Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.2980

World J Gastroenterol 2009 June 28; 15(24): 2980-2986
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Psychosocial stress and liver disease status

Cristin Constantin Vere, Costin Teodor Streba, Letitia Maria Streba, Alin Gabriel Ionescu, Felix Sima

Cristin Constantin Vere, Alin Gabriel Ionescu, Felix Sima, 1st Department of Internal Medicine, Emergency County Hospital of Craiova, Craiova 200322, Dolj, Romania
Costin Teodor Streba, University of Medicine and Pharmacy of Craiova, Craiova 200349, Dolj, Romania
Letitia Maria Streba, 3rd Department of Internal Medicine, "Filantropia" University Hospital of Craiova, Craiova 200136, Dolj, Romania
Author contributions: Vere CC and Streba CT equally contributed to this work; Vere CC initiated the literature review; Vere CC and Streba CT conducted the literature review; Streba LM provided important guidance throughout the preparation of this manuscript; Ionescu AG and Sima F reviewed the text.
Correspondence to: Costin Teodor Streba, University of Medicine and Pharmacy of Craiova, St. 1 Decembrie 1918, Bl. N11, Ap. 2, Craiova 200066, Dolj, Romania. costinstreba@gmail.com
Telephone: +40-722-389-906 Fax: +40-251-534523
Received: March 25, 2009 Revised: May 23, 2009
Accepted: May 30, 2009
Published online: June 28, 2009

Abstract

"Psychosocial stress" is an increasingly common concept in the challenging and highly-demanding modern society of today. Organic response to stress implicates two major components of the stress system, namely the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Stress is anamnestically reported by patients during the course of disease, usually accompanied by a decline in their overall health status. As the mechanisms involving glucocorticoids and catecholamines have been deciphered, and their actions on immune cell function deeper understood, it has become clear that stress has an impact on hepatic inflammatory response. An increasing number of articles have approached the link between psychosocial stress and the negative evolution of hepatic diseases. This article reviews a number of studies on both human populations and animal models performed in recent years, all linking stress, mainly of psychosocial nature, and the evolution of three important liver-related pathological entities: viral hepatitis, cirrhosis and hepatocellular carcinoma.

Key words: Stress; Chronic viral hepatitis; Cirrhosis; Carcinoma; Hepatocellular; Liver pathology

Peer reviewer: Frank J Burczynski, Professor, Faculty of Pharmacy, University of Manitoba, 50 Sifton Road, Winnipeg, Manitoba, R3T 2N2, Canada

Vere CC, Streba CT, Streba LM, Ionescu AG, Sima F. Psychosocial stress and liver disease status. *World J Gastroenterol* 2009; 15(24): 2980-2986 Available from: URL: http://www.wjgnet.com/1007-9327/15/2980.asp DOI: http://dx.doi.org/10.3748/wjg.15.2980

INTRODUCTION

Over time, stress has received a number of definitions in the scientific literature, more or less accurate or complete. One of the most commonly accepted psychological definitions has been that stress occurs when demands from the environment challenge an individual's adaptive capacity, or ability to cope[1]. Several life-changing or threatening events are considered to be "stressors"; factors that are either acute or chronic based on the duration of their interaction. Both have been associated with several immune system dysfunctions, whether or not the individual is affected by an acute or chronic disease[2].

Once an individual is subjected to such a stressor, specific pathways within the brain lead to the activation of the hypothalamic-pituitary-adrenal (HPA) axis as well as the central sympathetic outflow. This constitutes the stress response, releasing key peripheral mediators-glucocorticoids and catecholamines[3].

For a long time, it was suggested that stress influenced hepatic blood flow by inducing vasospasm and centrilobular hypoxia, leading to liver damage[4,5]. In more recent years, as the understanding of stress mediators has improved, the effect that stress has on the onset and development of liver damage during acute and chronic liver diseases has gained a new dimension[3,6].

This article reviews an important part of current literature on the effects of stress on the status of three major interrelated hepatic conditions: viral hepatitis, cirrhosis and hepatocellular carcinoma. We tried to cover the physiological aspects of the stress system and its relationship with several cellular pathways, the immune system effectors and the level of cellular alteration at the hepatic level.

THE HPA AXIS AND CENTRAL SYMPATHETIC NERVOUS SYSTEM

Physiology and interactions with immune-mediated inflammation

The HPA axis and the systemic sympathetic and adrenomedullary system are the key components of

the stress system. Their main function is to maintain basal and stress-related homeostasis[7,8]. They respond to several signaling molecules, such as cytokines produced by immune-mediated inflammatory reactions, tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), and interleukin-6 (IL-6)[7-9].

