenders stress-like effects and may thus contribute to MDD, and that cytokines (signaling molecules between immune cells) may be essential in mediating this relationship (1, 4-6). Support for this perspective has come from several lines of inquiry, including (a) animal studies indicating that cytokine manipulations may engender behaviors and brain neurochemical alterations that are consistent with those thought to be associated with MDD (7), (b) studies, in humans, showing that MDD is accompanied by elevated levels of several circulating cytokines, acute phase proteins,

and inflammatory factors (5), (c) occurrence of depressive symptoms was increased among patients with chronic inflammatory and autoimmune pathologies (8), (d) cytokine immunotherapy (using mainly interferon-alpha; IFN-a) in the treatment of hepatitis C and some forms of cancer may promote depressive illness in a large portion of patients, and that these effects can be attenuated by antidepressant medication (6, 9), and (e) the effects of IFN-a were particularly notable among patients with a history of depression, those who have the lowest tryptophan levels and individuals that exhibit the greatest cytokine variations (9).

The neurochemical changes exerted by pro-inflammatory cytokines are in many ways reminiscent of those associated with stressors, and it has been suggested that activation of the inflammatory immune system might be interpreted by the brain as a stressor (1). Of course, the consequences of psychological and physical stressors are not identical to those associated with systemic immune insults. In fact, even though cytokines, such as interleukin-1beta (IL-1b) and tumor necrosis factor-alpha (TNF-a) and traditional stressors have common effects (e.g., hypothalamic-pituitary-adrenal (HPA) activation), they may do so through different neural circuits (10). Furthermore, the cognitive changes associated with conventional stressors (e.g., shame, loss) would not occur with systemic stressors, such as cytokine activation. Yet, it is possible that the impact of systemic stressors may vary as a function of the background conditions upon which they are imposed. By example, the effects of IFN-a immunotherapy among individuals with severe diseases (e.g., cancer, hepatitis C) might not be the same as they are among individuals not experiencing major life disruption. Likewise, as already alluded to, IFN-a immunotherapy may have more profound effects among individuals disposed toward depression, or at least those with a negative cognitive perspective.

The processes by which cytokines promote depressive symptoms remain to be identified. Nevertheless, it has provisionally been suggested that the depressogenic effects of cytokines may stem from the effects of pro-inflammatory cytokines on central neurotransmitter and growth factors that may be related to depression (e.g., CRH, 5-HT and BDNF), as well as on enzymatic pathways involved in the production of oxidative species and other neurodegenerative factors (1, 7). The current review is meant to provide a broad perspective pertaining to the depressogenic effects associated with cytokine activation. However, as studies in humans do not permit analyses of cytokine effects on brain neurochemical processes, and studies in animals do not readily allow for the differentiation between sickness versus depressive affect elicited by immune activation, the present review borrows from both lines of research to derive a picture concerning the impact of immune activation on depressive-like illness. In this regard, we attempt to identify whether specific patterns of inflammatory immune activation are related to distinct components of the depressive profile.

3. CYTOKINE INFLUENCES ON THE CENTRAL NERVOUS SYSTEM

3.1. Cytokines within the brain

Circulating cytokines are ordinarily maintained at low levels, and they usually act in an autocrine (local cellular actions, operating in a feedback capacity) or paracrine (acting upon cells in proximity of where they are produced) manner at lymphoid organs, such as the spleen, lymph nodes or liver (11). Although cytokine spillover into circulation is typically diluted rapidly, in response to strong immunological challenge, circulating levels of pro-inflammatory cytokines are markedly increased (12). The increased cytokine activity may provoke release of acute phase proteins and elevated utilization of steroidal hormones (9).

As cytokines are large molecules, their access to the brain is relatively limited, but they may enter the brain at sites where the blood-brain barrier (BBB) is less efficient, such as at circumventricular organs (median eminence, subfornical organ, area postrema, organum vasculosum). It has also been reported that saturable transport mechanisms are present that serve to move cytokines (IL-1b and TNF-a) into the brain (13, 14). Significantly, immunologic challenges, cytokines, and stressors may compromise the integrity of the BBB, and might thus increase passage of cytokines into the brain (15, 16).

Having gained access to the brain, cytokines may stimulate receptors on cells lining the BBB, around the meninges as well as vascular areas of the brain (17). Ultimately, cytokines may reach hypothalamic, amygdaloid and brain stem nuclei where they interact with appropriate receptors that are present (18, 19). In addition, cytokines stimulate secondary mediators, such as prostaglandins, that may promote the central neurochemical effects of cytokines.

The actions of cytokines in the brain are not restricted to those that come from circulation, but may also reflect actions of cytokines endogenously synthesized in brain microglia and possibly in neurons as well. In this regard, both pro- and anti-inflammatory cytokine levels are elevated following traumatic insults (20-22), endotoxin and cytokine treatments (23-25), stroke and neurotoxins (21, 22, 26) and by neurogenic and psychogenic stressors (22, 27-29). These endogenous cytokines, like those derived from peripheral sources, could potentially act upon neurotransmission, and might thus affect behavioral outputs.

3.2. Neurochemical effects of cytokines

When administered systemically, bacterial endotoxins, as well as recombinant cytokines, markedly influence various hormonal and neurotransmitter processes, including those that are activated by psychological and physical stressors (1). Of the varied consequences of cytokine treatments, the best studied have been concerned with the marked activation of the HPA axis that culminates in the rise of circulating glucocorticoids. Like traditional

stressors, pro-inflammatory cytokines, including IL-1b and TNF-a, increase the CRH mRNA expression at the paraventricular nucleus of the hypothalamus (PVN), and also increase the expression of CRH at the central amygdala (7). Although IL-1b, TNF-a, and IL-6 all promote these neuroendocrine alterations, IL-1b is the most potent in this respect, and it generally appeared that IL-6 was least potent (30).

Like stressors, cytokines markedly influence central neurotransmitter activity. Specifically, IL-1b increased the utilization of serotonin (5-HT) and norepinephrine (NE) within several stressor-sensitive brain regions, including the PVN, medial prefrontal cortex (mPFC), and central amygdala (31-34). Such effects have been detected in analyses of postmortem tissues, and cytokine-induced release of these neurotransmitters was also shown *in vivo* within both the hypothalamus and hippocampus (35-39).

