EDITORIAL

CYTOKINES IN STRESS

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It has been detected that immunological activation induces stress-like behavioural and neurochemical changes in organs of animals and humans (1-6). Proinflammatory cytokines along with other compounds such as corticotropin releasing hormone (CRH) are clearly involved in the pathogenesis of stress (7-10). Activation of cytokine receptors and alterations in cytokine are thought to play important roles in neuronal dysfunction and pathogenesis of stress (11-15). Moreover, hyper secretion of cytokines in response to stress or to endogenous trigger factors may induce depressive symptoms. In addition AMP-activated protein kinase (AMPK) which is tightly regulated by the cellular AMP/ATP ratio, plays a central role in the regulation of energy, homeostasis and metabolic stress (12). Cytokine-like factors affect immune functions, such as cell motility, chemotaxis, phagocytosis, cytotoxicity and can also modulate muscle mass (16-18). For example epinephrine induces IL-6 synthesis in skeletal muscle *in vivo* and *in vitro* utilizing predominantly beta-2-adrenergic receptors.

Cytokines are also involved in invertebrate stress response in a manner very similar to that in vertebrates and participate in neurochemical, behavioural and endocrine changes due to illness.

In stress IL-β mRNA increased as well as the protein IL-1β particularly in the hypothalamus, hippocampus and pituitary gland while TNF-α decreased in cortex and pituitary gland. Glucocorticoids also decreased while IL-6 mRNA has no effect. However it has been reported that IL-6 increases following a neurogenic inflammatory stimulus (17). Exposure to the proinflammatory cytokine IL-1 beta can elevate circulating concentration of corticosterone (18). Caspase-1 is involved in inflammatory cascade by processing pro-IL-1 beta into the active cytokine mature IL-1 beta and it is an important mediator of neuronal cell death during in vitro hypoxia and in vivo ischemia (19). In addition, TNF alpha has been found to be harmful in the early phase and beneficial in the long-term phase after brain injury (20-22). In astrocytes, TNF-related apoptosis-inducing ligand (TRAIL) expression level is increased by IFN-gamma.

Key words: cytokine, stress, inflammation

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In stress conditions such as heart reperfusion, mast cells, HMC-1 produce TNF converting enzyme TACE and pro-TACE which cleaved the pro-TNF peptide. In infections LPS activated IL-1β in hippocampus. This effect is inhibited by IL-10 which is found as a protector of neuronal tissue in infections (23). In stress cytokines are generated which increases uterine contractility and may lead to preterm birth and play important roles in the pathogenesis of diseases in adult life. Prenatal IL-1 exposure results in decreased skeletal growth and a reduced amount of cortical bone (24). In addition to the production of IL-23 has been found to mediate experimental autoimmune encephalomyelitis (25). Moreover, stress may inhibit TNF-α stimulation of (vascular cell adhesion molecule) (26). Vascular endothelial growth factor (VEGF) is up regulated after various injuries to the brain and the cytokine affords protection to cultured neurons affected by oxidative or excitotoxic stress. VEGE is neurotrophic, neuroprotective and plays seminal pleiotropic roles in central nervous system development and repair. Oxidative stress inhibits NF-kappaβ activation and associated TNF-alpha expression; therefore, these actions on cells may limit tissue damage (27-28).

Stress can inhibit mitogen-activated protein (MAP) kinase signaling and TNR-associated factor-2 (TRAF-2) in condition of stress increase of IFN-γ and IL-5 under stress (29-31). MAP is a pivotal component in cytokine- and stress-induced apoptosis. It also regulates cell differentiation and survival through p38 MAP kinase activation (31-33). In some pathological conditions of the brain, p38 MAP transduces stress-related signals, increases expression of proinflammatory cytokines, and induces cellular damage or apoptosis. Moreover, p38 MAPK modulates STAT1 phosphorylation in IFN-gamma signaling in brain astrocytes.