Corticotrophin-releasing hormone (CRH) and noradrenergic neurons of the central stress system innervate and stimulate each other[7-10]. By using specific receptors, CRH stimulates norepinephrine secretion, while in turn norepinephrine stimulates CRH secretion primarily through α_1-noradrenergic receptors[7,8,10]. An ultrashort negative-feedback loop also exists for both CRH and norepinephrine, down-regulating their production. The serotonergic and cholinergic systems stimulate CRH, arginine vasopressin (AVP), and noradrenergic neurons whilst being inhibited by the opioid-peptide and γ-aminobutyric acid-benzodiazepine systems existing in the brain. Hypothalamic CRH neurons are inhibited by centrally secreted substance P while AVP neurons remain unaffected. Substance P also stimulates the central noradrenergic system[11-13].

CRH-induced secretion of proopiomelanocortin-derived and several other opioid peptides concurs with stress system activation[14,15] which enhances overall analgesia[7,8]. CRH also stimulates corticotrophin secretion through the corticotrophs of the anterior pituitary[16-18]. Adrenal medulla hormones, especially corticotrophin, are principal regulating factors of glucocorticoid secretion[19-23].

All key hormones secreted by HPA components play different roles in the modulation of the immune response and the development of the inflammatory reaction.

Some leukocyte functions are influenced by glucocorticoids, as they suppress cytokine immune activation by inhibiting the production of cytokines and other inflammation mediators, as well as causing resistance to cytokines[7,8,24,25]. The functionality of Type 1 helper T lymphocytes is suppressed whilst eosinophil apoptosis is stimulated. Adhesion molecule expression is inhibited along with their specific receptors[26], while the acute phase reaction is being potentiated[27]. The pituitary hormones, corticotrophin and β-endorphin[28,29], have immunopotentiating and proinflammatory properties. Additionally, β-endorphin produced at inflammatory sites is a potent local analgesic[30].

The hypothalamus exerts a regulatory effect over the HPA axis through CRH and AVP secretion. Their proinflammatory effects have been studied both *in vitro* and *in vivo*[31-38]. CRH concentrations remain high at inflammatory sites, while remaining undetectable in plasma samples obtained concurrently[31]. Rapid catabolism, uptake or binding are thought to be primary mechanisms which prevent CRH from remaining active in the systemic circulatory system[31,39,40]. In addition to the HPA axis, the central sympathetic nervous system is directly connected with the modulation of the stress response. Stimulation of the locus coeruleus-norepinephrine system activates the central nerve pathways, thus influencing peripheral sympathetic outflow[3,4]. This triggers catecholamine release from autonomic nerve endings and from the adrenal medulla[4]. Catecholamines can influence the hepatic inflammatory response by altering hemodynamics[3]. Recently, catecholamine receptors were discovered on immunocompetent cells, thus it is believed that catecholamines can directly influence the immune response[3,6].

STRESS AND CHRONIC VIRAL HEPATITIS

In recent years, a number of studies have established an increasingly clear link between psychosocial or psychophysical stress, personality types and the development of viral hepatitis. Both human clinical trials[41-46] and animal model studies[47-52] were devised in order to prove the interaction between the two.

A clinical trial, performed by Nagano *et al*[41] indicated a positive correlation between psychosocial stress and the severity of chronic hepatitis C. Type 1 personality subjects, due to the nature of their personality traits (low sense of control, object dependence of loss, unfulfilled need for acceptance and altruism) are highly likely to be affected by chronic psychosocial stress. Type 1 personality and psychosocial stress were positively linked to the severity of chronic hepatitis C. Stress was measured using a Stress Inventory questionnaire and a personality evaluation was devised using items from the Grossarth-Maticek theory (according to this theory, type-1 personality subjects are positively associated with malignant neoplasms and chronic diseases)[42]. Patients were divided into three groups depending on the severity of chronic hepatitis C, measured by liver function laboratory parameters (ALAT values, platelet count, albumin and total bilirubin levels). Ultimately, two distinct groups resulted by unifying the 2nd and 3rd initial groups, as their values were similarly elevated. Platelet count and serum albumin levels were positively correlated with hepatitis C severity, both of them being strongly correlated with elevated stress scores. ASAT values strongly correlated with both levels of stress and the presence of type 1 personality traits.

Kunkel *et al*[43] investigated the connections between depression scores, psychosocial stressors, social support, and biological markers of dysfunction of a group of 50 Korean immigrants with chronic viral hepatitis B. Several indicators of liver function, including hepatic transaminases, albumin levels, and prothrombin times (PT) were measured during routine clinic follow-up visits and were correlated with scores obtained from the short form Beck Depression Inventory (BDI-sf). Higher BDI-sf scores were significantly associated with elevated transaminases ($P < 0.001$). Both PT and decreased albumin levels were not significantly correlated with increased BDI-sf scores.

Both studies excluded patients with decompensated cirrhosis, malignant disease, coronary heart disease, stroke, co-infection or interferon treatment.

Clinical studies suggest that chronic psychosocial

stress affects antibody response after hepatitis B vaccination[43,44]. A higher score in stress inventory questionnaires given to the test subjects was positively correlated with a weaker immune response, when administering the same antigen dose[44,46].