Analyses of the neurochemical effects of cytokines have largely focused on that of IL-1b and to a lesser extent on IL-6 and TNF-a. In light of the clinical applications of IFN-a there has been research, albeit relatively limited, assessing the biological and behavioral effects of this cytokine (40). It has been shown that IFN-a dose-dependently increased plasma corticosterone levels, although these effects were far less pronounced than those elicited by IL-1b (41). In rodents, the effects of IFN-a declined with repeated administration (42), and in humans the increased circulating IFN-a associated with acute administration (43, 44) was not apparent with repeated treatment (45).

Like other cytokines, administration of IFN-a increased hypothalamic and hippocampal NE utilization as well as that of the amino acid transmitters, gamma-aminobutyric acid (GABA) and glutamate (42, 46). This cytokine also reduced dopamine (DA) concentrations within the amygdala (47), although it is uncertain whether this stemmed from excessive utilization or reduced synthesis. *In vitro* studies have also revealed that IFN-a stimulated CRH release from amygdala and hypothalamic neurons (48).

Inasmuch as systemic IFN-a administration provoked central neurochemical changes, it should not be surprising to find that when IFN-a was administered directly into the brain, changes of hypothalamic neuronal firing were apparent (49). This treatment also increased hippocampal DA activity (50, 51), increased mRNA expression of the 5-HT transporter (5-HTT) (51), but reduced 5-HT concentrations in the PFC (50). Interestingly, IFN-a administration also engendered 5-HT2C receptor mRNA editing (52), paralleling reports that such an effect was associated with anxiety and depressive symptoms in animal models (53), and reports that altered 5-HT2C editing was associated with depression/suicide (54, 55).

As previously described (1), there are several routes by which pro-inflammatory cytokines might affect 5-HT functioning, and hence depression. Specifically, the 5-HT changes may be secondary to CRH variations elicited by cytokines (7), or may be secondary to changes of growth factors (e.g., BDNF) that have been implicated in MDD (1). As well, cytokines, such as IFN-a may stimulate indoleamine-2,3-dioxygenase (IDO) and GTP-cyclohydrolase activity, which provoke degradation of the 5-HT precursor, tryptophan (56), hence reducing 5-HT functioning (57). In this regard, IFN-a also promotes metabolism of tryptophan into kynurenine and then into the oxidative metabolites, 3-hydroxy-kynurenine and quinolinic acid (which themselves are increased in depression), which may provoke neurotoxicity (58, 59). The generation of free radicals provoked by these kynurenine metabolites may also be related to neurodegenerative diseases, including Alzheimer's and Parkinson's, and might account for the comorbidity of these illnesses with MDD.

In closing this section it ought to be emphasized that activation of the inflammatory immune system, whether in response to pathogens or in the treatment of pathology, typically occurs on a chronic or subchronic basis. Yet, the vast majority of studies assessing the impact of cytokines have focused on the acute effects of these treatments (possibly owing to the prohibitive cost of recombinant cytokines). Unfortunately, the few studies that have addressed this have not yielded unequivocally consistent results. For instance, it was reported that sustained systemic or intracerebroventricular IL-1b administration resulted in marked and persistent HPA activation, including protracted variations of CRH, CRH receptor mRNA expression, as well as elevated adrenocorticotropic hormone (ACTH), beta-endorphin and corticosterone secretion (60, 61). It was also reported, however, that although acute IFN-a treatment produced little effect, repeated IFN-a treatment led to reduced DA utilization (62) and increased low-affinity for 5-HT1A receptors sites (63). Other investigators reported that neither acute nor chronic IFN-a treatment appreciably influenced HPA functioning, and acute IFN-a did not affect monoamine turnover. In contrast, with sustained IFN-a over 14 days, DA levels were reduced in the PFC, 5-HT turnover was increased in the amygdala, and 5-HT levels were diminished (64). Finally, it was also reported that with repeated systemic injections or with continuous IL-1b infusion, the sickness and the plasma corticosterone elevations ordinarily elicited by acute IL-1b were diminished, whereas the central cytokine mRNA changes were sustained (1).

In effect, it seems that in response to cytokines there are elements subject to an adaptation-like effect, whereas for other actions the adaptation was less apparent. In fact, it appeared that although peripherally released cytokines returned to basal levels with continuous exposure to recombinant cytokines, brain cytokine alterations persisted (1). It may be that adaptive mechanisms exist within the periphery, thereby limiting the damaging effects of chronic cytokine elevation, but these processes may be diminished or lacking within the brain, and might thus favor the development of brain and behavioral pathologies.

3.3. Synergies associated with cytokine treatments

Beyond their individual effects, cytokine combinations (e.g., IL-1b plus IL-6, or IL-1b plus TNF-a) synergistically increased neuroendocrine functioning (30, 65-67), and it seems that cytokines and stressors may synergistically influence behavioral and neurochemical responses. In particular, it was shown that IL-1b and a stressor synergistically increased the *in vivo* release of hippocampal 5-HT (36, 38). Moreover, when a cytokine (IFN-a), viral analogue (polyinosinic:polycytidylic acid; poly I:C) or bacterial endotoxin treatment (lipopolysaccharide; LPS) was administered to mice that had experienced a psychosocial stressor, the behavioral, corticoid and monoamine alterations ordinarily elicited by the immune challenges were greatly increased (42, 68-70). As will be seen shortly, such findings have implications for the therapeutic use of cytokines.

3.4. Sensitization of cytokine-provoked neuronal processes

Stressor treatments result in the sensitization of neuronal processes, so that upon later re-exposure to such an insult brain monoamine changes are markedly increased. It likewise appears that cytokines may engender sensitized neurochemical functioning so that the HPA response to subsequent cytokine treatments may be enhanced. Interestingly, this response was not only evident when animals were re-exposed to the cytokine, but also when the later challenge involved a stressor (cross-sensitization) (32, 33, 71-73). Conversely, it was shown that the initial stressor exposure also augmented the corticoid response elicited by later LPS administration (74, 75). However, if rats were pretreated with the IL-1 antagonist, IL-1ra, then the effect of the subsequent stressor treatment was attenuated (76).

