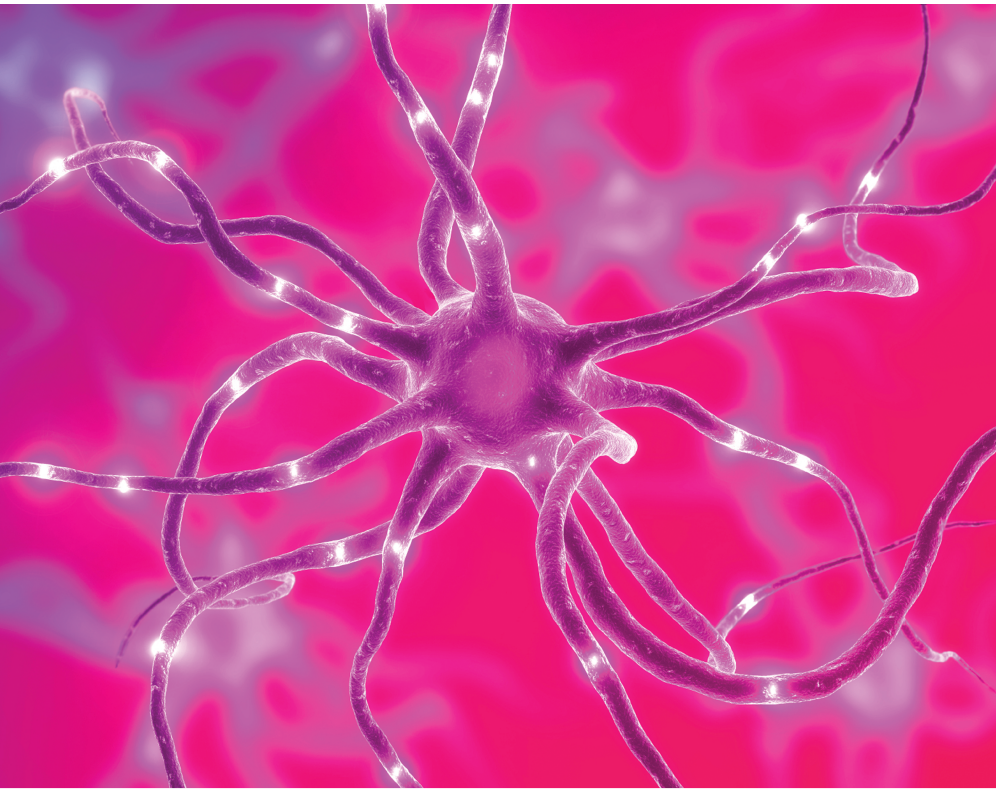
Update on Blood Brain Barrier



THE BLOOD BRAIN BARRIER AND THE ROLE OF CYTOKINES IN NEUROPSYCHIATRY

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ABSTRACT

Cytokines have emerged in the past two decades as some of the most extensively studied peptide molecules contributing to the pathophysiology of many diseases. As a result of these translational efforts, discovery of drugs aimed at reducing damage caused by cytokines has been accomplished for some conditions. The characterization of the role of cytokines in the pathophysiology of neuropsychiatric disorders is still in its infancy. This article highlights the growing correlation of brain cytokine levels with corresponding psychiatric symptoms, known as *cytokine-induced sickness behavior*, comprising increased sleep, decreased appetite, decreased sexual drive, and overwhelming fatigue frequently combined with fever.

KEY WORDS

blood brain barrier, cytokine, neuropsychiatry, neurotransmission

INTRODUCTION

Cytokines are inflammatory peptide molecules released as a result of the immune defense response to infection or injury anywhere in the body. Cytokines have unique immunomodulatory mechanisms in that they are pleotropic; that is, one cytokine can exert multiple different responses to a given immune reaction. Considering this, genetic polymorphism of various cytokines in association with different disease entities becomes more complicated.[1] Still, cytokine polymorphism in association with psychiatric illnesses remains largely unexplored despite mounting advances in the field.

Cytokines are classified into three different groups: (1) proinflammatory or those that help launch the immune response (IL-1, IL-6, and TNF); (2) anti-inflammatory or those that block or dampen the immune response (IL-4, IL-10, and IL-3); and (3) hematopoietic or those involved in stimulating the differentiation of hematologic progenitor cells into red and white blood cells (IL-3, IL-5, and G-CSF).