Psychosocial stress has intricate relationships with inflammatory and fibrosing changes of the liver during the course of hepatitis[47]. Kaji et *al*[48] reported that serum levels of transaminases increased due to stress in the galactosamine-injured liver of rats. Several animal models have suggested that inflammation-related HPA-activated pathways are influenced by stress.

Psychophysical stress simulated by inescapable foot-shock induced elevations of glucocorticoids (GCs), exacerbating α-galactosylceramide-triggered apoptosis through proliferation of liver natural killer T (NKT) cells and up-regulating the expression of Fas antigen on hepatocytes. GC directly elevates Fas antigen expression, probably through intracellular signal cascades[49]. Several other studies[50,51] established that *in vivo* administration of dexamethasone, an exogenous GC, enhanced the number of liver α-galactosylceramide-activated Vα14 natural killer T cells in mice. As NKT cells play an important immunological role in liver homeostasis[52,53] as well as in hepatocyte apoptosis through their Fas-ligand coated surface[54-56], it is clear that GC elevations during stress negatively influence the pathological state of the liver.

Tamada *et al*[57] found in mice the increased production of IL-4-hepatic NK1.11 T cells after exogenous administration of dexamethasone, thus demonstrating that these cells are resistant to glucocorticoid-induced apoptosis. Their study suggested that the process may play a role in determining the hepatic Th1/Th2 balance in times of stress or during GC therapy.

GCs downregulate expression of endothelial cell adhesion molecules, thus producing inhibitory effects on neutrophil recruitment in liver[3,58]. Increased circulating endogenous GC levels hence decrease hepatic neutrophil chemotaxis, as well as lymphocyte recruitment[58].

GCs inhibit IL-6 and TNF-α at transcriptional and translational levels[59,60]. Endogenous corticosterone, at normal or stress levels, induces IL-6 and TNF-α in an *in situ* liver perfusion, which lead to the conclusion that GCs have additional non-suppressive effects[60].

STRESS AND LIVER CIRRHOSIS

Psychosocial stress *per se* may exaggerate inflammatory and fibrosing change in the cirrhotic liver[3,6,47].

Nagano *et al*[41] included in their clinical test a subset of patients affected by cirrhosis. They found the same positive correlation between psychosocial stress and liver injury, as ALAT values strongly correlated with high stress scores in the cirrhosis cohort.

Tanaka *et al*[61] conducted a long-term follow-up study determining risk factors for malignant transformation of cirrhotic lesions in Japanese patients. His study also demonstrated a possible link between the presence of stress and precipitating indicators for cirrhosis.

Several animal studies were conducted, outlining important cellular mechanisms that link stress response of the sympathetic nervous system, as well as alterations of the HPA axis responsiveness, with liver inflammation in cirrhosis.

Electric foot shock stress exacerbated liver injury in rats treated with carbon tetrachloride[62]. Alterations of the HPA axis responsiveness, as well as elevated plasma cytokine levels, accompany experimental chronic liver disease in mice. Elevated TNF-α and IL-6 levels, coupled with liver injury, decrease hypothalamic mRNA and protein expression of CRH. When mice are exposed to psychological stress, HPA axis functions abnormally, suffering defective activation and significant attenuation in the resultant release of GCs, compared to control groups[63].

NKT cell activity was linked with fibrosing and inflammatory damage in cirrhosis[64]. Epinephrine and norepinephrine, *via* several subtypes of adrenoceptor (AdR), cause expansion of liver NKT cells[49-52,65,66], production of IL-6 from hepatocytes and TNF-α[3,6,49] from Kupffer cells, as well as impairment of hepatic blood flow (HBF). GCs inhibit the production of IL-10, IL-6, TNF-α, PGE_2 leukotrienes and nitric oxide[3,6,61,66] from Kupffer cells. Two mechanisms are involved, a direct one (affecting the stability of mRNA and gene transcription) and an indirect one, by inhibiting the production of the nuclear factor (NF)-κB and the activator protein (AP)-1.

Tjandra *et al*[67] suggested that psychosocial stress itself can influence the course of hepatic inflammation, by directly altering IL-6 and TNF-α production.

Also, Kitamura *et al*[68] studied how immobilization stress can induce increased IL-6 mRNA expression in the liver, as well as an elevation of the plasma IL-6 level. He made a clear distinction between IL-6 produced within hepatocytes and that produced in non-parenchymal cells, using immunohistochemical techniques.

This distinction was further demonstrated by an *in vitro* experiment, using primary cultured rat hepatocytes[68]. This study also explored the effect sympathetic nervous system mediators such as epinephrine and norepinephrine have on TNF-α and IL-6 produced by Kupffer cells and hepatocytes. An increase in norepinephrine is mediated through α_1-, α_2- and β_1- adrenergic receptors, leading to an increased production of pro-inflammatory cytokines[68-72].

Nakajima *et al*[73] discovered that patients with liver cirrhosis and decreased NKT cell activity were at a higher risk of developing hepatocellular carcinoma than those with normal natural killer cell activity.