Beyond sensitized monoamine neuronal activity, cytokine treatments may engender sensitization of neuropeptide systems, such as CRH and AVP. Interestingly, the sensitization appears to become more pronounced with the passage of time. Specifically, in response to stressors, as well as to IL-1b and TNF-a, these treatments elicited progressively more pronounced and persistent elevations in the co-expression of AVP and CRH within CRH terminals located within the external zone of the median eminence. Typically, the co-expression of these peptides became apparent over several weeks following the cytokine treatment, and once evident, persisted for an extended period. Inasmuch as CRH and AVP synergistically stimulate ACTH secretion from the anterior pituitary, it was maintained that the phenotypic change within CRH neurons accounted for the greater effects of cytokines (and stressors) on HPA functioning. Given the persistence of these effects, it was suggested that stressor- and cytokine-elicited CRH-AVP co-expression might contribute to the depressive symptoms provoked in response to later stressor or cytokine challenges (33, 72, 73, 77).

Typically, studies assessing sensitized neuronal responses to stressors and cytokines have done so in adult animals. It is similarly possible that such processes might be operative in determining the protracted effects of these treatments applied early in life. In this regard, paralleling the effects of early life stressors, it has been shown that among rats pups that had been exposed to an endotoxin challenge during the early postnatal period, stressor challenges experienced in adulthood augmented stressor-elicited corticosterone reactivity, lymphocyte sensitivity to suppression by stressors, and protection against adjuvant-induced arthritis (78). At this time, it is uncertain whether the effects of early life stressors and early life cytokine treatments involve similar neural circuits. However, it is possible that epigenetic processes are involved in the response to cytokines as they might be with respect to early life experiences (79), thereby influencing adult responses to stressor and cytokine challenges.

4. BEHAVIORAL EFFECTS ASSOCIATED WITH CYTOKINES – ANIMAL STUDIES

4.1. Sickness behaviors

The release of pro-inflammatory cytokines, in response to inflammation, has been associated with a constellation of behavioral and physiological changes in animal models, collectively referred to as sickness behaviors. These include fever, sleep irregularities (e.g., somnolence, fatigue), anorexia, reduced motor activity (e.g., lethargy, apathy), as well as piloerection, ptosis and curled body posture (110). In addition to neurovegetative symptoms, inflammatory challenges also provoke psychosocial alterations, including diminished social interactions, coupled with cognitive and affective dysfunction, the latter characterized by disturbed operant performance and anhedonia (6, 18, 80). Although some of these effects are nonspecific and might reflect general malaise elicited by cytokine release, other symptoms may result from alterations of a centrally-mediated motivational state relevant to depression (1, 6).

Sickness behavior was initially described as a passive response reflecting the debilitating effects of an illness; however, it has also been characterized as an adaptive response geared towards recuperation (81). Many of the changes that occur during immune activation function to either minimize heat loss (i.e. the curled body position in animals), decrease energy expenditure (i.e. lethargy and reduced exploratory or social activity) or to produce the energy required to mount a febrile response (i.e. shivering). The febrile response is essential to recuperation as high core body temperatures stimulate the proliferation of immune cells necessary to combat the invasion, and concurrently slow the growth and proliferation of pathogens (81). In effect, the physiological and behavioral alterations, instead of reflecting general, nonspecific malaise engendered by cytokine release, may also be considered an organized strategy that is critical to the survival of the organism. Interestingly, the behavioral expression of sickness is contextually dependent in the sense that the signs of malaise are suppressed under conditions where sickness would be a disadvantage (e.g., in a novel or threatening environment; 82, 83), further emphasizing the view that sickness is a motivational state, rather than strictly a physiological one.

During an acute inflammatory reaction, several cytokines (IL-1b, TNF-a, and IL-6) are released as part of the organism's orchestrated immune response. Paralleling the neurochemical changes, behavioral alterations elicited by IL-1b are more pronounced than those of TNF-a, which are more pronounced than those of IL-6 (30) or those associated with IFN-a (42). These differential actions are evident irrespective of the route of administration (84). Aside from the direct effects of exogenous IL-1b administration, this cytokine also plays a significant role in the development of sickness behavior elicited by other cytokines, such as TNF-a, as well as a bacterial endotoxin and the viral imitator poly I:C (85). For instance, treatment with the antagonist, IL-1ra, not only diminishes the effects of IL-1b, but also inhibits the effects of LPS (86) and poly I:C (87). Additionally, compensatory mechanisms may exist should IL-1b be unavailable. For instance, IL-1b deficient mice demonstrated a typical response to an endotoxin challenge (85, 88), including the induction of sickness behavior, possibly by promoting increased release of TNF-a (85).

In addition to its involvement in cytokine-induced behavioral variations, IL-1b has also been implicated as a mediator in stressor-induced depressive-like behavior. For instance, it was reported that the behavioral and neuroendocrine effects of a chronic mild stressor were prevented among IL-1b type 1 receptor knockout mice (89). As well, mice lacking the IL-1b receptor also failed to display the usual reduction of neuroplasticity (hippocampal neurogenesis) that was evident in wild-type mice that received this stressor treatment (89). In contrast, genetic ablation of the TNF-a p55 receptor did not influence the HPA response provoked by restraint or LPS, although, as predicted, the corticoid elevation elicited by TNF-a was greatly attenuated (90). Hence, there is reason to suppose that selective IL-1b changes that foster the emergence depressive-like consequences might occur following exposure to certain stressors.

The sickness induced by TNF-a, it will be recalled, is less pronounced than that provoked by IL-1b. Importantly, however, in paradigms that have been associated with anhedonia (e.g., sucrose preference test) and motor disturbances (e.g., immobility in the forced swim test) that could reflect depression, mice lacking TNF-a receptors were more resilient than wild-type mice (91). Furthermore, mice with targeted deletion of TNF-a receptors displayed increased levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) within several brain regions, which could be associated with this resilience (92). Therefore, although the involvement of TNF-a in the emergence of sickness behavior may not be as integral as IL-1b, its role in the development of depressive-like behavior seems more significant.

