LIPPINCOTT WILLIAMS & WILKINS

Condensed JCP Normal Article

Jobname: jcp246ed

Creator: cs31

Page: 577 to 581

Date: 10/12/2004

Time: 0:7

Template version: 2.0

August 29, 2004

Modified by: WTD

Strip-in Program Ready (GetTables)

Brain Cytokines and Neuropsychiatric Disorders

Theoharis C. Theoharides, MS, MPhil, PhD, MD,†‡§*
Craig Weinkauf[1], BS, and Pio Conti, PhD‖*

Many neuropsychiatric diseases still elude full understanding and effective therapy. It has become increasingly obvious that some of the prevailing explanations of their pathology are overly simplistic since only a small fraction of patients appear to be successfully helped, at best. One possibility is that the role of lymphocytes and neuroimmune interactions in the central nervous system (CNS) have been largely neglected,[1] except in clear cases that are autoimmune in nature, as in multiple sclerosis (MS).[2] Much can be learned from rare diseases about apparent links between the immune and the nervous system. For example, systemic mastocytosis is characterized by mast cell proliferation and activation in most organs, including the CNS.[3] The prevalence of psychiatric problems in these patients is much higher than the general population, and acute stress is known to exacerbate their symptoms.[3]

The main family of immune system molecules implicated in neurologic diseases are cytokines, which may be secreted under stress[4,5] and affect cerebral neurotransmission.[6] Cytokines are modulatory molecules that control the development and differentiation of all bone marrow–derived pluripotent stem cells. Cytokines also have inflammatory and regulatory actions.[7–9] Acute stress induces leukocyte trafficking and augments immune responses.[10] In fact, acute stress can increase mast cell–dependent serum interleukin-6 (IL-6)[11,12] that involves selective release without degranulation.[13] Elevated serum IL-6 is characteristic in systemic mastocytosis patients[14] in whom stress can precipitate seizures.[15] IL-6 overproduction is also involved in anticonvulsant hypersensitivity.[16]

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA)

Cytokines and chemokines have been implicated in inflammation of the CNS.[6,17,18] and in neuropsychiatric conditions.[19,20] Cytokines are expressed in the brain and are involved in regulating the HPA axis.[21] Stressors activate the HPA axis, resulting in elevated plasma levels of cortisol in humans and modulation of proinflammatory cytokine responses. However, acute stress could induce neurogenic inflammation in a variety of organs,[5] including the brain.[2] Stress leads to an increased expression of proinflammatory cytokines such as IL-1 and IL-6,[6,22] which play a critical role in the regulation of the HPA axis.[21] In particular, IL-1 and IL-6 induce up-regulation of corticotropin-releasing hormone (CRH) which regulates the HPA axis.[23] CRH and related peptides can also activate brain mast cells[24] through a number of CRH

*Departments of Pharmacology and Experimental Therapeutics; †Internal Medicine; ‡Biochemistry and §Psychiatry, Tufts University School of Medicine, Tufts-New England Medical Center, Boston, MA and ‖Immunology Division, Department of Oncology and Neuroscience, University of Chieti, Chieti, Italy.
[1]MD/PhD student.
Address correspondence and reprint requests to Theoharis C. Theoharides, PhD, MD, Department of Pharmacology and Experimental Therapeutics, TUFTS University School of Medicine, 136 Harrison Avenue, Boston, MA 02111. E-mail: theoharis.theoharides@tufts.edu.