INFLUENCE OF STRESS ON HEPATOCELLULAR CARCINOMA (HCC) PROGNOSIS

The effects psychosocial stress has on immune suppression in patients with malignant metaplasia are well

established[74]. However, its effects on hepatocarcinoma are yet to be determined. It has been hypothesized that several psychosocial factors, including stress, may account in part for rapid hepatocarcinoma development. Biobehavioral models were suggested in order to demonstrate this interaction[74,75]. Cancers with a strong immune-mediation component, such as HBV-related HCC are believed to be the most appropriate[75].

Several studies proved the correlation between stress and progression of various types of cancer in humans[76-79]. In these studies, positive correlations were found between stress and the grade of dysplasia[76], overall survival[77,78] and cancer recurrence[79].

By using this knowledge, psychological intervention was used as a tool to improve immune functioning and to reduce progression[80-82]. Similar studies were conducted by Spiegel *et al* who observed extended survival in patients affected by cancer after group therapy and other forms of stress-relieving techniques[83].

Carcinoma is associated with high concentrations of TNF-α. Stress, as outlined in several studies, directly influences TNF-α, IL-1, and IL-6 expression[59-61,66-68], in turn influencing the activity of NKT cells[48,50,51]. As a result, stress and depression can influence tumor progression at a cellular level.

Several animal models demonstrated relationships between stress, immune reactivity and tumor growth, by influencing IL-2 production, plasma L3T4 antigen and elevating GCs[74,75].

Liu *et al*[83] demonstrated in a recent study that survival time of mice affected by HCC is greatly reduced when subjected to social isolation stress. He compared the titer of antibody to sheep red blood cell (SRBC), as well as IL-2 levels, and survival time between two groups. Individuals exposed to isolation stress positively correlated with a lower survival time as well as with negatively altered serum values of both SRBC antibodies and IL-2.

Psychosocial stress was also linked to increased DNA damage, alterations in DNA repair and inhibition of apoptosis[84-88].

Sivonova *et al*[84] studied how academic stress during student examinations positively affects oxidative stress and induces direct DNA damage. Single strand breaks of DNA as well as sensitivity to lipid oxidation and the antioxidant status were studied on examination day, as well as at a random time between examinations. They found that in stressful conditions oxidative damage to DNA as well as sensitivity to lipid oxidation were significantly increased ($P < 0.05$), while plasma antioxidant activity was severely decreased ($P < 0.05$), in comparison to the control group of non-stressed individuals.

Glaser *et al*[85,86] proved the association between rotational stress and low concentrations of O6-methyltransferase, an enzyme linked to DNA repair induced in response to carcinogen damage. Their animal study was conducted on forty-four rats to whom dimethylnitrosamine was administered. The group was divided into two, half being randomly assigned to a rotational stress condition[85].

In a study regarding psychological stress, Tomei *et al*[89] found that cellular death decreased during examination compared with a control group, after phorbol ester (tumor promoter through activation of protein kinase C[90]) inhibition of radiation-induced apoptosis. This goes on to demonstrate that stress, having a negative impact on apoptosis, serves as a tumoral proliferation promoter.

CONCLUSION

As seen above, stress has been identified in recent years as an important factor in the progression and outcome of several important liver pathologies. It influences the immune system and several intra- and inter-cellular mechanisms. Comprehensive models that try to integrate these complex mechanisms are being developed.

From a clinical perspective, a better understanding of how stress alters hepatic inflammation would provide additional tools for the management of important liver diseases. It would influence the quality of life of patients by shortening hospitalization times and ensuring a correct therapeutic approach.

For a better understanding of the relationship between stress and liver pathology, we suggest that further studies on both human and animal models be conducted. Comprehensive clinical trials could be devised, which would test positive correlations between elevated stress scores and a number of both serological and imaging parameters assessing disease in hepatic patients. Animal studies should investigate immunohistochemical and genetic alterations at cellular level in the liver of stress-challenged hepatic-impaired rodents.

REFERENCES

1 **Cohen S**, Kessler RC, Gordon LU. Strategies for measuring stress in studies of psychiatric and physical disorders. In: Cohen S, Kessler RC, Gordon LU, editors. Measuring stress: A guide for health and social scientists. New York: Oxford University Press, 1995: 3-26
2 **Segerstrom SC**, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004; **130**: 601-630
3 **Swain MG**. I. Stress and hepatic inflammation. *Am J Physiol Gastrointest Liver Physiol* 2000; **279**: G1135-G1138
4 **Hirose S**, Hirayama C, Ikemi Y. The influence of emotional stress on the liver blood flow. *Kyushu J Med Sci* 1961; **12**: 319-323
5 **Kaplan MH**, Wheeler WF. Stress and diseases of the upper gut. I. Stress and liver disease. *Mt Sinai J Med* 1983; **50**: 225-227
6 **Chida Y**, Sudo N, Kubo C. Does stress exacerbate liver diseases? *J Gastroenterol Hepatol* 2006; **21**: 202-208
7 **Chrousos GP**, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 1992; **267**: 1244-1252
8 **Chrousos GP**. Regulation and dysregulation of the hypothalamic-pituitary-adrenal axis. The corticotropin-releasing hormone perspective. *Endocrinol Metab Clin North Am* 1992; **21**: 833-858
9 **Sawchenko PE**, Imaki T, Potter E, Kovacs K, Imaki J, Vale