In contrast to IL-1b and TNF-a, which peak early following an immune challenge and have relatively short half-lives, levels of IL-6 peak more gradually, and can remain in circulation for several hours (93). Studies using IL-6 deficient mice demonstrated that this cytokine might be fundamental in mediating LPS-induced immune activation (85, 94), but in general, the immediate behavioral effects of exogenously administered recombinant IL-6 are relatively subtle (30). It seems that despite its fever inducing actions (95, 96), the behavioral effects of IL-6 (such as reduced social exploration) are limited. Nonetheless, there has been progressively more attention focused on the involvement of this cytokine in mediating MDD (1). In fact, one recent report suggested that IL-6 might act directly within the hippocampus or amygdala to influence depressive-like behaviors and stressor-sensitive factors involved in neuroplasticity (97).

4.2. Depressive-like features elicited in response to pro-inflammatory factors

In addition to their sickness inducing effects, cytokines have also been reported to disrupt operant responding for food reward (98, 99) and markedly influence exploration and social interaction (100). However, these outcomes may be secondary effects of the treatments (e.g., general malaise) rather than variations of motivational or affective functioning. Unfortunately, it is often difficult to dissociate the sickness behavior elicited by cytokines from behaviors that may be related to depression.

Although sickness behavior has been thought to reflect human depressive symptoms, there are actually only a small number of studies that have attempted to dissociate symptoms linked to sickness from those of depression in animal models. There does, however, appear to be a difference in the time course between sickness emerging (within hours post-injection) and depression that appears as a second wave up to days post-injection (101, 102). For instance, although cytokine-induced motor retardation (a pivotal symptom of sickness) was attenuated 24 hours following an acute endotoxic challenge, decreased sucrose intake, and increased immobility in both the tail suspension and forced swim tests (paradigms thought to assess depressive-like behavior) persisted for several days, as did the increased c-fos expression in brain regions associated with depression, including the PVN, arcuate nucleus, and the amygdala (101). Similar results were found with more protracted immune activation, using chronic inoculation with Bacillus Calmette-Guerin, with sickness behavior becoming apparent almost immediately post-treatment and depressive-like symptoms emerging within several days and persisting up to several weeks with chronic treatment (102).

Consistent with the view that cytokines and bacterial endotoxins elicit a depressive-like state, it was shown that activation of the inflammatory immune system gives rise to anhedonia, a core symptom of depression. Specifically, endotoxin treatment disrupted responding for rewarding brain stimulation (31, 103-106). It is of particular significance that in the paradigm employed (i.e., assessing the response to a descending and then to an ascending series of currents), animals appeared to be fully capable of responding for rewarding stimulation. However, when the reward value was too low, those animals injected with LPS exhibited far greater reductions of responding relative to vehicle-treated animals. Thus, it seems that the

effects of LPS likely reflected anhedonia (and thus depression) rather than motor decreases and malaise associated with sickness.

Paralleling these findings, it was shown that the anorexic and motivational (anhedonic) effects of cytokines (such as IL-1b) were distinguishable from one another. In fact, treatment with an antidepressant over 3 weeks primarily influenced the anhedonic effects of cytokines, without affecting sickness in general (106); see (107, 108). Specifically, IL-1b treatment markedly disrupted free-chow consumption as well as responding for sucrose reinforcement in rats performing on a progressive ratio (PR) schedule (i.e., a reward schedule in which a progressively greater number of operant responses are required for a fixed amount of sucrose, hence providing an index of the motivation to work for reward). Chronic antidepressant (fluoxetine) treatment attenuated the PR performance deficit for sucrose reward, but did not alter the diminished free-chow consumption provoked by the cytokine. Thus, the anhedonic and anorexic effects of cytokine treatment were dissociable, and antidepressant treatment preferentially influenced the motivational effects of IL-1b (anhedonia), and had little effect on the neurovegetative impact of the cytokine. As will be described in the ensuing sections, studies in humans have largely supported this perspective.

4.3. Processes governing cytokine-induced behavioral variations

The behavioral alterations provoked by the exogenous administration of pro-inflammatory cytokines (such as IL-1b, IL-6, and TNF-a) or bacterial endotoxins are thought to involve the central effects of peripherally released cytokines, as the impact of immune activation are attenuated by manipulations that influence brain cytokine functioning. For example, sickness behavior provoked by systemically administered LPS can be limited or precluded by the central administration of anti-inflammatory cytokines, such as IL-10, or cytokine receptor antagonists (e.g. IL-1ra; 100, 109).

Two distinct communication pathways might link peripheral inflammatory responses to CNS processing: a quick neural pathway and a slower humoral pathway (18). The former comprises a rapid wave that begins in the peritoneum where local immune cells secrete pro-inflammatory cytokines that activate vagal afferent fibers (6, 18, 65, 110). When these fibers are disrupted (by vagotomy) sickness behaviors induced by systemically administered IL-1b (111) and LPS (65) were attenuated. However, it was also posited that although vagal afferents are involved in relaying immune signals from the periphery to the CNS, other pathways are likely also involved.

Once the cytokine signals reach the CNS, the nucleus of the solitary tract (located in the brainstem) serves as a hub, relaying signals to other brain regions important in provoking the behavioral effects that accompany the inflammatory immune activation. Analysis of c-fos indicated that following activation of the vagus nerve and nucleus solitary tract, secondary projections of the vagus nerve, namely the parabrachial nucleus, PVN and supraoptic nuclei of the hypothalamus, the central and medial nuclei of the amygdala, and the bed nucleus of the stria terminalis may also be affected (112, 113).

The second communication pathway, which involves a humoral response, is a much slower process. As indicated earlier, peripheral cytokines gain access to the CNS via the circumventricular organs (CVOs) and choroid plexus, or enter the brain through an active transport mechanism (13), and then slowly diffuse by volume transmission into the brain parenchyma and to other brain targets such as the amygdaloid complex (18). The humoral pathway involves a series of second messenger molecules, including the prostaglandins, which diffuse into the brain and act on specialized receptors (namely EP3 and EP4) to innervate the brain regions involved in HPA activation and body temperature control, such as hypothalamic nuclei (18).