ISSN: 0271-0749/04/2406-0577
DOI: 10.1097/01.jcp.0000148026.86483.4f

TABLE 1. Publications Discussing the Role of the Immune System in the CNS

Immune System	Nervous System	Reference
Mast cells	Inflammatory diseases, acute stress	Theoharides and Cochrane[2]
Mast cell degranulation	Opioid withdrawal	Taiwo et al[32]
Cytokines	Neuroinflammation and Alzheimer disease	Cacquevel et al[69]
IL-6	Dementia	Wada-Isoe et al[68]
IL-6 receptor	Neurologic diseases	Michalopoulou et al[49]
Mast cells	Tumor growth	Theoharides and Conti[80]
IL-10	Multiple sclerosis	Adikari et al[47]; Jung et al[48]
Cytokines	Multiple sclerosis	Flachenecker et al[51]; Calabresi et al[50]
IL-6 and IL-10	Alzheimer disease	Arosio et al[66] l; Quintanilla et al[70]; Zhang et al[67]
Blood lymphocytes	Depression, Alzheimer's disease, schizophrenia, stress	Gladkevich et al[1]*
Cytokines	Hypothalamic-pituitary network	Kariagina et al[21]
IL-1 polymorphisms	Dysthymia	Fertuzinhos et al[57]
IFN-gamma, IL-4, TNF-alpha	Roles the CNS	Shapshak et al[36]
Cytokines	Stress and depression	O'Brien et al[59]; Anisman and Merali[19]; Steptoe et al[5]
Proinflammatory cytokines	Migraines, phobias	Covelli et al[64]*
IL-10	Inflammation	Conti et al[44]
IFN-alpha treatments	Depression and neuropsychiatric side effects	Van Gool et al[37]*; Schaefer et al[38]*; Malaguarnera et al[39]
Cytokines and kinins	Neuropsychiatric lupus	Dellalibera-Joviliano et al[73]
IL-6	Meningitis, vascular permeability	Paul et al[34]
Mast Cells	Blood-brain barrier	Peroutka and Allen[89]
Autoantibodies, Proinflammatory cytokines	Neuropsychiatric systemic lupus erythematosus	Hermosillo-Romo and Brey[72]
Cytokines and kinins	Nervous system signaling	Kronfol and Remick[20]*
IL-1 and IL-6	Cachexia-anorexia syndrome	Plata-Salaman et al[42]*
Chemokines	Nervous system inflammation	Huang et al[11]; Mennicken et al[17]
Cytokines	Cerebral neurotransmission	Dunn et al[6]
IL-10	Cerebrovascular disease	Pelidou et al[46]
Chemokines	Depression, neuroprotection and neurotoxicity	Licinio and Wong[56]
Cytokines	Panic disorder	Weizman et al[61]
Cytokines	Blood-brain barrier permeability	de Boe and Breimer[27]
IL-1	Panic disorder	Brambilla et al[60]

*Denotes review article.

receptor isoforms[25] leading to disruption of the blood-brain barrier.[26,27] Mast cells are a rich source of cytokines as well as CRH and related peptides.[28] Mast cells could accumulate in response to the specific chemoattractant RANTES,[29] which is secreted in inflammatory sites.[30,31] Brain mast cells were recently shown to redistribute and become activated in the mouse thalamus during naloxone-induced withdrawal.[32]

NEUROLOGIC DISORDERS

Cytokines could promote neurodegeneration or neuroprotection in different animal models. Injection of lipopolysaccharide to induces changes in brain cytokine mRNA and protein levels of such cytokines as IL-1-β, IL-6, and TNF-β.[33] Moreover, IL-6 appears to be involved with increased vascular permeability in bacterial meningitis.[34] The human immunodeficiency virus (HIV) invades the CNS inside immune cells and leads to behavioral problems that include depression and psychosis.[35] Elevated expression of interferon (IFN)-γ and decreased IL-4 are correlated with greater toxicity in HIV-1-infected brains.[36] It is interesting that there is increased incidence of depression in AIDS patients, over and beyond what may be expected due to the disease, and a causal relationship has been reported between brain IFN-α levels and the development of depressive symptoms.[37,38] In addition to altering the brain cytokine profile,[39] IFN-α may be modulating the serotonin, dopamine,

and glutamate systems.[40] Interestingly, nonsteroidal anti-inflammatory drugs appear to counteract IFN-induced depression, potentially through inhibition of both cytokine and stress hormone release.[41] Cytokines may also be involved in the cachexia-anorexia syndrome by affecting specific brain regions.[42] The anti-inflammatory cytokine IL-10[43,44] has recently been shown to promote survival of neurons and block lipopolysaccharide-induced brain IL-1 signaling.[45] Increased numbers of IL-10 secreting cells were reported in the blood of patients with cerebrovascular diseases.[46] IL-10 also regulates the proinflammatory environment in MS[47]; this survival-promoting activity is due to IL-10 signaling through the Stat-3 pathway, which inhibits cell death. Moreover, the drug glatiramer acetate used in MS induces IL-10 production.[48] Activated microglia produce high levels of IL-1β and IL-1α, as well as IL-6, the soluble receptor of which was increased in the cerebrospinal fluid (CSF) of MS patients.[49] In fact, a number of cytokines have been found to be increased in the CSF of MS patients.[50,51] Moreover, the mast cell unique protease tryptase was also elevated in the CSF of MS patients,[52] and tryptase is known to cause widespread inflammation by stimulating protease-activated receptors.[53] In this context, it is significant that gene array analysis of affected brains from deceased MS patients showed up-regulation only of mast cell–related markers.[54]