W. The functional neuroanatomy of corticotropin-releasing factor. *Ciba Found Symp* 1993; **172**: 5-21; discussion 21-29
10 **Saper CB**, Loewy AD, Swanson LW, Cowan WM. Direct hypothalamo-autonomic connections. *Brain Res* 1976; **117**: 305-312
11 **Larsen PJ**, Jessop D, Patel H, Lightman SL, Chowdrey HS. Substance P inhibits the release of anterior pituitary adrenocorticotrophin via a central mechanism involving corticotrophin-releasing factor-containing neurons in the hypothalamic paraventricular nucleus. *J Neuroendocrinol* 1993; **5**: 99-105
12 **Culman J**, Tschope C, Jost N, Itoi K, Unger T. Substance P and neurokinin A induced desensitization to cardiovascular and behavioral effects: evidence for the involvement of different tachykinin receptors. *Brain Res* 1993; **625**: 75-83
13 **Jessop DS**, Chowdrey HS, Larsen PJ, Lightman SL. Substance P: multifunctional peptide in the hypothalamo-pituitary system? *J Endocrinol* 1992; **132**: 331-337
14 **Nikolarakis KE**, Almeida OF, Herz A. Stimulation of hypothalamic beta-endorphin and dynorphin release by corticotropin-releasing factor (in vitro). *Brain Res* 1986; **399**: 152-155
15 **Burns G**, Almeida OF, Passarelli F, Herz A. A two-step mechanism by which corticotropin-releasing hormone releases hypothalamic beta-endorphin: the role of vasopressin and G-proteins. *Endocrinology* 1989; **125**: 1365-1372
16 **Lamberts SW**, Verleun T, Oosterom R, de Jong F, Hackeng WH. Corticotropin-releasing factor (ovine) and vasopressin exert a synergistic effect on adrenocorticotropin release in man. *J Clin Endocrinol Metab* 1984; **58**: 298-303
17 **Rittmaster RS**, Cutler GB Jr, Gold PW, Brandon DD, Tomai T, Loriaux DL, Chrousos GP. The relationship of saline-induced changes in vasopressin secretion to basal and corticotropin-releasing hormone-stimulated adrenocorticotropin and cortisol secretion in man. *J Clin Endocrinol Metab* 1987; **64**: 371-376
18 **Elkabir DR**, Wyatt ME, Vellucci SV, Herbert J. The effects of separate or combined infusions of corticotrophin-releasing factor and vasopressin either intraventricularly or into the amygdala on aggressive and investigative behaviour in the rat. *Regul Pept* 1990; **28**: 199-214
19 **Calogero AE**, Norton JA, Sheppard BC, Listwak SJ, Cromack DT, Wall R, Jensen RT, Chrousos GP. Pulsatile activation of the hypothalamic-pituitary-adrenal axis during major surgery. *Metabolism* 1992; **41**: 839-845
20 **Hinson JP**. Paracrine control of adrenocortical function: a new role for the medulla? *J Endocrinol* 1990; **124**: 7-9
21 **Andreis PG**, Neri G, Mazzocchi G, Musajo F, Nussdorfer GG. Direct secretagogue effect of corticotropin-releasing factor on the rat adrenal cortex: the involvement of the zona medullaris. *Endocrinology* 1992; **131**: 69-72
22 **Vinson GP,** Whitehouse BJ, Henvill KL. The actions of alpha-MSH on the adrenal cortex. In: Hadley ME, editor. The actions of a-MSH on the adrenal cortex, the melanotropic peptides. Vol. II. Biological roles. Boca Raton, Fla.: CRC Press, 1988: 87-133
23 **Ottenweller JE**, Meier AH. Adrenal innervation may be an extrapituitary mechanism able to regulate adrenocortical rhythmicity in rats. *Endocrinology* 1982; **111**: 1334-1338
24 **Boumpas DT**, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med* 1993; **119**: 1198-1208
25 **Chrousos GP**, Detera-Wadleigh SD, Karl M. Syndromes of glucocorticoid resistance. *Ann Intern Med* 1993; **119**: 1113-1124
26 **Cronstein BN**, Kimmel SC, Levin RI, Martiniuk F, Weissmann G. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proc Natl Acad Sci USA* 1992; **89**: 9991-9995
27 **Hirano T**, Akira S, Taga T, Kishimoto T. Biological and clinical aspects of interleukin 6. *Immunol Today* 1990; **11**: 443-449
28 **Blalock JE**. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. *Physiol Rev* 1989; **69**: 1-32
29 **Bateman A**, Singh A, Kral T, Solomon S. The immune-hypothalamic-pituitary-adrenal axis. *Endocr Rev* 1989; **10**: 92-112
30 **Schafer M**, Carter L, Stein C. Interleukin 1 beta and corticotropin-releasing factor inhibit pain by releasing opioids from immune cells in inflamed tissue. *Proc Natl Acad Sci USA* 1994; **91**: 4219-4223
31 **Karalis K**, Sano H, Redwine J, Listwak S, Wilder RL, Chrousos GP. Autocrine or paracrine inflammatory actions of corticotropin-releasing hormone in vivo. *Science* 1991; **254**: 421-423
32 **Crofford LJ**, Sano H, Karalis K, Webster EL, Goldmuntz EA, Chrousos GP, Wilder RL. Local secretion of corticotropin-releasing hormone in the joints of Lewis rats with inflammatory arthritis. *J Clin Invest* 1992; **90**: 2555-2564
33 **Crofford LJ**, Sano H, Karalis K, Friedman TC, Epps HR, Remmers EF, Mathern P, Chrousos GP, Wilder RL. Corticotropin-releasing hormone in synovial fluids and tissues of patients with rheumatoid arthritis and osteoarthritis. *J Immunol* 1993; **151**: 1587-1596
34 **Scopa CD**, Mastorakos G, Friedman TC, Melachrinou M, Merino MJ, Chrousos GP. Presence of immunoreactive corticotropin releasing hormone in thyroid lesions. *Am J Pathol* 1994; **145**: 1159-1167
35 **Patchev VK**, Mastorakos G, Brady LS, Redwine J, Wilder RL, Chrousos GP. Increased arginine vasopressin secretion may participate in the enhanced susceptibility of Lewis rats to inflammatory disease. *Neuroendocrinology* 1993; **58**: 106-110
36 **Stephanou A**, Jessop DS, Knight RA, Lightman SL. Corticotrophin-releasing factor-like immunoreactivity and mRNA in human leukocytes. *Brain Behav Immun* 1990; **4**: 67-73
37 **Ekman R**, Servenius B, Castro MG, Lowry PJ, Cederlund AS, Bergman O, Sjogren HO. Biosynthesis of corticotropin-releasing hormone in human T-lymphocytes. *J Neuroimmunol* 1993; **44**: 7-13
38 **Aird F**, Clevenger CV, Prystowsky MB, Redei E. Corticotropin-releasing factor mRNA in rat thymus and spleen. *Proc Natl Acad Sci USA* 1993; **90**: 7104-7108
39 **Woods RJ**, Grossman A, Saphier P, Kennedy K, Ur E, Behan D, Potter E, Vale W, Lowry PJ. Association of human corticotropin-releasing hormone to its binding protein in blood may trigger clearance of the complex. *J Clin Endocrinol Metab* 1994; **78**: 73-76
40 **Chrousos GP**. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995; **332**: 1351-1362
41 **Nagano J**, Nagase S, Sudo N, Kubo C. Psychosocial stress, personality, and the severity of chronic hepatitis C. *Psychosomatics* 2004; **45**: 100-106
42 **Grossarth-Maticek R**, Eysenck HJ. Personality, stress and disease: description and validation of a new inventory. *Psychol Rep* 1990; **66**: 355-373
43 **Kunkel EJ**, Kim JS, Hann HW, Oyesanmi O, Menefee LA, Field HL, Lartey PL, Myers RE. Depression in Korean immigrants with hepatitis B and related liver diseases. *Psychosomatics* 2000; **41**: 472-480
44 **Jabaaij L**, van Hattum J, Vingerhoets JJ, Oostveen FG, Duivenvoorden HJ, Ballieux RE. Modulation of immune response to rDNA hepatitis B vaccination by psychological stress. *J Psychosom Res* 1996; **41**: 129-137
45 **Burns VE**, Carroll D, Ring C, Harrison LK, Drayson M.