Environment and Stress

A reciprocal regulation exists between the immune and nervous systems in responding to environmental signal due to lifestyle and work activity (34-36). Environmental stimulation may be helpful or dangerous for human health depending on dose. Moreover, the efficacy of immune response depend on concurrent neuroendocrine events upon which they are superimposed. In this regard, genetic predisposition as well as stability of the mental status, which influence both lifestyle and work, plays an important role an active lifestyle and success at work generally stimulate both immune and neuroendocrine mechanisms and maintain good physical and psychological health. On the contrary, repetitive work, unemployment or uncertainty in maintaining or achieving a job, work without gratification and shift work, which derange the circadian biorhythm depress both immune and neuroendocrine functions.

Generally, a variety of stimulation over a short period is helpful for human health, while marked and or repetitive signals inducing a condition of stress are harmful. Stress affects the sympathetic-adrenal medullary, the hypothalamic pituitary adrenocortical and the autacoid systems. Several cytokines, peptide hormones, neurotransmitters as well as their receptors ligands present in both neuroendocrine and immune systems, are stimulated by stress (37-54). Studies in the field of public health and occupational medicine demonstrated the following effects of poor lifestyle and work activities: a) reduction of cytotoxic immune activity both in the body and peripheral human blood, b) shift in Th1/Th2 balance of the immune response toward Th2-dominant immunity.

This exerts detrimental effects on the prevention of cancer and infectious diseases, stimulates sensitization and allergic responses in atopic patients as well as inducing premature ageing.

Today, not only neurohumoral substances (such as blood cortisol, ACTH. TSH prolactin, urinary melatonin and metabolites of catecholamine) but also immune parameters may be used as markers of stress in occupational medicine These include salivary IgA as well as lymphokine activated killer cell activities and natural killer cells values in peripheral blood (55).

REFERENCES

1. **Anisman H. and Z. Merali**. 2003. Cytokines, stress and depressive illness: brain-immune interactions. *Ann. Med. 35:2.*
2. **Mann D.L.** 2003. Stress-activated cytokines and the heart: from adaptation to maladaptation. *Annu. Rev. Physiol. 65:81.*
3. **Dhabhar F.S.** 2002. Stress-induced augmentation of immune function - the role of stress hormones, leukocyte