Recent attention has focused on the induction of cyclooxygenases (COX) in the mediation of the inflammatory immune response. The induction of COX activity leads to the synthesis of prostaglandins (by converting arachidonic acid into prostaglandin endoperoxide H2), which then provoke behavioral and neurochemical alterations (114). The two distinct COX subtypes, COX-1 and COX-2, share 60% homology (114). However, whereas COX-1 is ubiquitously expressed in most cell types and is responsible for maintaining normal physiological functioning, COX-2 is only expressed in certain cell types (e.g. endothelial cells), and is induced primarily by inflammatory stimuli (115). Considering its role in inflammation, most studies have focused on COX-2 receptors, and both LPS and IL-1b have been shown to increase its expression in brain endothelial cells (116). Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs), which function by inhibiting COX expression, were found to attenuate LPS- and IL-1b-induced behavioral disturbances. Specifically, selective COX-2 inhibitors, such as indomethacin (117, 118) as well as nonselective inhibitors such as celecoxib (119), reduced the behavioral effects associated with an acute immune challenge. These results are supported by studies using COX knockout mice, where the behavioral effects of inflammation were reduced or absent following a challenge, although the distinct roles of both COX subtypes remain unclear (114). Taken together, it seems that although high levels of circulating cytokines provoke behavioral disturbances, their actions are at least partly dependent on the action of COX enzymes.

5. INFLAMMATORY FACTORS ASSOCIATED WITH DEPRESSION IN HUMANS

In addition to the sickness and depressive-like behaviors elicited by pro-inflammatory cytokines or bacterial endotoxins in animal models, converging evidence has also implicated activation of the inflammatory immune system in the promotion of human depressive symptoms. These findings come from studies in humans indicating that melancholic depression was associated with elevated circulating levels and mitogen-stimulated

production of pro-inflammatory cytokines (4) and with increased concentrations of positive acute phase proteins (e.g., C-reactive protein; CRP; 120). In addition, it was found that the administration of inflammatory factors such as endotoxins promoted depressive-like symptoms (121) and that the prevalence of major depression was relatively high among patients with chronic inflammatory pathologies (8). Furthermore, IFN-a immunotherapy in the treatment of hepatitis C and certain cancers was associated with the development or the exacerbation of depressive symptoms and this outcome was reduced by antidepressant treatments (9).

5.1. Cytokine and acute phase protein correlates in patients with depressive disorders

Increased plasma/serum levels and production of several pro-inflammatory cytokines have been reported in patients with MDD (4). In this regard, elevations of IL-6 and of TNF-a were particularly notable in depressed individuals (122-130). Increased circulating levels of IL-1b also were found in MDD patients (4, 131, 132), although conflicting observations have been reported (130). Consistent with the view that peripheral cytokines are related to depression, treatment with antidepressants and mood stabilizers was associated with the normalization of IL-6 concentrations in depressed patients, but such an outcome was less apparent with respect to other cytokines (133). Moreover, depressed patients treated with antidepressant medication coupled with a COX-2 inhibitor displayed augmented effectiveness of the treatment (134), another illustration of the importance of inflammatory processes in subserving depression. Given the risk of gastrointestinal disturbances that may come about owing to sustained NSAID use, however, the usefulness of this combined treatment may be limited (135). Microglial activation, which is indicative of increased neuroinflammatory processes, was found within the dorsolateral PFC, anterior cingulate cortex, and mediodorsal thalamus of depressed, bipolar, and schizophrenic patients who committed suicide relative to patients who did not (136). However, there have been reports that depression was not associated with elevated circulating cytokine levels or with mitogen-stimulated cytokine production (1). In fact, higher production of IL-6 was reported in non-suicidal depressed patients than in patients who attempted suicide or normal controls (137).

Exaggerated activation of the inflammatory immune system also seemed to predict response to treatment in depressed patients. Higher serum levels of soluble receptor IL-2R and lower CC16 concentrations (a natural anti-inflammatory protein known to suppress IL-1b, IL-6, and IFN-gamma (IFN-g) secretion; 138) were observed in treatment non-responders (128). Similarly, particularly elevated production of IL-6 and of TNF-a was reported in depressed patients resistant to selective serotonin reuptake inhibitor (SSRI) and tricyclic treatment (127, 139), but not in former SSRI resistant patients who became euthymic (140). As well, anti-depressants decreased TNF-a production primarily in depressed patients who were treatment responders (127).

The varied cytokine irregularities reported in depressed individuals, coupled with differences in inflammatory states among patients who do or do not respond to antidepressant treatments, raises the possibility that cytokine variations may be related to the heterogeneity of symptoms or the severity of illness. Indeed, higher serum levels of IL-1b (141) and decreased production of IL-2, IFN-g, and IL-10 (142) were found in melancholic depressed patients compared to those with non-melancholic features. Other investigators, however, reported elevated production of IL-1b and of its receptor, IL-1ra, exclusively in non-melancholic patients (143). Likewise, increased IL-1b production was evident in patients with chronic mild depression (dysthymia), suggesting that illness chronicity was fundamental in promoting cytokine alterations (144).

Parenthetically, MDD has been increasingly documented as a risk factor for cardiovascular and cerebrovascular events (145). Given that elevated levels of the acute phase protein CRP was reported in depressed individuals (146-149) and in patients with cardiovascular diseases (149-152) the possibility was raised that this inflammatory marker might be the common denominator for the high comorbidity that exists between depressive and cardio- and cerebro-vascular disorders. In this regard, however, the role of CRP in mediating the association between depression and these vascular diseases was not consistently demonstrated (145, 153, 154) and thus, it seems that CRP may not systematically contribute to the relationship between depression and these vascular illnesses. Nevertheless, it is possible that CRP may be relevant for specific depression subtypes and/or for specific cardiovascular events. Unfortunately, unlike cytokines, differential patterns of CRP activation have not been reported in this regard.

5.2. Depressive symptoms in relation to allergies, chronic inflammatory diseases and cancer

A growing body of evidence has pointed to a link between allergies, depressive symptoms, and suicide. Mood worsening and a seasonal peak in suicide have been associated with high atmospheric pollen conditions and with peaks of seasonal allergen exposure (155-157). It was proposed that allergic inflammation might result from an abnormal activation of the Th2 cytokine system, such as IL-4, IL-5, and IL-13, which may influence brain functioning and potentially contribute to the development of depressive symptoms and, in some individuals, to suicide (158). Indeed, increased mRNA expression of Th2 cytokines was found in the orbitofrontal cortex (specifically Broadman 11 area) of suicide victims, and this outcome was moderated by gender, as IL-4 expression was elevated in women, whereas IL-13 expression was elevated in men (159). No differences, however, were reported for Th1 cytokines such as IL-1b, IL-6, TNF-a, and IL-5 in the same brain region (159). As discussed earlier, several Th1 cytokines, including TNF-a and IFN-a, have been implicated in depressive illness. Ultimately, it might be an imbalance in the ratio of Th1/ Th2 cytokines that negatively affects neurochemical activity in emotion regulatory brain regions.