Stress, coping, and hepatitis B antibody status. *Psychosom Med* 2002; **64**: 287-293
46 **Marsland AL**, Cohen S, Rabin BS, Manuck SB. Trait positive affect and antibody response to hepatitis B vaccination. *Brain Behav Immun* 2006; **20**: 261-269
47 **Fukudo S**, Suzuki J, Tanaka Y, Iwahashi S, Nomura T. Impact of stress on alcoholic liver injury; a histopathological study. *J Psychosom Res* 1989; **33**: 515-521
48 **Kaji I**, Sekiya C. NamikI M. Psychosomatic study of the patients with liver disorders: including an experimental study. *Jap J psychosom Med* 1981; **21**: 302-312
49 **Chida Y**, Sudo N, Sonoda J, Sogawa H, Kubo C. Electric foot shock stress-induced exacerbation of alpha-galactosylceramide-triggered apoptosis in mouse liver. *Hepatology* 2004; **39**: 1131-1140
50 **Kakimi K**, Guidotti LG, Koezuka Y, Chisari FV. Natural killer T cell activation inhibits hepatitis B virus replication in vivo. *J Exp Med* 2000; **192**: 921-930
51 **Gonzalez-Aseguinolaza G**, de Oliveira C, Tomaska M, Hong S, Bruna-Romero O, Nakayama T, Taniguchi M, Bendelac A, Van Kaer L, Koezuka Y, Tsuji M. alpha -galactosylceramide-activated Valpha 14 natural killer T cells mediate protection against murine malaria. *Proc Natl Acad Sci USA* 2000; **97**: 8461-8466
52 **Nuti S**, Rosa D, Valiante NM, Saletti G, Caratozzolo M, Dellabona P, Barnaba V, Abrignani S. Dynamics of intrahepatic lymphocytes in chronic hepatitis C: enrichment for Valpha24+ T cells and rapid elimination of effector cells by apoptosis. *Eur J Immunol* 1998; **28**: 3448-3455
53 **Ishigami M**, Nishimura H, Naiki Y, Yoshioka K, Kawano T, Tanaka Y, Taniguchi M, Kakumu S, Yoshikai Y. The roles of intrahepatic Valpha14(+) NK1.1(+) T cells for liver injury induced by Salmonella infection in mice. *Hepatology* 1999; **29**: 1799-1808
54 **Kawano T**, Cui J, Koezuka Y, Toura I, Kaneko Y, Motoki K, Ueno H, Nakagawa R, Sato H, Kondo E, Koseki H, Taniguchi M. CD1d-restricted and TCR-mediated activation of valpha14 NKT cells by glycosylceramides. *Science* 1997; **278**: 1626-1629
55 **Osman Y**, Kawamura T, Naito T, Takeda K, Van Kaer L, Okumura K, Abo T. Activation of hepatic NKT cells and subsequent liver injury following administration of alpha-galactosylceramide. *Eur J Immunol* 2000; **30**: 1919-1928
56 **Nakagawa R**, Nagafune I, Tazunoki Y, Ehara H, Tomura H, Iijima R, Motoki K, Kamishohara M, Seki S. Mechanisms of the antimetastatic effect in the liver and of the hepatocyte injury induced by alpha-galactosylceramide in mice. *J Immunol* 2001; **166**: 6578-6584
57 **Tamada K**, Harada M, Abe K, Li T, Nomoto K. IL-4-producing NK1.1+ T cells are resistant to glucocorticoid-induced apoptosis: implications for the Th1/Th2 balance. *J Immunol* 1998; **161**: 1239-1247
58 **Tjandra K**, Kubes P, Rioux K, Swain MG. Endogenous glucocorticoids inhibit neutrophil recruitment to inflammatory sites in cholestatic rats. *Am J Physiol* 1996; **270**: G821-G825
59 **Liao J**, Keiser JA, Scales WE, Kunkel SL, Kluger MJ. Role of corticosterone in TNF and IL-6 production in isolated perfused rat liver. *Am J Physiol* 1995; **268**: R699-R706
60 **Beutler B**, Krochin N, Milsark IW, Luedke C, Cerami A. Control of cachectin (tumor necrosis factor) synthesis: mechanisms of endotoxin resistance. *Science* 1986; **232**: 977-980
61 **Tanaka K**, Sakai H, Hashizume M, Hirohata T. A long-term follow-up study on risk factors for hepatocellular carcinoma among Japanese patients with liver cirrhosis. *Jpn J Cancer Res* 1998; **89**: 1241-1250