trafficking, and cytokines. *Brain Behav. Immun. 16:785.*

4. **Steptoe A., N. Owen, S. Kunz-Ebrecht and V. Mohamed-Ali.** 2002. Inflammatory cytokines, socioeconomic status, and acute stress responsivity. *Brain Behav. Immun. 16:774.*
5. **Elenkov I.J. and G.P. Chrousos.** *2002.* Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann. N.Y. Acad. Sci. 966:290.*
6. **Dunn A.J., J. Wang and T. Ando.** 1999. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv. Exp. Med. Biol. 461:117.*
7. **Connor T.J. and B.E. Leonard.** 1998. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci. 62:583.*
8. **Licinio J. and M.L. Wong.** 1999. 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 4:317.*
9. **Ottaviani E, A. Franchini and C. Franceschi.** 1997. Pro-opiomelanocortin-derived peptides, cytokines, and nitric oxide in immune responses and stress: an evolutionary approach. *Int. Rev. Cytol. 170:79.*
10. **Maes M., G. Kenis and M. Kubera.** 2003. In humans, corticotropin releasing hormone antagonizes some of the negative immunoregulatory effects of serotonin. *Neuroendocrinol. Lett. 24:420.*
11. **Jin Q., B.S. Jhun, S.H. Lee, J. Lee, Y. Pi, Y.H. Cho, H.H. Baik and I. Kang.** 2004. Differential regulation of phosphatidylinositol 3-kinase/Akt, mitogen-activated protein kinase, and AMP-activated protein kinase pathways during menadione-induced oxidative stress in the kidney of young and old rats. *Biochem. Biophys. Res. Commun. 315:555.*
12. **Nagata D., M. Mogi and K. Walsh.** 2003. AMP-activated protein kinase (AMPK) signaling in endothelial cells is essential for angiogenesis in response to hypoxic stress. *J. Biol. Chem. 278:31000.*
13. **Barnes K., J.C. Ingram, O.H. Porras, L.F Barros, E.R. Hudson, L.G. Fryer, F. Foufelle, D. Carling, D.G. Hardie and S.A. Baldwin.** 2002. Activation of GLUT1 by metabolic and osmotic stress: potential involvement of AMP-activated protein kinase (AMPK). *J. Cell Sci. 115:2433.*
14. **Frost R.A., G.J. Nystrom and C.H. Lang.** 2004.Epinephrine stimulates IL-6 expression in skeletal muscle and C2C12 myoblasts: role of c-Jun NH2-terminal kinase and histone deacetylase activity. *Am. J. Physiol. Endocrinol. Metab. 286:809.*
15. **Hansen M.K., P. Taishi, Z. Chen and J.M. Krueger.** 1998. Vagotomy blocks the induction of interleukin-1beta (IL-1beta) mRNA in the brain of rats in response to systemic IL-1beta. *J. Neurosci. 18:2247.*
16. **O'Connor K.A., J.D. Johnson, M.K. Hansen, F.J.L. Wieseler, E. Maksimova, L.R. Watkins and S.F. Maier.** 2003. Peripheral and central proinflammatory cytokine response to a severe acute stressor. *Brain Res. 991:123.*
17. **Paul R., U. Koedel, F. Winkler, B.C. Kieseier, A. Fontana, M. Kopf, H.P. Hartung and H.W. Pfister.** 2003. Lack of IL-6 augments inflammatory response but decreases vascular permeability in bacterial meningitis. *Brain 126:1873.*
18. **Alheim K., Z. Chai, G. Fantuzzi, H. Hasanvan D, Malinowsky, E. Di Santo, P. Ghezzi, C.A. Dinarello and T. Bartfai.** 1997.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. U S A. 94:2681.*
19. **Hayashi Y., I. Jikihara, T. Yagi, M. Fukumura, Y. Ohashi, Y. Ohta, H. Takagi and M. Maeda.** 2001. Immunohistochemical investigation of caspase-1 and effect of caspase-1 inhibitor in delayed neuronal death after transient cerebral ischemia. *Brain Res. 893:113.*
20. **Trembovler V., S. Abu-Raya and E. Shohami.** 2003. Synergism between tumor necrosis factor-alpha and H2O2 enhances cell damage in rat PC12 cells. *Neurosci. Lett. 353:115*
21. **Lee J., J.S. Shin, J.Y. Park, D. Kwon, S.J. Choi, S.J. Kim and I.H. Choi.** 2003. 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. 74:884.*
22. **Gilles S., S. Zahler, U. Welsch, C.P. Sommerhoff and B.F. Becker.** 2003. Release of TNF-alpha during myocardial reperfusion depends on oxidative stress and is prevented by mast cell stabilizers. *Cardiovasc. Res. 60:608.*
23. **Lynch A.M., C .Walsh, A. Delaney, Y. Nolan, V.A. Campbell and M.A. Lynch.** 2004. Lipopolysaccharide-induced increase in signalling in hippocampus is abrogated by IL-10 - a role for IL-1 beta? *J. Neurochem. 88:635.*
24. **Ji S.Q., S. Neustrom, G.M. Willis and M.E. Spurlock.** 1998. Proinflammatory cytokines regulate myogenic cell proliferation and fusion but have no impact on myotube protein metabolism or stress protein expression. *J. Interferon Cytokine Res. 18:879.*
25. **Chakrabarty A., M.M. Danley and S.M. LeVine.** 2004. Immunohistochemical localization of phosphorylated protein kinase R and phosphorylated eukaryotic initiation factor-2 alpha in the central nervous system of SJL mice