Cytokines are mostly derived from T cells, specifically CD4-positive T-helper lymphocytes. The T-helper cells (Th) are currently classified into Th type 1 (Th1) and Th type 2 (Th2) cells. The Th1 lineage promotes the anti-inflammatory response and is

associated with cytokines interleukin 1 alpha and beta (IL-1α and IL-1β), interleukin 2 (IL-2), interferon gamma (IFN-γ) and tumor necrosis factor beta (TNF-β). Th2 lineage cells, which promote antibody and allergic responses, are associated with cytokines such as IL-4, IL-6 and IL-10. The right balance between the two cell types is critical in maintenance of normal immune homeostasis. In a healthy individual, cytokines alert the brain of any immune responses to peripheral inflammatory processes secondary either to infection, injury, or disease by signaling an immunoneuropsychiatric (INP) cascade of events.

CYTOKINES AND BLOOD BRAIN BARRIER (BBB)

It is becoming more evident that integrity of the BBB plays a major role in the pathophysiology of neuropsychiatric illnesses.[2] Extensive experimental research by various groups over the past 20 years has demonstrated the direct passage of cytokines through the BBB causing considerable damage.[3] It has now become clear that some cytokines can directly and rapidly cross the BBB, in some cases within thirty minutes of injection (e.g., TNF-α).[4] Mechanisms by which this process is accomplished may involve the following: (a) a saturable influx transport (SIT) or retrograde axonal transport system (IL-1α and α, IL-6, and TNF-α) and (b) circumventricular organs, areas in the brain where the BBB is incomplete and cytokines may cross by simple diffusion (GDNF, glial cell-derived neurotrophic factor). Cytokines may also damage the BBB and increase its permeability without entering the brain, such as through activation and destruction of tight junctions of microvascular endothelial cells forming the BBB (TNF-α).[5]

CYTOKINES, HORMONES, AND CALCIUM

Cytokines share similarities with hormones in that they activate second messengers and signaling molecules, such as calcium. These substances mobilize many crucial reactions in the central nervous system by serving as catalysts for rate-limiting enzymes involved in neurotransmission. Cytokines differ from hormones in that they are pleiotropic, and, therefore, their release, unlike hormones, has more complicated effects on the regulation of neurotransmission. They can cross the BBB with ease, activate free calcium, and by potentially disrupting the compartmental model of brain calcium homeostasis, compromise the integrity of the BBB. Some cytokines, however, are known to be endogenous to the brain. IL-1 and TNF-α are commonly seen in the hypothalamic region of the brain. Localization of IL-1 in the hypothalamic region also explains the pyrogenic property of this particular cytokine.[6]

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CYTOKINES AND NEUROPSYCHIATRY

Cytokine-induced sickness behavior was first described in the literature in 1995.[7] It shares symptoms with fibromyalgia, such as fever, fatigue, pain, anorexia, and irritability. Immunoneuropsychiatric (INP) concepts were first introduced in the study of the pathophysiology of major depression. Dr. Michael Maes paved the path for the current explosion into cytokine research by linking the vegetative symptoms of major depression with increased production of IL-1, IL-6, and haptoglobin, an acute-phase reactant.[8] The study of cytokine involvement in the pathophysiology of other neuropsychiatric and metabolic disorders, such as anxiety disorders,[9,10] bipolar disorder,[11] schizophrenia,[12] headaches,[13] epilepsy,[14] dementia,[15] and delirium,[16] is also rapidly gaining momentum.

DISCUSSION

Psychiatrists, especially those serving in consultation liaison services, are faced with enormous challenges by the direct and indirect impact of cytokines on their patients. Medical conditions frequently cause alternations in endogenous cytokines levels with neuropsychiatric sequelae. In addition, cytokines are increasingly being used in the treatment of major medical conditions such as infections (hepatitis C) and cancers (leukemia).[17] Exogenous introduction of cytokines for treatment purposes may directly impact the neuropsychiatric status of an individual.

Depending on the rate and amount at which cytokines cross the blood brain barrier, a myriad of resulting neuropsychiatric symptomatology could emerge, such as low or depressed mood, anxiety, or psychosis. Increased levels of cytokines are desired in some conditions, as in the injection of IFN-α for hepatitis C and G-CSF for neutropenia. Exogenously administered cytokines directly influence the amount of cytokines that cross the BBB. Autoimmune conditions, on the other hand, have a more indirect impact on cytokine levels crossing the BBB. Autoimmune conditions may increase the permeability of the BBB, allowing more cytokines to cross. Treatments for autoimmune and inflammatory diseases commonly aim to reduce inflammation, thereby reducing circulating levels of cytokines. Crohn's disease, ulcerative colitis, and rheumatoid arthritis serve as classic examples of conditions in which blocking or dampening of cytokine levels is desired.