62 **Iwai M**, Saheki S, Ohta Y, Shimazu T. Foot-shock stress accelerates carbon tetrachloride-induced liver injury in rats: implication of the sympathetic nervous system. *Biomed Res* (Tokyo) 1986; **7**: 145-154
63 **Swain MG**, Appleyard C, Wallace J, Wong H, Le T. Endogenous glucocorticoids released during acute toxic liver injury enhance hepatic IL-10 synthesis and release. *Am J Physiol* 1999; **276**: G199-G205
64 **Biron CA**, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu Rev Immunol* 1999; **17**: 189-220
65 **Aldrighetti L**, Pulitane C, Arru M, Finazzi R, Catena M, Soldini L, Comotti L, Ferla G. Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: a prospective randomized study. *Liver Transpl* 2006; **12**: 941-949
66 **Elenkov IJ**, Papanicolaou DA, Wilder RL, Chrousos GP. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. *Proc Assoc Am Physicians* 1996; **108**: 374-381
67 **Tjandra K**, Sharkey KA, Swain MG. Progressive development of a Th1-type hepatic cytokine profile in rats with experimental cholangitis. *Hepatology* 2000; **31**: 280-290
68 **Kitamura H**, Konno A, Morimatsu M, Jung BD, Kimura K, Saito M. Immobilization stress increases hepatic IL-6 expression in mice. *Biochem Biophys Res Commun* 1997; **238**: 707-711
69 **Jung BD**, Kimura K, Kitamura H, Makondo K, Okita K, Kawasaki M, Saito M. Norepinephrine stimulates interleukin-6 mRNA expression in primary cultured rat hepatocytes. *J Biochem* 2000; **127**: 205-209
70 **Kajiyama Y**, Ui M. Switching from alpha 1- to beta-subtypes in adrenergic response during primary culture of adult-rat hepatocytes as affected by the cell-to-cell interaction through plasma membranes. *Biochem J* 1994; **303** (Pt 1): 313-321
71 **Hasko G**, Szabo C. Regulation of cytokine and chemokine production by transmitters and co-transmitters of the autonomic nervous system. *Biochem Pharmacol* 1998; **56**: 1079-1087
72 **Jacob LS**. Sympathomimetic agents. In: Jacob LS, editor. Pharmacology. 4th ed. Maryland: Williams & Wilkins, 1996: 22-30
73 **Nakajima T**, Mizushima N, Kanai K. Relationship between natural killer activity and development of hepatocellular carcinoma in patients with cirrhosis of the liver. *Jpn J Clin Oncol* 1987; **17**: 327-332
74 **Steel J**, Carney M, Carr BI, Baum A. The role of psychosocial factors in the progression of hepatocellular carcinoma. *Med Hypotheses* 2004; **62**: 86-94
75 **Andersen BL**, Kiecolt-Glaser JK, Glaser R. A biobehavioral model of cancer stress and disease course. *Am Psychol* 1994; **49**: 389-404
76 **Steplewski Z**, Vogel WH, Ehya H, Poropatich C, Smith JM. Effects of restraint stress on inoculated tumor growth and immune response in rats. *Cancer Res* 1985; **45**: 5128-5133
77 **Bagenal FS**, Easton DF, Harris E, Chilvers CE, McElwain TJ. Survival of patients with breast cancer attending Bristol Cancer Help Centre. *Lancet* 1990; **336**: 606-610
78 **Spiegel D**, Kato PM. Psychosocial influences on cancer incidence and progression. *Harv Rev Psychiatry* 1996; **4**: 10-26
79 **Kiecolt-Glaser JK**. Norman Cousins Memorial Lecture 1998. Stress, personal relationships, and immune function: health implications. *Brain Behav Immun* 1999; **13**: 61-72
80 **Ramirez AJ**, Craig TK, Watson JP, Fentiman IS, North WR, Rubens RD. Stress and relapse of breast cancer. *BMJ* 1989; **298**: 291-293
81 **Fawzy FI**, Cousins N, Fawzy NW, Kemeny ME, Elashoff R, Morton D. A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. *Arch Gen Psychiatry* 1990; **47**: 720-725
82 **Fawzy FI**, Fawzy NW, Hyun CS, Elashoff R, Guthrie D, Fahey JL, Morton DL. Malignant melanoma. Effects of an early structured psychiatric intervention, coping, and