PSYCHIATRIC DISORDERS

Several studies have reported associations between psychologic stress, cytokines, and psychiatric illness.[19,55–57] For instance, cytokines have specifically been implicated in depression.[6,55,56,58,59] Increased cytokine production has also been reported in plasma,[60] and cytokines are secreted from peripheral mononuclear cells of panic disorder patients.[61] In fact, panic disorder was linked to the same chromosome as interstitial cystitis,[62] an inflammatory condition of the urinary bladder characterized by increased cytokine production.[63] Patients with phobias and migraines have also been characterized by increased release of proinflammatory cytokines.[64] IL-1β gene polymorphisms have been reported to increase the risk of psychosis, especially schizophrenia.[65]

Cytokines appear to be involved in Alzheimer disease, as IL-6 gene polymorphism has been demonstrated in this disease[66,67]; IL-6 is elevated in the CSF of such patients.[68,69] Moreover, IL-6 induces phosphorylation of the tau protein that is considered important in Alzheimer pathology.[70] Alzheimer patients treated with an acetylcholinesterase inhibitor had higher IL-4 and lower IL-1β expression from peripheral blood mononuclear cells.[71]

Of those with systemic lupus erythematosus, 75% have neuropsychiatric systemic lupus erythematosus, which was found to be associated with increased CSF levels of kinins and cytokines.[72,73] Vascular endothelial growth factor is up-regulated after various injuries to the brain[74] and is also released by mast cells.[75] Vascular endothelial growth factor is neurotrophic and neuroprotective and plays seminal pleiotropic roles in CNS development and repair. It was recently shown that CRH can stimulate selective secretion of vascular endothelial growth factor from human cultured mast cells.[24] Stress can inhibit mitogen-activated protein kinase signaling,[76] a pivotal component in cytokine- and stress-induced apoptosis.[77] It also regulates cell differentiation and survival through p38 mitogen-activated protein kinase activation.[78] In some pathologic conditions of the brain, p38 mitogen-activated protein transduces stress-related signals, increases expression of proinflammatory cytokines, and induces cellular damage or apoptosis.[79] Moreover, p38 mitogen-activated protein kinase modulates STAT1 phosphorylation in IFN-γ signaling in brain astrocytes.

Stress may increase/permit brain tumor metastases through mast cell activation,[80] supporting the use of anxiolytic and antidepressant medications in such patients.[81] Reduction of cytotoxic immune activity and a shift in T_H1/T_H2 balance of the immune response toward T_H2-dominant immunity may help explain these findings.[82] For instance, IL-18 is a potent proinflammatory cytokine that enhances innate immunity by activating both T_H1 and T_H2 responses depending on the cytokine microenvironment.[83]

A number of dietary supplements have recently emerged as potentially effective for allergies, asthma, and also in a variety of CNS conditions discussed above, such as anxiety, depression, and migraines.[84] It is noteworthy that many of these molecules appear to affect mast cell activation.[84] Mast cell inhibitors especially select natural flavonoids can block release of IL-6, IL-8 and TNF-α,[85,86] as well as experimental allergic encephalomyelitis.[87] These flavonoids appear to be particularly potent mast cell blockers and anti-inflammatory agents[88]; they could therefore potentially be useful in some of the conditions discussed above.

Table 1 lists publications that discuss the role of the immune system in the CNS.

ACKNOWLEDGMENTS

Aspects of our own work discussed were supported by grants from the US National Institutes of Health NS38326 and AR47652. Thanks are due to Ms Jessica Christian for her patience and word processing skills. US patents 5,250,529, 5,855,884, 6,689,748, 09/771,669 (allowed August 10, 2004) and US Patent Application 10/166,088 (filed February 10, 2002) awarded to TCT cover the use of mast cell and IL-6 action blockers in neuroinflammatory diseases.