In addition to the variations of depressive and suicide outcomes that occurred in association with allergic reactions, neuropsychiatric symptoms, including depression, were reported among patients suffering from pathological conditions involving chronic immune system alterations. This included individuals with chronic viral infections (e.g., hepatitis C), autoimmune inflammatory diseases such as rheumatoid arthritis, diabetes, and multiple sclerosis (MS), and some cancers (8). Although depressive manifestations in these patients may result from nonspecific factors, such a general malaise or psychological distress, there is also evidence that the comorbidity of these illnesses with depression may stem from the sustained activation of inflammatory processes.

For instance, non-medicated patients with chronic hepatitis C displayed higher plasma TNF-a levels than non-infected patients and this was coupled with an increase in the intensity of depressive manifestations (160). Interestingly, plasma cytokine levels in infected patients correlated significantly with three specific depressive symptoms clusters derived from the 21 items of the Beck Depression Inventory-II (161). Specifically, IL-1b correlated positively with negative cognitions (e.g., negative appraisal of self), whereas TNF-a correlated positively with negative cognitions, psychomotor-anhedonia (e.g., decreased satisfaction, loss of interest in people, psychomotor retardation or agitation) and vegetative symptoms (e.g., decreased appetite, insomnia; 160).

As in the case of hepatitis C, increased serum levels of TNF-a (128, 162, 163) were reported in non-medicated MS patients. Likewise, MS was associated with elevated mRNA expression of TNF-a, IFN-g, and IL-10 in whole blood cells and cerebrospinal fluid cells (164-166). Moreover, elevations in blood cytokine expression was more pronounced during an acute MS flare and this was correlated with depression scores (164). Further support for the contribution of inflammatory processes to the pathogenesis of MS-related depressive symptoms comes from imaging studies suggesting pre-existing signs of brain inflammation in MS patients influenced the progression of depressive symptoms (167).

Increased pro-inflammatory cytokine levels have been reported in cancer patients presenting with depressive symptoms. In this regard, depressed cancer patients displayed higher plasma concentrations of IL-6 than cancer patients without depression, or patients with major depression but without cancer (168, 169). Moreover, in advanced-stage cancer, depression and plasma IL-6 concentrations were found to be highly correlated (170). These data in themselves are obviously insufficient to warrant strong conclusions concerning the causal connection between IL-6 and depression. A case for IL-6 in mediating depression is somewhat strengthened by studies showing that IL-6 levels in depressed patients normalized with pharmacotherapy (133). Ultimately, however, it will be necessary to show that IL-6, in fact, might cause the emergence of depressive symptoms.

5.3. Depressive disorder induced by IFN-a activation

The data described earlier showing that certain cytokines and acute phase proteins were associated with major depression are simply correlational, hence precluding causal attributions concerning the inflammation-depression relationship. Stronger evidence supporting a causal role for cytokines in the provocation of MDD comes from the many studies showing that IFN-a immunotherapy (in the treatment of hepatitis C and some types of cancer) frequently provoked depressive symptoms, often necessitating discontinuation of the treatment (reviewed in 9). It ought to be underscored from the outset that patients in these studies were, no doubt, under considerable distress (given that they are suffering from life-threatening illnesses), and hence the outcomes may reflect the synergistic actions of the cytokines being administered on a stressor backdrop. Indeed, as described earlier in rodent studies, IFN-a had only modest (if any) behavioral effects, but marked behavioral and neurochemical alterations were apparent when the cytokine was administered in stressed animals (42).

Likewise, in line with the view that 5-HT changes associated with immunotherapy might contribute to depression, it was found that pre-existing biological markers (e.g., alterations of tryptophan, increased immune activation or elevated TNF-R1 and low IL-6R levels) predicted the development of depression during IFN-a therapy (171-173). Moreover, depression was most prominent among individuals that showed particularly marked tryptophan or cortisol elevations in response to the initial IFN-a administration (174, 175). As well, an association was observed between a specific polymorphism of the 5-HT1A receptor and the occurrence of depression during IFN-a treatment of chronic hepatitis C (176).

Despite its beneficial effects in the treatment of chronic hepatitis C and cancer, IFN-a therapy was associated with the development and/or exacerbation of depression as well as with a high incidence of nonspecific, neurovegetative symptoms such as fever, fatigue, lethargy, insomnia or hypersomnia, loss of appetite, malaise, anorexia, asthenia, myalgia, and social withdrawal (177-182). As described earlier, sickness behaviors associated with cytokine treatment in rodents have frequently been paralleled with human depressive/motivational symptoms of MDD. However, most of the features that comprise the sickness profile seem reminiscent of these neurovegetative symptoms of depression. In this regard, the reduced activity and increased sleep elicited by pro-inflammatory cytokines in rodents are characteristic of the neurovegetative features of atypical depression. In fact, pro-inflammatory cytokines are potent soporifics that increase slow wave sleep and reduce REM sleep, features that are aligned with atypical depression (183, 184). In contrast, the anorexia associated with cytokine or endotoxin treatment is more closely aligned with the typical form of depression (1). Thus, a given treatment, both in humans and in animal models, may instigate symptoms characteristic of both subtypes of depression, making it difficult to argue that a discrete set of neurovegetative (or motivational) features of depression are provoked by immune activation.

The depressive-like symptoms induced by IFN-a frequently resolved with treatment discontinuation or the use of antidepressants (185-187). Interestingly, antidepressants seemed more effective in attenuating symptoms such as depressed mood, anxiety, cognitive dysfunction, and pain, and were less efficacious for neurovegetative symptoms, such as fatigue, psychomotor slowing, altered sleep, or anorexia (see 9, 180). The latter symptoms correspond with the sickness behaviors characteristic of cytokine treatments in animal studies, and it was indeed reported in animal models that an SSRI was more effective in attenuating anhedonia than the anorexia elicited by a cytokine (106). Nevertheless, it has been reported that the initial neurovegetative effects elicited by IFN-a may be a marker for the subsequent development of depressive symptoms (58). Of course, this does not necessarily imply common mechanisms for the two sets of symptoms, but might simply be an index of those patients most reactive to the IFN-a.