affective state on recurrence and survival 6 years later. *Arch Gen Psychiatry* 1993; **50**: 681-689

83 **Liu H**, Wang Z. Effects of social isolation stress on immune response and survival time of mouse with liver cancer. *World J Gastroenterol* 2005; **11**: 5902-5904

84 **Sivonova M**, Zitnanova I, Hlincikova L, Skodacek I, Trebaticka J, Durackova Z. Oxidative stress in university students during examinations. *Stress* 2004; **7**: 183-188

85 **Glaser R**, Thorn BE, Tarr KL, Kiecolt-Glaser JK, D'Ambrosio SM. Effects of stress on methyltransferase synthesis: an important DNA repair enzyme. *Health Psychol* 1985; **4**: 403-412

86 **Kiecolt-Glaser JK**, Stephens RE, Lipetz PD, Speicher CE, Glaser R. Distress and DNA repair in human lymphocytes. *J Behav Med* 1985; **8**: 311-320

87 **Cohen L**, Marshall GD Jr, Cheng L, Agarwal SK, Wei Q. DNA repair capacity in healthy medical students during and after exam stress. *J Behav Med* 2000; **23**: 531-544

88 **Forlenza MJ**, Baum A. Psychosocial influences on cancer progression: alternative cellular and molecular mechanisms. *Curr Opin Psychiatry* 2000; **13**: 639-645

89 **Tomei LD**, Kiecolt-Glaser JK, Kennedy S, Glaser R. Psychological stress and phorbol ester inhibition of radiation-induced apoptosis in human peripheral blood leukocytes. *Psychiatry Res* 1990; **33**: 59-71

90 **Blumberg PM**. Protein kinase C as the receptor for the phorbol ester tumor promoters: sixth Rhoads memorial award lecture. *Cancer Res* 1988; **48**: 1-8

S- Editor Tian L **L- Editor** Logan S **E- Editor** Ma WH