REFERENCES

1. Gladkevich A, Kauffman HF, Korf J. Lymphocytes as a neural probe: potential for studying psychiatric disorders. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2004;28:559–576.

2. Theoharides TC, Cochrane DE. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J Neuroimmunol*. 2004;146:1–12.
3. Theoharides TC. Mast cells and stress—A psychoneuroimmunological perspective. *J Clin Psychopharmacol*. 2002;22:103–108.
4. Chen E, Fisher EB, Bacharier LB, et al. Socioeconomic status, stress, and immune markers in adolescents with asthma. *Psychosom Med*. 2003;65:984–992.
5. Steptoe A, Owen N, Kunz-Ebrecht S, et al. Inflammatory cytokines, socioeconomic status, and acute stress responsivity. *Brain Behav Immun*. 2002;16:774–784.
6. Dunn AJ, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv Exp Med Biol*. 1999;461:117–127.
7. Kempuraj D, Frydas S, Kandere K, et al. Interleukin-19 (IL-19) network revisited. *Int J Immunopathol Pharmacol*. 2003;16:95–97.
8. Kempuraj D, Frydas S, Conti P, et al. Interleukin-25: a new IL-17 family member with growth factor/inflammatory actions. *Int J Immunopathol Pharmacol*. 2003;16:185–188.
9. Kempuraj D, Donelan J, Frydas S, et al. Interleukin-28 and 29 (IL-28 and IL-29): new cytokines with anti-viral activities. *Int J Immunopathol Pharmacol*. 2004;17:103–106.
10. Dhabhar FS. Stress-induced augmentation of immune function—The role of stress hormones, leukocyte trafficking, and cytokines. *Brain Behav Immun*. 2002;16:785–798.
11. Huang M, Pang X, Karalis K, et al. Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in apolipoprotein E knockout mice. *Cardiovasc Res*. 2003;59:241–249.
12. Huang M, Berry J, Kandere K, et al. Mast cell deficient W/W(v) mice lack stress-induced increase in serum IL-6 levels, as well as in peripheral CRH and vascular permeability, a model of rheumatoid arthritis. *Int J Immunopathol Pharmacol*. 2002;15:249–254.
13. Kandere-Grzybowska K, Letourneau R, Boucher W, et al. IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. *J Immunol*. 2003;171:4830–4836.
14. Theoharides TC, Boucher W, Spear K. Serum IL-6 reflects disease severity and osteoporosis in mastocytosis patients. *Int Arch Allergy Immunol*. 2002;128:344–350.
15. Pehlivanidis C, Fotoulaki M, Boucher W, et al. Acute stress-induced seizures and loss of consciousness in a ten-year-old boy with cutaneous mastocytosis. *J Clin Psychopharmacol*. 2002;22:221–224.
16. Chiappinl E, Peruzzi M, Galli G, et al. Dose-related IL-6 overproduction by phenobarbital-incubated peripheral blood mononuclear cells in a child with anticonvulsant hypersensitivity syndrome. *Int J Immunopathol Pharmacol*. 2002;15:239.
17. Mennicken F, Maki R, DeSouza EB, et al. Chemokines and chemokine receptors in the CNS: a possible role in neuroinflammation and patterning. *Trends Pharmacol Sci*. 1999;20:73–78.
18. Huang D, Han Y, Rani MR, et al. Chemokines and chemokine receptors in inflammation of the nervous system: manifold roles and exquisite regulation. *Immunol Rev*. 2004;177:52–67.
19. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. *Ann Med*. 2003;35:2–11.
20. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry*. 2000;157:683–694.
21. Kariagina A, Romanenko D, Ren SG, et al. Hypothalamic-pituitary cytokine network. *Endocrinology*. 2004;145:104–112.
22. O'Connor KA, Johnson JD, Hansen MK, et al. Peripheral and central proinflammatory cytokine response to a severe acute stressor. *Brain Res*. 2003;991:123–132.
23. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332:1351–1362.
24. Theoharides TC, Donelan JM, Papadopoulou N, et al. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol Sci*. 2004. (In press). AQ1
25. Papadopoulou N, Kempuraj D, Cao J, et al. Corticotropin-releasing hormone receptors 1 and 2 types are expressed in human umbilical cord-blood–derived mast cells; regulation of expression by interleukin-4. P3-535, Proceedings of the 86th Annual Meeting of the Endocrine Society. June 16–June 19, 2004; N. Orleans, LA.