with experimental allergic encephalomyelitis. *J. Neurosci. Res. 76:822.*

26. **Chiu J.J., P.L Lee., C.N. Chen, C.I. Lee, S.F. Chang, L.J. Chen, S.C. Lien, Y.C. Ko, S. Usami and S. Chien.** 2004. Shear stress increases ICAM-1 and decreases VCAM-1 and E-selectin expressions induced by tumor necrosis factor-[alpha] in endothelial cells. *Arterioscler. Thromb. Vasc. Biol. 24:73.*
27. **Strassheim D., K. Asehnoune, J.S. Park, J.Y. Kim, Q. He, D. Richter, S. Mitra, J. Arcaroli, K. Kuhn and E. Abraham.** 2004. Modulation of bone marrow-derived neutrophil signaling by H_2O_2: disparate effects on kinases, NF-kappaB, and cytokine expression. *Am. J. Physiol. Cell Physiol. 286:683.*
28. **Yamawaki H., S. Lehoux and B.C. Berk.** 2003. Chronic physiological shear stress inhibits tumor necrosis factor-induced proinflammatory responses in rabbit aorta perfused ex vivo. *Circulation 108:1619.*
29. **Chen E., E.B. Fisher, L.B. Bacharier and R.C. Strunk.** 2003. Socioeconomic status, stress, and immune markers in adolescents with asthma. *Psychosom. Med. 65:984.*
30. **Kim S. and H. Iwao.** 2003. Stress and vascular responses: mitogen-activated protein kinases and activator protein-1 as promising therapeutic targets of vascular remodeling. *J. Pharmacol. Sci. 91:177.*
31. **Takeda K., A. Matsuzawa, H .Nishitoh and H. Ichijo.** 2003Roles of MAPKKK ASK1 in stress-induced cell death. *Cell Struct. Funct. 28:23.*
32. **Cowan K.J.and K.B. Storey.** 2003. Mitogen-activated protein kinases: new signaling pathways functioning in cellular responses to environmental stress. *J. Exp. Biol. 206:1107.*
33. **Takeda K. and H. Ichijo.** 2002. Neuronal p38 MAPK signalling: an emerging regulator of cell fate and function in the nervous system. *Genes Cells 7:1099 .*
34. **Grossi G., A. Perski, B. Evengard, V. Blomkvist and K. Orth-Gomer.** 2003. Physiological correlates of burnout among women. *J. Psychosom. Res. 55:309.*
35. **Cohen S., E. Frank, W.J. Doyle, D.P. Skoner, B.S. Rabin and J.M. Gwaltney Jr.** 1998. Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol. 17:214.*
36. **Elenkov I.J. and G.P. Chrousos.** 1999. Stress Hormones, Th1/Th2 patterns, Pro/Anti-inflammatory Cytokines and Susceptibility to Disease. *Trends Endocrinol. Metab. 10:359.*
37. **Kempuraj D., J. Donelan, S. Frydas, T. Iezzi, P. Conti, W. Boucher, N.G. Papadoopoulou, B. Madhappan, L. Letourneau, G. Sabatino, G. Riccioni and T.C. Theoharides.** 2004. Interleukin-28 and 29 (IL-28 and IL-29): new cytokines with anti-viral activities. *Int. J. Immunopathol. Pharmacol. 17:103.*
38. **Cross M.L.** 2004. Immune-signalling by orally-delivered probiotic bacteria: effects on common mucosal immunoresponses and protection at distal mucosal sites. *Int. J. Immunopathol. Pharmacol. 17:127*
39. **Kempuraj D., B. Madhappan, R. Sheeladevi, M. Nazer, S. Christodoulou, J. Reginald, N. Suthinthirarajan and A. Namasivayam.** 2004. T lymphocyte subsets and immunoglobulins in intracranial tumor patients before and after treatment, and based on histological type of tumors. *Int. J. Immunopathol. Pharmacol. 17:57.*
40. **Sodin-Semrl S., A. Spagnolo, R. Mikus, B. Barbaro, J. Varga and S. Fiore.** 2004. Lipoxin A_4 and serum amyloid A elicit opposite interleukin-8 and NF-κB responses via the common ALX receptor. *Int. J. Immunopathol. Pharmacol. 17:145.*
41. **Pannellini T., M. Iezzi, E. Di Carlo, E. Eleuterio, A. Coletti, A. Modesti, S. Rosini, M. Neri and P. Musiani.** 2004. The expression of LEC/CCL16, a powerful inflammatory chemokine, is upregulated in ulcerative colitis. *Int. J. Immunopathol. Pharmacol. 17:171.*
42. **Sardella G., D. Accapezzato, A. Di Roma, C. Iacoboni, V. Francavilla, G. Benedetti, C. Musto, F. Fedele, G. Bruno and M. Paroli.** 2004. Integrin β_2-chain (CD18) over-expression on $CD4^+$ T cells and monocytes after ischemia/reperfusion in patients undergoing primary percutaneous revascularization. *Int. J. Immunopathol. Pharmacol. 17:165.*
43. **Hitoglou S., S. Frydas, M. Hatzistilianou, D. Gougoustamou, F. Conti and A. Kotsis.** 2004. Response of ADA and its isoenzymes in mice infected by *Trichinella spiralis* and treated with mimosine. *Int. J. Immunopathol. Pharmacol. 17:191.*
44. **Vojdani A., J.B. Pangborn, E. Vojdani and E.L. Cooper.** 2003. Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. *Int. J. Immunopathol. Pharmacol. 16:189*
45. **Bogdanos D. P., M. Lenzi, M. Okamoto, E.I. Rigopoulou, P. Muratori, Y. Ma, L. Muratori, D. Tsantoulas, G. Mieli-Vergani, F.B. Bianchi and D. Vergani.** 2004. Multiple viral/self immunological cross-reactivity in liver kidney microsomal antibody positive hepatitis C virus infected patients is associated with the possession of HLA b51. *Int. J. Immunopathol. Pharmacol. 17:83.*
46. **Battistoni A., M. Ajello, S. Ammendola, F. Superti, G. Rotilio and P. Valenti.** 2004. Involvement of reactive oxygen species in bacterial killing within epithelial cells.