The mechanisms by which IFN-a exerts its adverse behavioral effects are not yet fully understood. This cytokine is known to enhance the production of several pro-inflammatory cytokines, including IL-6 and TNF-a (188, 189). It was also reported that during IFN-a therapy in hepatitis C patients, the increased depressive symptoms were positively correlated with baseline or elevations of IL-2R, TNF-ą and IL-6 concentrations (188, 190). This peripheral cytokine release may, in turn, affect central NE and 5-HT neurotransmission as well as HPA activity, which might thus promote MDD (191, 192). Indeed, severity of depressive symptoms (especially anorexia, pessimistic thoughts, suicidal ideations, and loss of concentration) after one month of IFN-a therapy was positively correlated with a decline of serum tryptophan concentrations (185).

As in the case of IFN-a immunotherapy, it was reported that IFN-b treatment in MS patients was also associated with confusion, depression, and anxiety. Unlike IFN-a, however, clinical reports of IFN-b-induced depressive features have been inconsistent (180). Depression and suicide attempts were more frequently reported during IFN-b therapy than during placebo administration (180, 193), yet several studies failed to show any evidence of increased depression or suicide in MS patients treated with IFN-b and in some instances, a decline of depression rates was even reported (194-196). It was suggested that depression in MS patients might not be a direct side effect of immunotherapy, but that pre-existing depressive episodes might favor the development of depressive symptoms during IFN-b treatment (197). It will be recalled that in hepatitis C and cancer patients treated with IFN-a, those individuals with premorbid depressive symptoms were also most likely to exhibit a depressive episode with the cytokine therapy. Thus, the inconsistent results reported concerning the actions of IFN-b may reflect basal differences in depressive characteristics that patients might have displayed.

5.4. Cognitive disturbances associated with cytokine (IFN) immunotherapy

In addition to the development of neurovegetative and depressive-like symptoms during IFN-a immunotherapy, this cytokine has been associated with the development and/or exacerbation of neuropsychiatric complications, including mania and anger/hostility symptoms, and with cognitive disturbances such as mnemonic problems and lack of concentration (180, 181, 198). Typically, within 6-8 hours of the initial administration IFN-a an acute influenza-like syndrome is apparent, including fever, chills, malaise, myalgias, arthralgias, and tachycardia, and symptoms gradually subside after about 2 weeks of treatment (192, 199). Sleep disturbances, irritability, weight loss, reduction of appetite, low mood, and cognitive dysfunction occurred later during IFN-a therapy, usually within about 1 to 3 months (57, 178). For instance, cognitive impairments, such as deficits in short term and working memory, as well as word fluency have been reported after 12 weeks of low-dose treatment with IFN-a (200). These cognitive dysfunctions associated with IFN-a were suggested to be indicative of prefrontal, temporo-cortical, and hippocampal alterations (200). Essentially, different brain systems may be affected during the course of IFN-a treatment, leading to diffuse symptoms. The early effects of the cytokine might occur within brain regions related to the neurovegetative symptoms, whereas other brain alterations (e.g., PFC, hippocampus) that follow, might be responsible for the cognitive impairments and depressive manifestations.

6. INFLAMMATORY PROCESSES IN RELATION TO NEUROPSYCHIATRIC MANIFESTATIONS IN PATHOLOGICAL CONDITIONS OTHER THAN DEPRESSION

6.1. Confusional states and cognitive disturbances in relation to acute inflammation and surgical insult

Beyond the neurovegetative, depressive, and cognitive manifestations already described, delirium symptoms, such as deranged consciousness, confusional states, and other cognitive disturbances occur frequently in acutely ill or postoperatively patients among the elderly (201). Inflammatory processes were proposed as contributing to this syndrome by facilitating access of cytokines into the brain and increasing their damaging neuronal effects (202). Indeed, low premorbid circulating levels of the insulin growth factor (IGF-1) were found in acutely admitted elderly patients who developed delirium (203, 204). As IGF-1 has inhibitory effects on cytotoxic action of cytokines (205), it was suggested that low levels of this growth factor may favor brain susceptibility to the deleterious effects of cytokines (204).

Likewise, elevated circulating levels of chemokines (e.g., locally acting cytokines that enhance migration of inflammatory cells into the brain by weakening the BBB), but not of pro-inflammatory cytokines, were reported during the first 6h post-surgery in patients who developed delirium. The chemokine elevations were no longer detectable 4 days later, suggesting that they may play a role in the initial events associated with delirium (202). In contrast, pro-inflammatory cytokines and acute phase proteins may participate in the pathogenesis of delirium in later phases. In fact, elevated plasma levels of IL-6 were reported 24 to 48 hr after abdominal surgery in elderly patients who

experienced post-operative confusion (206). Delirium incidence was also associated with increased levels of CRP 48 hours after stabilization from sepsis (207) and 48-60 hours after hip surgery in elderly patients (208, 209). Similarly, relative to cognitively normal patients, elderly patients with impaired mental status showed increased serum levels of IL-6, IL-8, and IL-10, four weeks after hip surgery, however, this outcome was independent of infectious, delirious, or cardiovascular complications (209). Contrary to cytokine and chemokine variations, CRP elevations after hip surgery were more prominent among patients with impaired mental status and infectious, delirious, or vascular complications (209).

6.2. Inflammation and cognitive decline in non-demented elderly and in demented patients

Recent evidence has suggested that inflammatory processes may also play a role in the normal age-related decline in cognitive functioning. Using the Edinburg Artery Study data base, elevated circulating IL-6 concentrations in non-demented older people were associated with a significantly steeper 4-year decline in general cognition and in nonverbal reasoning ability (210). Similar conclusions were found using the Rotterdam Study and the Leiden 85-plus Study data bases. Specifically, higher baseline levels of IL-6 were associated with worse cognitive functioning and more pronounced cognitive decline (211). Mild cognitive decline in elderly patients was also associated with higher levels of IFN-a and COX-2 relative to healthy elderly controls (212).