26. Esposito P, Chandler N, Kandere-Grzybowska K, et al. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood-brain barrier permeability induced by acute stress. *J Pharmacol Exp Ther*. 2002;303:1061–1066.
27. de Boe AG, Breimer DD. Cytokines and blood-brain barrier permeability. *Prog Brain Res*. 1998;115:425–451.
28. Kempuraj D, Papadopoulou NG, Lytinas M, et al. Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells. *Endocrinology*. 2004;145:43–48.
29. Conti P, Reale M, Barbacane RC, et al. Intramuscular injection of hrRANTES causes mast cell recruitment and increased transcription of histidine decarboxylase: lack of effects in genetically mast cell-deficient W/W^v mice. *FASEB J*. 1998;12:1693–1700.
30. Di Gioacchino M, Verna N, Cavallucci E, et al. Steroid and antihistamines modulate RANTES release in cultured peripheral blood mononuclear cells of atopic patients. *Int J Immunopathol Pharmacol*. 2002;15:27–34.
31. Conti P, Reale M, Barbacane RC, et al. Differential production of RANTES and MCP-1 in synovial fluid from the inflamed human knee. *Immunol Lett*. 2002;80:105–111.
32. Taiwo OB, Kovacs KJ, Sperry LC, et al. Naloxone-induced morphine withdrawal increases the number and degranulation of mast cells in the thalamus of the mouse. *Neuropharmacology*. 2004;46:824–835.
33. Alheim K, Chai Z, Fantuzzi G, et al. Hyperresponsive febrile reactions to interleukin (IL) 1alpha and IL-1beta, and altered brain cytokine mRNA and serum cytokine levels, in IL-1beta-deficient mice. *Proc Natl Acad Sci USA*. 1997;94:2681–2686.
34. Paul R, Koedel U, Winkler F, et al. Lack of IL-6 augments inflammatory response but decreases vascular permeability in bacterial meningitis. *Brain*. 2003;126:1873–1882.
35. Rausch DM, Stover ES. Neuroscience research in AIDS. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2001;25:231–257. AQ2
36. Shapshak P, Duncan R, Minagar A, et al. Elevated expression of IFN-gamma in the HIV-1 infected brain. *Front Biosci*. 2004;9:1073–1081.
37. Van Gool AR, Kruit WH, Engels FK, et al. Neuropsychiatric side effects of interferon-alfa therapy. *Pharm World Sci*. 2003;25:11–20.
38. Schaefer M, Engelbrecht MA, Gut O, et al. Interferon alpha (IFNalpha) and psychiatric syndromes: a review. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2002;26:731–746.
39. Malaguarnera M, Laurino A, Di Fazio I, et al. Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res*. 2001;21:273–278.
40. Schaefer M, Schwaiger M, Pich M, et al. Neurotransmitter changes by interferon-alpha and therapeutic implications. *Pharmacopsychiatry*. 2003;3:S203–S206.
41. Asnis GM, De la Garza R2, Kohn SR, et al. IFN-induced depression: a role for NSAIDs. *Psychopharmacol Bull*. 2003;37:29–50. AQ3
42. Plata-Salaman CR. Central nervous system mechanisms contributing to the cachexia-anorexia syndrome. *Nutrition*. 2000;16:1009–1012.
43. Kempuraj D, Frydas S, Conti P, et al. IL-10 subfamily members: IL-19, IL-20, IL-22, IL-24 and IL-26. *Immunol Lett*. 2003;88:171–174.
44. Conti P, Kempuraj D, Kandere K, et al. IL-10, an inflammatory/inhibitory cytokine, but not always. *Immunol Lett*. 2003;86:123–129.
45. Lynch AM, Walsh C, Delaney A, et al. Lipopolysaccharide-induced increase in signalling in hippocampus is abrogated by IL-10—A role for IL-1 beta? *J Neurochem*. 2004;88:635–646.
46. Pelidou SH, Kostulas N, Matusevicius D, et al. High levels of IL-10 secreting cells are present in blood in cerebrovascular diseases. *Eur J Neurol*. 1999;6:437–442.
47. Adikari SB, Pettersson A, Soderstrom M, et al. Interleukin-10-modulated immature dendritic cells control the proinflammatory environment in multiple sclerosis. *Scand J Immunol*. 2004;59:600–606.
48. Jung S, Siglienti I, Grauer O, et al. Induction of IL-10 in rat peritoneal macrophages and dendritic cells by glatiramer acetate. *J Neuroimmunol*. 2004;148:63–73.
49. Michalopoulou M, Nikolaou C, Tavernarakis A, et al. Soluble interleukin-6 receptor (sIL-6R) in cerebrospinal fluid of patients with inflammatory and non inflammatory neurological diseases. *Immunol Lett*. 2004;94:183–189.
50. Calabresi PA, Tranquill LR, McFarland HF, et al. Cytokine gene