The impact of cytokines—whether exogenous or endogenous—on the brain may have lasting neuropsychiatric implications if left unchecked. Hence, determining the timing of these events is crucial, as earlier interventions, such as treatment with anti-inflammatory agents, administration of antibodies to cytokines, or injection of cytokines directly, in many instances, may prevent the development of chronic neuropsychiatric complications. This becomes especially relevant with the onset of first-break psychosis seen in schizophrenia, childhood onset of seizures, and delirium due to acute metabolic conditions.

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An association between inflammatory processes and neuropathology is becoming more evident in experimental models.[18] In particular, increased levels of white blood cells, particularly monocytes, increased circulating cytokine levels, and damage to the BBB have been implicated. Specific biomarkers to confirm damage to the BBB are currently unavailable. However, there is sufficient indirect evidence linking neuropsychiatric symptomatology of various conditions to a common underlying pathology of cytokine-mediated BBB compromise. Increased levels of S100B, a nonspecific protein biomarker believed to represent damaged BBB function, are seen in Down syndrome and Alzheimer's disease.[19] Antibodies to glutamic acid decarboxylase (GAD), an enzyme found in neurons and pancreatic islet cells, are present in tardive dyskinesia and other movement disorders,[20,21] potentially representing GABAergic neuronal damage. The above are only a few examples of the possible results of BBB compromise and subsequent neuronal exposure to inflammatory cytokines.

In summary, the interface between psychiatry and other medical disciplines deserves closer attention than previously thought, considering the mounting evidence available to us in clinical practice and the published literature. Effective and timely treatment strategies for acute medical conditions, especially infections and autoimmune conditions, could potentially decrease the devastating neuropsychiatric complications frequently seen in psychiatric patient populations. The implications of cytokine biology affecting neuropsychiatric conditions remain unexplored. Hypotheses-derived, prospective, clinical studies based on existing knowledge, in our opinion, should be encouraged.

PROPOSED INTERVENTIONS

We propose the following examples of potential large clinical trials directly involving the administration of cytokines to target neuropsychiatric syndromes:

1. Filgastrim[22] (a recombinant G-CSF) pretreatment prior to initiating clozapine in treatment-resistant schizophrenia, to minimize neutropenia and prevent the need for clozapine treatment discontinuation.
2. Treatment with antidepressants[23] before and after initiation of IFN-α (a pro-inflammatory cytokine) for hepatitis C, to prevent the development of depression.
3. Treatment with anti-

inflammatory cytokines capable of blocking ongoing damage in certain chronic autoimmune and infectious conditions, with the goal of decreasing neuropsychiatric manifestations.

Alternatively, the neuropsychiatric effects of cytokines could be approached indirectly, as in the following examples:

1. As the brain has limited capability to launch its own immune response, interventions could target signaling mechanisms of centrally active second messengers, especially calcium,[24] calcium binding proteins,[25] and GTP.[26]
2. Treatments could be administered to modulate the cytokine response to medical conditions so as to reduce their neuropsychiatric consequences. The use of cofactors as prophylaxis, such as B-vitamins for Wernicke-Korsakoff syndrome and acetylsalicylic acid for rheumatoid arthritis, serve as good examples of current efforts of this type. Potential clinical trials in the prevention and treatment of delirium could include the aggressive management of acute infections with antibiotics and anti-inflammatory drugs, as well as the correction of metabolic imbalances.
3. Standardization and monitoring of peripheral blood levels of key cytokines or their ratios in overall clinical practice could be used to evaluate for or detect those at risk for neuropsychiatric sequelae of medical conditions.

CONCLUSIONS

Translational research advances related to cytokine involvement in the brain are making a fast entry into the daily practice of medicine. These novel treatment modalities may directly affect the neuropsychiatric status of an individual. As practicing psychiatrists, an understanding of why a patient develops mood variations, psychosis, or seizures deserves the same attention as how to treat depression, schizophrenia, and epilepsy. Simple yet effective treatment strategies (e.g., correction of electrolyte imbalances, anti-inflammatory drugs, antibodies to certain cytokines, or in some cases the use of cytokines directly), when used alone or in combination with psychotropics, may have a tremendous impact on overall outcomes in neuropsychiatry.

