

■ C O M M E N T

Psychological stress and the inflammatory response system

In this issue of *Clinical Science*, Steptoe et al. [1] report that acute psychological stress in humans (computerized colour-word interference task and mirror tracing) significantly increases the serum concentrations of interleukin-6 (IL-6) and the IL-1 receptor antagonist (IL-1Ra). IL-6 is a pleiotropic cytokine which is involved in T-cell activation, B-cell differentiation and the initiation of the acute-phase response [2]. The IL-1Ra is produced by and released from activated cells of the monocyte/macrophage lineage. It is a pure IL-1 receptor antagonist which may inhibit some of the pro-inflammatory effects of IL-1 [2]. Thus the results of Steptoe et al. [1] suggest that psychological stress elicits an activation of the inflammatory response system (IRS).

These important findings of Steptoe et al. [1] extend those of previous studies performed in experimental animals and humans. Indeed, in experimental animals, plasma IL-6 concentrations and the expression of IL-6 mRNA in the midbrain are significantly elevated by various psychological stressors, such as exposure to electric foot shocks, physical restraint, immobilization stress, open field stress and other aversive stimuli (reviewed in [3]). Recently, it was shown: (i) that peripheral corticotropin-releasing hormone mediates the plasma IL-6 elevations in response to immobilization stress [4]; and (ii) that the liver, and not the intestinal microflora, is one of the major sources responsible for increased plasma IL-6 during restraint stress [5].

Our laboratory was the first to report that in healthy volunteers academic examination stress significantly elevated the stimulated production of IL-6 by whole blood [6]. These findings were replicated by Paik et al. [7]. The speaking task, another acute psychological stressor, significantly increases the lipopolysaccharide-induced production of IL-6 [8]. In older women, chronic stressors are associated with significant elevations in plasma IL-6 [9]. In patients with rheumatoid arthritis, plasma IL-6 is significantly elevated only when there is mental stress [10].

There are only a few papers which have examined the effects of psychological stress on the IL-1Ra. Thus in various rat brain regions immobilization stress significantly increases IL-1Ra and IL-1 levels [11]. Song et al. [12] reported that academic examination stress increases plasma IL-1Ra concentrations only in students who experience high levels of subjective distress. Also, the production of IL-1Ra by stimulated whole blood is significantly increased by academic examination stress [6].

It should be emphasized that a large number of other studies report that psychological stress may activate the IRS. In the rodent, various stressors, such as mild inescapable foot shock and restraint stress, increase IL-1 mRNA expression in brain regions and IL-1 activity in peripheral blood immune cells (reviewed in [3]). In humans, psychological stressors induce the stimulated production of tumour necrosis factor- α and interferon- γ , T-cell activation and an acute-phase response, and an increase in salivary IL-1 and serum neopterin [3,6].

The findings published by Steptoe et al. [1] and the other reports described above suggest that pro-inflammatory cytokines may be involved in the stress response. The stress response to organic stressors, such as injury, toxins and infections, entails an activation of the hypothalamic-pituitary-adrenal axis and enhanced catecholamine and 5-hydroxytryptamine turnover in the brain, phenomena which are, in part, related to the stress-induced enhanced production of pro-inflammatory cytokines [3]. Thus through the secretion of pro-inflammatory cytokines, the IRS may act as a sensory organ, informing the brain of the presence of organic stressors. Therefore we have hypothesized that psychological stress is also perceived by the IRS and, through production of pro-inflammatory cytokines, could take part in a homeostatic response involving hypothalamic-pituitary-adrenal-axis hyperactivity and increased turnover of catecholamines and 5-hydroxytryptamine [3,6].

The discovery that psychological stress can induce the production of pro-inflammatory cytokines has important implications for human psychopathology and, in particular, for the aetiology of major depression. (i) Psychological stressors, such as negative life events, are emphasized in the aetiology of depression. Thus psychosocial and environmental stressors play a role as direct precipitants of major depression or they function as vulnerability factors which predispose humans to develop major depression [13]. (ii) Major depression is accompanied by activation of the IRS with, among other things, an increased production of pro-inflammatory cytokines, such as IL-1 β , IL-6, tumour necrosis factor- α and interferon- γ , signs of monocytic- and T-cell activation and an acute-phase response [3]. (iii) Activation of the IRS and administration of pro-inflammatory cytokines has depressogenic effects in animals and humans. For example, acute or repeated administration of lipopolysaccharide, IL-1 or IL-6 to the rodent induces a symptom called complex labelled sickness behaviour,

i.e. psychomotor retardation, anorexia, weight loss, sleep disorders, suppression of social behaviour and loss of interest [14]. These symptoms correspond with the vegetative symptoms of major depression. Endotoxin administration to rats decreases the free consumption of saccharine, a model of anhedonia or the inability to experience pleasure, another key symptom of major depression [15]. Chronically elevated levels of IL-6 obtained by infecting MRL +/+, C3H.SW and Balb/C mice with adenovirus vector carrying cDNA for murine IL-6, induces a significant decline in the preference for sucrose, which again indicates anhedonia [16]. Immunotherapy with interferon- α induces a depressed mood, slowness, severe fatigue, hypersomnia, lethargy, irritability, emotional lability, social withdrawal, lack of concentration and full-blown major depression in a considerable number of patients (> 40%) [17].