expression in cells derived from CSF of multiple sclerosis patients. *J Neuroimmunol*. 1998;89:198–205.
51. Flachenecker P, Bihler I, Weber F, et al. Cytokine mRNA expression in patients with multiple sclerosis and fatigue. *Mult Scler*. 2004;10: 165–169.
52. Rozniecki JJ, Hauser SL, Stein M, et al. Elevated mast cell tryptase in cerebrospinal fluid of multiple sclerosis patients. *Ann Neurol*. 1995;37:63–66.
53. Schmidlin F, Bunnett NW. Protease-activated receptors: how proteases signal to cells. *Curr Opin Pharmacol*. 2001;1:575–582.
54. Lock C, Hermans G, Pedotti R, et al. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat Med*. 2002;8:500–508.
55. Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci*. 1998;62:583–606.
56. Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol Psychiatry*. 1999;4:317–327.
57. Fertuzinhos SM, Oliveira JR, Nishimura AL, et al. Analysis of IL-1alpha, IL-1beta, and IL-1RA [correction of IL-RA] polymorphisms in dysthymia. *J Mol Neurosci*. 2004;22:251–256.
58. De Jongh R, Vissers KC, Booij LH, et al. Interleukin-6 and perioperative thermoregulation and HPA-axis activation. *Cytokine*. 2003;21:248–257.
59. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol*. 2004;19:397–403.
60. Brambilla F, Bellodi L, Perna G, et al. Plasma interleukin-1 beta concentrations in panic disorder. *Psychiatry Res*. 1994;54:135–142.
61. Weizman R, Laor N, Wiener Z, et al. Cytokine production in panic disorder patients. *Clin Neuropharmacol*. 1999;22:107–109.
62. Theoharides TC. Panic disorder, interstitial cystitis and mast cells. *J Clin Psychopharmacol*. 2004;24:361–364.
63. Theoharides T, Sant GR. Immunomodulators for the treatment of interstitial cystitis. *Urology*. 2004 (In press). AQ1
64. Covelli V, Pellegrino NM, Jirillo E. A point of view: the need to identify an antigen in psychoneuroimmunological disorders. *Curr Pharm Des*. 2003;9:1951–1955.
65. Craig D, Hart DJ, McCool K, et al. The interleukin 1beta gene promoter polymorphism (-511) acts as a risk factor for psychosis in Alzheimer's dementia. *Ann Neurol*. 2004;56:121–124.
66. Arosio B, Trabattoni D, Galimberti L, et al. Interleukin-10 and interleukin-6 gene polymorphisms as risk factors for Alzheimer's disease. *Neurobiol Aging*. 2004;25:1009–1015.
67. Zhang Y, Hayes A, Pritchard A, et al. Interleukin-6 promoter polymorphism: risk and pathology of Alzheimer's disease. *Neurosci Lett*. 2004;362:99–102.
68. Wada-Isoe K, Wakutani Y, Urakami K, et al. Elevated interleukin-6 levels in cerebrospinal fluid of vascular dementia patients. *Acta Neurol Scand*. 2004;110:124–127.
69. Cacquevel M, Lebeurrier N, Cheenne S, et al. Cytokines in neuroinflammation and Alzheimer's disease. *Curr Drug Targets*. 2004;5: 529–534.
70. Quintanilla RA, Orellana DI, Gonzalez-Billault C, et al. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. *Exp Cell Res*. 2004;295:245–257.
71. Gambi F, Reale M, Larlori C, et al. Alzheimer patients treated with an AchE inhibitor show higher IL-4 and lower IL-1 beta levels and expression in peripheral blood mononuclear cells. *J Clin Psychopharmacol*. 2004;24:314–321.
72. Hermosillo-Romo D, Brey RL. Diagnosis and management of patients with neuropsychiatric systemic lupus erythematosus (NPSLE). *Best Pract Res Clin Rheumatol*. 2002;16:229–244.