REFERENCES

1. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry*. 2000;157(5):683–694.
2. Dermietzel R, Spray DC, Nedergaard M. *Blood-Brain Interface: From ontogeny to Artificial Barriers*. Weinhein, Germany:WILEY-VCH VerlagGmbh & Co.;2006
3. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun*. 2007;21(2):153–160. Epub 2006 Nov 7.
4. Gutierrez EG, Banks WA, Kastin AJ. Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. *J Neuroimmunol*. 1993;47(2):169–176.
5. Pan W, Xiang S, Tu H, Kastin A. Cytokines Interact with the Blood-brain-barrier. In: Dermietzel R, Spray D, Nedergaard M (ed)s. *Blood-Brain Interface: From ontogeny to Artificial Barriers*. Weinhein, Germany: WILEY-VCH VerlagGmbh & Co;2006:247–258.
6. Breder CD, Dinarello CA, Saper CB. Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science*. 1988;240(4850):321–324.
7. Aubert A, Vega C, Dantzer R, Goodall G. Pyrogens specifically disrupt the acquisition of a task involving cognitive processing in the rat. *Brain Behav Immun*. 1995;9(2):129–148.
8. Maes M. A review on the acute phase response in major depression. *Rev Neurosci*. 1993;4(4):407–416.
9. Brambilla F, Perna G, Bellodi L, et al. Plasma interleukin-1 beta and tumor necrosis factor concentrations in obsessive-compulsive disorders. *Biol Psychiatry*. 1997;42(11):976–981.
10. Brambilla F, Bellodi L, Perna G, et al. Plasma interleukin-1 beta concentrations in panic disorder. *Psychiatry Res*. 1994;54(2):135–142.
11. Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009;116(3):214–217. Epub 2009 Feb 28.
12. Ganguli R, Rabin BS, Kelly RH, et al. Clinical and laboratory evidence of autoimmunity in acute schizophrenia. *Ann NY Acad Sci*. 1987;496:676–685.
13. Asuni C, Stochino ME, Cherchi A, et al. Migraine and tumour necrosis factor gene polymorphism. An association study in a Sardinian sample. *J Neurol*. 2009;256(2):194–197. Epub 2009 Mar 1.
14. Marchi N, Angelov L, Masaryk T, et al. Seizure-promoting effect of

blood-brain barrier disruption. *Epilepsia*. 2007;48(4):732–742. Epub 2007 Feb 23.
15. Aisen PS, Davis KL. Inflammatory mechanisms in Alzheimer's disease: implications for therapy. *Am J Psychiatry*. 1994;151(8):1105–1113.
16. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing*. 2009;38(3):326–332; discussion 251. Epub 2009 Mar 5.
17. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. *Hepatology*. 1997;26(3 Suppl 1):112S–121S.
18. Banks WA. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. *Curr Pharm Des*. 2005;11(8):973–984.
19. Griffin WS, Stanley LC, Ling C, et al. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci U S A*. 1989;86(19):7611–7615.
20. Yarlagadda A, Helvink B, Chou C, et al. Glutamic acid decarboxylase (GAD) antibodies in tardive dyskinesia (TD) as compared to patients with schizophrenia without TD and normal controls. *Schizophr Res*. 2008;105(1–3):287-8. Epub 2008 Aug 16.
21. Lohmann T, Londei M, Hawa M, Leslie RD. Humoral and cellular autoimmune responses in stiff person syndrome. *Ann N Y Acad Sci*. 2003;998:215–222.
22. Hägg S, Rosenius S, Spigset O. Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol*. 2003;18(3):173–174.
23. Levenson JL, Fallon HJ. Fluoxetine treatment of depression caused by interferon-alpha. *Am J Gastroenterol*. 1993;88(5):760–761.
24. Yarlagadda A. Role of calcium regulation in pathophysiology model of schizophrenia and possible interventions. *Med Hypotheses*. 2002;58(2):182–186.
25. Lidow MS. Calcium signaling dysfunction in schizophrenia: a unifying approach. *Brain Res Brain Res Rev*. 2003;43(1):70–84.
26. Nelson TJ, Quattrone A, Kim J, et al. Calcium-regulated GTPase activity in the calcium-binding protein calexcitin. *Comp Biochem Physiol B Biochem Mol Biol*. 2003;135(4):627–638.

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