CYTOKINES AND [NEUROTROPHINS] IN PSYCHIATRIC DISORDERS

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In addition to their immune cell origin and immunological effects, cytokines are produced by neuronal and glial cells and can influence nerve growth and plasticity. Likewise, in addition to their target tissue origin and neurotrophic effects, the neurotrophins nerve growth factor and brain-derived neurotrophic factor are secreted by immune cells and can promote immune cell growth and activity. Cytokines and neurotrophic factors are thus essential mediators in the complex network of neuromuneuendoctrine interactions. Psychiatric patients, as well as psychotropic drugs, can display abnormal expression of these molecules and their receptors. Such studies point to the potential contribution of both cytokines and neurotrophins to the neuropathology of certain psychiatric diseases. This article highlights the role played by the cytokines interleukin-1,-2,-3,-6 and by the neurotrophins nerve growth factor and brain-derived neurotrophic factor in the development of schizophrenia and depression. Biomed Rev 1999; 10: 69-73.

INTRODUCTION

Cytokines are multifunctional molecules secreted (synthesized, usually stored, and released) by a wide variety of cells in the body, using para-, auto-, and endocrine pathways (1-3). The cytokine research began in 1944, when Menkin reported the isolation of a fever-inducing factor, pyroxin, from inflammatory exudate (4). Subsequent studies demonstrated that lymphocyte-derived humoral factors exert proliferative effect on lymphocytes (5,6). Such substances secreted by immune and inflammatory cells were named lymphokines, monokines, interleukins (ILs), and interferons, until the term "cytokines" embodied these all molecules, targeted to multiple cells within specific networks (1-3). This heterogeneous group of glycoproteins has a number of common characteristics, both in structure and function. Likewise, individual cytokines exert multiple overlapping cell regulatory effects, interacting in a network by (i) inducing each other, (ii) modulating cytokine cell surface receptors, and (Hi) exerting synergistic, additive or antagonistic effects on a given cell function (1). In a broader sense, "cytokines" is a term which overlaps both "growth factors" and "hormones". Cytokines and neurotrophic factors, including ILs, tumor necrosis factor-alpha (TNF-cc), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF), play an important role in many physiological responses, are involved in the pathobiology of various diseases, and have certain therapeutic potentials (1-3,7-10). NGF and BDNF are members of the neurotrophin family of proteins which also includes neurotrophin-3 (NT-3), NT-4/ 5, and NT-6 (7,9). Neurotrophins play crucial roles in differentiation, survival, and activity of specific populations of central and peripheral neurons. In addition, various nonneuronal cells are responsive to neurotrophins (7,9), as well as cytokines elicit various effects from neuronal and glial cells (11,12).

Since Aloe and Levi-Montalcini's first demonstration (in 1977) of NGF-induced increase in the number of mast cells in various tissues, and Besedovsky et al's first demonstration (in...
In 1995, we reported that exposure of rats to restrictive stress upregulated IL-1 expression in the hypothalamus (23). Since the elevation was observed within a few minutes after loading the stress, we suggested that IL-1 was produced not by translation of mRNA\(^{IL-1}\) into protein, but by IL-1 converting enzyme, from the neuronal pool of proIL-1. Recent work supported these findings (24). In 1991, we reported that circulating plasma levels of IL-6 are elevated in schizophrenic patients (25). Further, accumulating findings provide supportive evidence that IL-1 (3) and IL-6 plasma levels (26,27) as well as cerebrospinal fluid IL-1 and IL-2 levels (28) are significantly high in schizophrenic patients. Other studies also demonstrate altered circulating levels of IL-1 and IL-3 (29), IL-1 andTNF-a(30),IL-2 (31), and soluble IL-2 receptor, IL-6, and IL-1 receptor antagonist (IL-IRa) (32) in patients with schizophrenia. Figure 1 illustrates the elevated IL-6 plasma levels in medicated chronic schizophrenic patients.