73. Dellalibera-Joviliano R, Dos Reis ML, Cunha Fde Q, et al. Kinins and cytokines in plasma and cerebrospinal fluid of patients with neuropsychiatric lupus. *J Rheumatol*. 2003;30:485–492.
74. Kim S, Iwao H. Stress and vascular responses: mitogen-activated protein kinases and activator protein-1 as promising therapeutic targets of vascular remodeling. *J Pharmacol Sci*. 2003;91:177–181.
75. Boesiger J, Tsai M, Maurer M, et al. Mast cells can secrete vascular permeability factor/vascular endothelial cell growth factor and exhibit enhanced release after immunoglobulin E-dependent upregulation of FcEϵ receptor I expression. *J Exp Med*. 1998;188:1135–1145.
76. Nagata D, Mogi M, Walsh K. AMP-activated protein kinase (AMPK) signaling in endothelial cells is essential for angiogenesis in response to hypoxic stress. *J Biol Chem*. 2003;278:31000–31006.
77. Cowan KJ, Storey KB. Mitogen-activated protein kinases: new signaling pathways functioning in cellular responses to environmental stress. *J Exp Biol*. 2003;206:1107–1115.
78. Lee J, Shin JS, Park JY, et al. p38 mitogen-activated protein kinase modulates expression of tumor necrosis factor-related apoptosis-inducing ligand induced by interferon-gamma in fetal brain astrocytes. *J Neurosci Res*. 2003;74:884–890.
79. Takeda K, Ichijo H. Neuronal p38 MAPK signalling: an emerging regulator of cell fate and function in the nervous system. *Genes Cells*. 2002;7:1099–1111.
80. Theoharides TC, Conti P. Mast cells: the JEKYLL and HYDE of tumor growth. *Trends Immunol*. 2004;25:235–241.
81. Theoharides TC. Antidepressants and risk of cancer: a case of misguided associations and priorities. *J Clin Psychopharmacol*. 2003;13:1–4.
82. Elenkov IJ, Chrousos GP. Stress hormones, T_H1/T_H2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends Endocrinol Metab*. 1999;10:359–368.
83. Nakanishi K, Yoshimoto T, Tsutsui H, et al. Interleukin-18 is a unique cytokine that stimulates both T_H1 and T_H2 responses depending on its cytokine milieu. *Cytokine Growth Factor Rev*. 2001;12:53–72.
84. Theoharides TC, Bielory L. Mast cells and mast cell mediators as targets of dietary supplements. *Ann Allergy Asthma Immunol*. 2004;93(suppl 2):24–34.
85. Kempuraj D, Huang M, Kandere-Grzybowska K, et al. Azelastine inhibits secretion of IL-6, TNF-α and IL-8 as well as NF-κB activation and intracellular calcium ion levels in normal human mast cells. *Int Arch Allergy Immunol*. 2003;132:231–239.
86. Gilles S, Zahler S, Welsch U, et al. Release of TNF-alpha during myocardial reperfusion depends on oxidative stress and is prevented by mast cell stabilizers. *Cardiovasc Res*. 2003;60:608–616.
87. Dimitriadou V, Pang X, Theoharides TC. Hydroxyzine inhibits experimental allergic encephalomyelitis (EAE) and associated brain mast cell activation. *Int J Immunopharmacol*. 2000;22:673–684.
88. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol Rev*. 2000;52:673–751.
89. Peroutka SJ, Allen GS. The calcium antagonist properties of cyproheptadine: implications for antimigraine action. *Neurology*. 1984;34: 304–309. AQ4

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

AQ1 = Please provide update if published already (page range, volume number). Please confirm also validity of the given date.
AQ2 = Please check page range (should last page be ‘‘257’’?)
AQ3 = Please check first name initials.
AQ4 = This reference ws not cited.

END OF ALL QUERIES