MICHAEL MAES

*Department of Psychiatry and Neuropsychology,
University Hospital of Maastricht, Postbus 5800,
6202 AZ Maastricht, The Netherlands*

(ON BEHALF OF THE EDITORIAL BOARD)

REFERENCES

- 1 Steptoe, A., Willemsen, G., Owen, N., Flower, L. and Mohamed-Ali, V. (2001) Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. *Clin. Sci.* **101**, 185–192
- 2 Cavaillon, J.-M. (1996) *Les Cytokines*, Masson, Paris
- 3 Maes, M. (1999) Psychological stress, cytokines and the inflammatory response system. *Curr. Opin. Psychiatry* **12**, 695–700
- 4 Ando, T., Rivier, J., Yanai, H. and Arimura, A. (1998) Peripheral corticotropin-releasing factor mediates the elevation of plasma IL-6 by immobilization stress in rats. *Am. J. Physiol.* **275**, R1461–R1467
- 5 Nukina, H., Sudo, N., Aiba, Y., Oyama, N., Koga, Y. and Kubo, C. (2001) Restraint stress elevates the plasma interleukin-6 levels in germ-free mice. *J. Neuroimmunol.* **115**, 46–52
- 6 Maes, M., Song, C., Lin, A. et al. (1998) The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine* **10**, 313–318
- 7 Paik, I. H., Toh, K. Y., Lee, C., Kim, J. J. and Lee, S. J. (2000) Psychological stress may induce increased humoral and decreased cellular immunity. *Behav. Med.* **26**, 139–141
- 8 Goebel, M. U., Mills, P. J., Irwin, M. R. and Ziegler, M. G. (2000) Interleukin-6 and tumor necrosis factor- α production after acute psychological stress, exercise, and infused isoproterenol: differential effects and pathways. *Psychosom. Med.* **62**, 591–598
- 9 Lutgendorf, S. K., Garand, L., Buckwalter, K. C., Reimer, T. T., Hong, S. Y. and Lubaroff, D. M. (1999) Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. *J. Gerontol. A. Biol. Sci. Med. Sci.* **54**, M434–M439
- 10 Hirano, D., Nagashima, M., Ogawa, R. and Yoshino, S. (2001) Serum levels of interleukin 6 and stress related substances indicate mental stress condition in patients with rheumatoid arthritis. *J. Rheumatol.* **28**, 490–495
- 11 Suzuki, E., Shintani, F., Kanba, S., Asai, M. and Nakaki, T. (1997) Immobilization stress increases mRNA levels of interleukin-1 receptor antagonist in various rat brain regions. *Cell. Mol. Neurobiol.* **17**, 557–562
- 12 Song, C., Kenis, G., van Gastel, A. et al. (1999) Influence of psychological stress on immune-inflammatory variables in normal humans. Part II. Altered serum concentrations of natural anti-inflammatory agents and soluble membrane antigens of monocytes and T lymphocytes. *Psychiatry Res.* **85**, 293–303
- 13 Agid, O., Kohn, Y. and Lerer, B. (2000) Environmental stress and psychiatric illness. *Biomed. Pharmacother.* **54**, 135–141
- 14 Bluthé, R. M., Dantzer, R. and Kelley, K. W. (1992) Effects of interleukin-1 receptor antagonist on the behavioral effects of lipopolysaccharide in rat. *Brain Res.* **573**, 318–320
- 15 Yirmiya, R. (1996) Endotoxin produces a depressive-like episode in rats. *Brain Res.* **711**, 163–174
- 16 Sakic, B., Szechtman, H., Braciak, T., Richards, C., Gaudie, J. and Denburg, J. A. (1997) Reduced preference for sucrose in autoimmune mice: a possible role of interleukin-6. *Brain Res. Bull.* **44**, 155–165
- 17 Bonaccorso, S., Meltzer, H. Y. and Maes, M. (2000) Psychological and behavioral effects of interferons. *Curr. Opin. Psychiatry* **13**, 673–677