Altogether, a conclusion is approached that various pro-inflammatory cytokines may associate with the development of schizophrenia (33,34). It is noteworthy that the circulating cytokine levels are significantly higher in acute than in remission phase of the disease. And the administration of various psychotropic drugs results in greater expression of mRNA\(^{IL-1}\)Ra than that of mRNA\(^{IL-1}\) in the brain (35). Furthermore, genetic analyses of the polymorphism of IL-1 gene complex suggest that cytokine abnormalities in schizophrenia are, at least partly, genetically determined (36).

**Neurotrophins and schizophrenia**

As indicated above (20,21), neuropathological findings have suggested that schizophrenia development could be related to defective embryology in specific brain areas, thus predisposing and/or leading to abnormal neuronal circuitry and function in the mature brain. NGF and BDNF are highly expressed in the brain and a variety of brain neurons are able to secrete and respond to the action of these neurotrophins during embryonic and early and late postnatal life (37), and also to various environmental stimuli (38). Because of their crucial roles in neurogenesis and neurotopogenesis, it has been hypothesized that significant alterations in the secretion of neurotrophins during critical developmental time could alter the function of specific brain neurons in pre- and postnatal life, thus neurotrophins may be involved in the pathogenesis of schizophrenia (39-44). As indicated above for a link between antipsychotic medication and cytokines (35), there is also such a link between the neuroleptic haloperidol and the levels of NGF in both hypothalamus and blood plasma (45,46).

**Cytokines and neurotrophins in depression**

Depression is a disease that affect hundreds of millions of people worldwide. Generally, studies addressing both the pathogenesis and the therapy of depression are focused on...
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the monoamine hypothesis. That is, the role played by the brain neurotransmitters 5-hydroxytryptamine (5-HT; serotonin) and noradrenalin (NA). However, recent studies also suggest an important role for both cytokines and neurotrophins in the neuropathology of depression.

Cytokines and depression

The abnormalities seen in depressive patients might be a reflection of some balance failure in certain cytokine networks in the brain (47). Plasma levels of IL-1β, IL-6, soluble IL-2, and transferrin receptors are altered in patients with major depression (48). This is especially associated with patients with tri-cyclic antidepressant-resistant depression (refractory depression). Further, Kanba et al (49) reported a negative correlation between severity of depression and lymphoblast transformation, implying some abnormality in the signal transduction events in "depressed" lymphocytes.

Neurotrophins and depression

While the classical study of depression is mainly focused on the brain serotonergic and noradrenergic neurons, emerging evidence demonstrates a potential link between neurotrophins and depression, as a subtle form of neurodegenerative disease (reviewed in 50). For instance, BDNF and NT-3 are reported to promote the growth and function of 5-HT- and NA-containing neurons in the adult brain. Likewise, stress, which often positively correlates with depression development, is shown to decrease mRNABDNF(50). Note that NGF (51) and BDNF (52) are also implicated in epilepsy. In is also noteworthy that 5-HT- and also NA-targeted antidepressants can work to promote the serotonergic and adrenergic neurons by increasing the endogenous BDNF and/or NT-3 brain levels, thus suggesting that neurotrophin-releasing agents may be a candidate of new generation antidepressants (50,53). Accordingly, since human platelets contain BDNF (54) and are linked to depression (50) and schizophrenia (42), and since lymphocytes produce NGF (13), these all cells could be peripheral markers for (f) alterations in neurotrophin levels in these psychiatric diseases, and (f) neurotrophin responses to antipsychotic and antidepressant drugs.

CONCLUSION

The studies discussed above, taken together, strongly suggest that dysfunction(s) in the neuroimmunoendocrine pathways mediated by certain cytokines and neurotrophins could interactively be involved in the neuropathology of schizophrenia and depression. Potential involvement of cytokines derived from adipose tissue and from thymus and expressed in the brain (55-59) may also be considered.
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