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CYTOKINES AND [\SEUROTROPHSI\iS 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 jznd neurotrophic factors are thus essential mediators in the complex network of neuroimmunoendocrine 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 (*/*) 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

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1986) that IL-1 treatment increases the plasma levels of neurohormones, there is accumulating evidence of interactions among the cells of nervous, immune and endocrine system (reviewed in 13-17). Cytokines and neurotrophins play a central role in the mediation of these interactions. Furthermore, cytokines are not only important regulatory factors in immune and inflammatory processes, but also exert neurotrophic activity of their own (18) or indirectly, through upregulation of neurotrophin expression (11,12,19). Likewise, it is very likely that the neuroendocrine system may produce a variety of cytokines, just as immune system produces a plethora of neuroendocrine hormones, neurotrophic factors, and neuropeptide neurotransmitters (13-16).

In this article, I will focus on the involvement of various cytokines, particularly, IL-1, IL-2, IL-3, and IL-6 in the pathobiology of schizophrenia and depression. Also, implications of NGF and BDNF in these diseases, as well as of antipsychotic and antidepressant drugs in the biology of cytokines and neurotrophins, will be outlined.

CYTOKINES AND NEUROTROPHIMS IN SCHIZOPHRENIA

Schizophrenia is a severe psychiatric disease affecting approximately 1% of the population worldwide. Although there is evidence of an important genetic contribution to schizophrenia, its etiology is largely unknown. Perhaps equally important are findings that such a genetic contribution is only part of this multiplex disease. Accumulating evidence suggests that impaired brain neurogenesis and neurotopogenesis might prominently be involved in the neuropathology of schizophrenia, leading to the brain developmental hypothesis of schizophrenia (reviewed in 20,21). Based on this hypothesis, also on the neuroimmunoendocrine pathyaws implicated in this disease (19), both cytokines and neurotrophins are increasingly pursued in the study of pathogenesis of schizophrenia.

Cytokines and schizophrenia

Given the effects of cytokines on neuronal and immune cell growth and activity and on synaptic neurotransmission and plasticity, it would not be surprising if some, cytokine production-inducing environmental events, such as birth trauma, maternal viral infections, and nutritional disorders, are implicated in schizophrenia. Likewise, it is known that during clinical trials of cytokines for therapy of various diseases, patients exhibited schizophrenia-like symptoms.

Hypothesis on relationship between ILs and schizophrenia was reported in 1995 by Holden and Pakula (22). These authors also suggested estrogen as a possible therapeutic option, since estrogen could inhibit IL-6 production. Certain epidemiological evidences further support such an immunological hypothesis, showing that women are more likely to develop schizophrenia during menopause and less likely during pregnancy, while men usually develop schizophrenia during adolescence.

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 cere-brospinal 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 EL-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 schizophrenia 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 $mRNA^{IL\ IRa}$ than that of $mRNA^{IL\text{-}1\beta}$ 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), neuropalhological 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 neurortrophins 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 antipsy-chotic 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).

CYTOKIHES AMD HEUROTROPHIMS IM 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

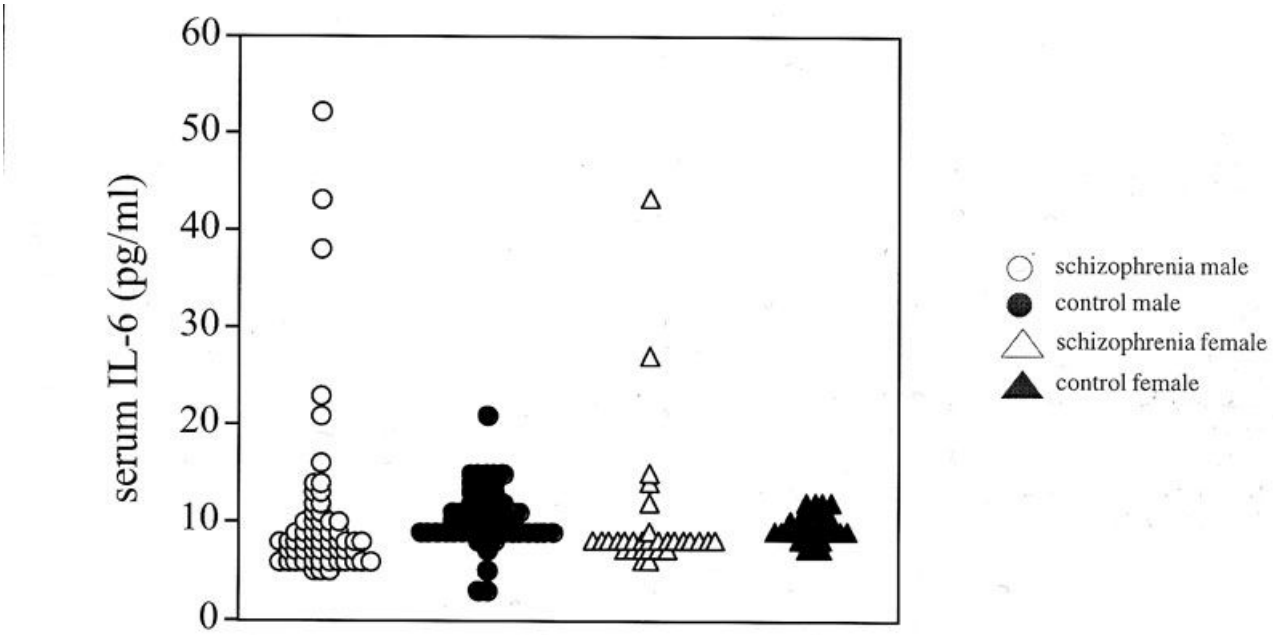

Figure 1. *The serum interleukin-6 (IL-6) concentration, illustrating a significant difference between the schizophrenic and the control group ($F=10.9$, $p < 0.002$). The difference in distribution is also statistically significant by Kolmogorov-Smirnov (chi-square=45.0, $p < 0.001$).*

the monoamine hypothesis. That is, the role played by the brain neurotransmitters 5-hydroxytryptamine (5-HT; serotonin) and noradrenaline (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-1J3, 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 $mRAN^{BDNF}$(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 canditate 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 *(if)* neurotrophin responses to antipsychotic and antide-pressant 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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