Int. J. Immunopathol. Pharmacol. 17:71.

47. **Frydas S., M. Papazahariadou, N. Papaioannou, M. Hatzistilianou, M. Trakatellis, D. Merlitti, M. Di Gioacchino, A. Grilli, M.A. DeLutiis, G. Riccioni, P. Conti and I. Vlemmas.** 2003. Effect of the compound l-mimosine in an in vivo model of chronic granuloma formation induced by potassium permanganate ($KMNO_4$). *Int. J. Immunopathol. Pharmacol. 16:99.*
48. **Santino I., A. Iori, M. Nicoletti, S. Valletta, C. Cimmino, G.L. Scoarughi, D. Santapaola, R. Sessa and M. del Piano.** 2003. Prevalence of *Borrelia burgdorferi* sensu lato genomospecies and of the human granulocitic ehrlichiosis (HGE) agent in *Ixodes ricinus* ticks collected in the area of Monti Lepini, Italy. *Int. J. Immunopathol. Pharmacol. 16:105*
49. **Kempuraj D., S. Frydas, K. Kandere, B. Madhappan, R. Letourneau, S. Christodoulou, W. Boucher, G. Riccioni, P.Conti and T. C. Theoharides.** 2003. Interleukin-19 (IL-19) network revisited. *Int. J. Immunopathol. Pharmacol. 16:95.*
50. **Camera E., S. Lisby, M.L. Dell'Anna, B. Santucci, R. Paganelli, O. Baadsgaard and M. Picardo.** 2003. Mononuclear cell antioxidant pattern and skin reactivity to irritants. *Int. J. Immunopathol. Pharmacol. 16:49.*
51. **Austen W.G. Jr., L. Kobzik, M.C. Carroll, H.B. Hechtman and F.D. Moore Jr.** 2003. The role of complement and natural antibody in intestinal ischemia-reperfusion injury. *Int. J. Immunopathol. Pharmacol. 16:1.*
52. **Romano A., C. Mondino, M. Viola and P. Montuschi.** 2003. Immediate allergic reactions to β-lactams: diagnosis and therapy. *Int. J. Immunopathol. Pharmacol. 16:19.*
53. **Bruno G., F. Tega, A. Bruno, U. Graf, F. Corelli, R. Molfetta and M. Barucco.** 2003. The role of substance P in the cerebral ischemia. *Int. J. Immunopathol. Pharmacol. 16:67.*
54. **Guhad F.A. and J. Hau.** 1996. Salivary IgA as a marker of social stress in rats. *Neurosci. Lett. 216:137.*
55. **Esterling B.A., J.K. Kiecolt-Glaser, J.C. Bodnar and R. Glaser.** 1994. Chronic stress, social support, and persistent alterations in the natural killer cell response to cytokines in older adults. *Health Psychol. 13:291.*