The purpose of the present review is not one of relating cytokines to cell loss and dementia. Nevertheless, there has been increasing data supporting the proposition that some of the manifestations associated with dementia (e.g., Alzheimer's disease) may involve inflammatory processes (reviewed in 1). For example, as reported in delirious patients, reduced serum concentrations of IGF-1 was observed in familial Alzheimer's disease (213), possibly predisposing the brain to inflammatory factors. Likewise, elevations of plasma IL-6, TNF-a and COX-2 levels were recently reported in Alzheimer patients relative to elderly individuals with mild cognitive impairments and to healthy elderly controls (212).

6.3. Immune activation and neuropsychiatric symptoms in schizophrenia

Although particular attention has been devoted to the analysis of cytokines in relation to major depressive illness and cognitive dysfunction, it is important to indicate that cytokines have also been implicated in other psychiatric disorders, in particular in schizophrenia. Indeed, activation of the inflammatory system was described in patients with schizophrenia and other psychotic disorders. Much like the correlates of MDD, higher concentrations and production of several cytokines (e.g., IL-6, IL-1R, IL-2, IL-8, IL-10, IFN- g, TNF-ą, and lower levels of CC16 and of IL-4) were observed in schizophrenic patients (4, 214-218), although there have been contradictory reports in this regard (e.g., 219). Again, cytokine variations associated with schizophrenia were related to particular aspects of the disorder with elevated IL-2 levels being correlated to positive symptoms (220). Moreover, schizophrenia was associated with dysfunction related to the IL-3 gene in two population samples (221), and irregularities related to the IL-3 receptor were also reported (222). Interestingly, there have been reports of psychosis in hepatitis C patients during IFN-a therapy (223, 224). Admittedly, these reports have been infrequent, but together with the findings that circulating cytokines are elevated in schizophrenia, they support a role for inflammation in the pathogenesis of psychotic symptoms.

Normalization of cytokine elevations has been reported after antipsychotic medication in schizophrenic patients. For example, treatment with risperidone and haloperidol (atypical and typical antipsychotics, respectively) reduced IL-2 and IFN-g elevations, but failed to normalize IL-6 and IL-8 (225, 226). Risperidone also increased IL-2R and IL-10 levels and normalized CC16 concentrations (215, 225). Interestingly, as in depressed individuals, exaggerated activation of the inflammatory response also seemed to predict resistance to treatment in schizophrenic patients. Increased circulating levels of IL-6, IL-8, IL-10, IL-2, and IL-1ra (220, 227-229) were shown in treatment-refractory schizophrenics, but not in patients who responded to medication. Once more, however, other reports indicated that elevations of some cytokines were comparable among patients who were responders versus non-responders (219, 228). The differential effects of neuroleptic medication on schizophrenic symptoms, as well as on cytokine production, coupled with differential responsiveness to pharmacological treatments raises the possibility that different sub-classifications of schizophrenic symptoms (e.g. positive vs. negative) or subgroups of schizophrenia (e.g., paranoid vs. non paranoid) may be related to different cytokine (and neurotransmitter) activation profiles. Indeed, it has been reported that schizophrenic patients with elevated stimulated production of IFNs presented with more positive symptoms (e.g., delusions, hallucinations), whereas those with low IFN production showed more negative symptoms (e.g., social withdrawal, flat affect; 230).

Given that many of the same cytokines involved in MDD were also elevated in schizophrenia begs the question of how these same cytokine disturbances could be involved in these very different psychological disorders. One possibility is that the cytokine variations are a nonspecific index of disturbances being present. That is, inflammatory processes set the stage (acting as a vulnerability factor), but other hormonal and neurotransmitter changes come to promote the actual symptom profile presented. Alternatively, it could be that particular illnesses may be associated with a specific constellation of cytokine alterations, or that the effects of cytokines on pathology are largely determined by pre-existing vulnerabilities to particular pathological states.

7. SUMMARY AND PERSPECTIVE

Considerable evidence points to a role for inflammatory processes in MDD. These include correlational studies showing that (a) cytokine and acute

phase protein levels are elevated among depressed individuals, (b) illnesses associated with immune activation are often comorbid with MDD, (c) cytokine treatments, such as IFN-a, give rise to a constellation of abnormal behaviors, including MDD, that can be attenuated by antidepressant medications, and (d) cytokines induce several neurochemical changes in animals, like those elicited by stressors, that have been implicated in MDD in humans. In both humans and animal models, the influence of inflammatory processes in provoking behavioral changes is particularly marked when applied on a stressor backdrop. Moreover, it also appears that activation of the inflammatory immune system may result in the sensitization of neuronal processes so that later stressor experiences are more apt to induce neurochemical changes that provoke MDD.

Together, clinical data on MDD, delirium, mild cognitive decline, and schizophrenia suggest that in otherwise apparently healthy patients, cytokine activation may exert little or no deleterious effects. However, under certain challenges (e.g., stressor background), or when neuronal damage is present, such as in patients suffering from chronic inflammatory pathologies, neurodegenerative dementia, or schizophrenia, in acutely ill or postoperative patients with brain inflammation, after IFN-a immunotherapy, or even as a result of normal aging of the brain, cytotoxic action of circulating cytokines may enhance neurodegenerative processes, thus leading to behavioral abnormalities (205).

Despite these multiple sources of support for a role for cytokines in mediating depressive illness, a fundamental caveat ought to be mentioned. Specifically, activation of the inflammatory immune system provokes a wide range of neurochemical and hormonal changes. Although some of these might contribute to MDD, others might result in neuronal loss leading to neurodegenerative disorders, or to toxicity that could promote a wide range of nonspecific symptoms (e.g., confusion, memory loss, delusions). Thus, it is possible that depression might be only one of many pathological outcomes that are promoted as result of widespread neuronal changes. This said, cytokines have been implicated in several pathological outcomes that involve CNS processes, and indeed, MDD is frequently comorbid with some neurodegenerative disorders as well as cardiovascular illness. It is possible, as previously suggested (1), that cytokines may represent a common denominator for these pathologies, and may be responsible for their comorbidity.

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