Psychosocial stress and liver disease status

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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.

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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.

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

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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 severe 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]. 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[5].

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. 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). Corticotrophin-releasing hormone (CRH) and noradrenergic neurons of the central stress system innervate and stimulate each other. By using specific receptors, CRH stimulates norepinephrine secretion, while in turn norepinephrine stimulates CRH secretion primarily through α1-noradrenergic receptors. 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-henzodiazepine 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.

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

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. 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, while the acute phase reaction is being potentiated. The pituitary hormones, corticotrophin and β-endorphin, have immunopotentiating and proinflammatory properties. Additionally, β-endorphin produced at inflammatory sites is a potent local analgesic.

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. CRH concentrations remain high at inflammatory sites, while remaining undetectable in plasma samples obtained concurrently. Rapid catabolism, uptake or binding are thought to be primary mechanisms which prevent CRH from remaining active in the system. 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. This triggers catecholamine release from autonomic nerve endings and from the adrenal medulla. Catecholamines can influence the hepatic inflammatory response by altering hemodynamics. Recently, catecholamine receptors were discovered on immunocompetent cells, thus it is believed that catecholamines can directly influence the immune response.

**STRESS AND CHRONIC VIRAL HEPATITIS**

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

A clinical trial, performed by Nagano et al., 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). 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. 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 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. 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.

Psychosocial stress has intricate relationships with inflammatory and fibrosing changes of the liver during the course of hepatitis. Kaji et al. 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-galactosyleramide-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 intracapsular signal cascades. Several other studies established that in vivo administration of dexamethasone, an exogenous GC, enhanced the number of liver α-galactosylceramide-activated Vγ14 natural killer T cells in mice. As NKT cells play an important immunological role in liver homeostasis, as well as in hepatocyte apoptosis through their Fas-ligand coated surface, it is clear that GC elevations during stress negatively influence the pathological state of the liver.

Tamada et al. found in mice the increased production of IL-4-hepatic NK1.1 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. Increased circulating endogenous GC levels hence decrease hepatic neutrophil chemotaxis, as well as lymphocyte recruitment.

GCs inhibit IL-6 and TNF-α at transcriptional and translational levels. 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.

STRESS AND LIVER CIRRHOSIS

Psychosocial stress per se may exaggerate inflammatory and fibrosing change in the cirrhotic liver. Nagano et al. 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. 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. 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.

NKT cell activity was linked with fibrosing and inflammatory damage in cirrhosis. Epinephrine and norepinephrine, via several subtypes of adrenoceptor (AdR), cause expansion of liver NKT cells, production of IL-6 from hepatocytes and TNF-α from Kupffer cells, as well as impairment of hepatic blood flow (HBF). GCs inhibit the production of IL-10, IL-6, TNF-α, PGE2 leukotrienes and nitric oxide 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. 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. 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. 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 α1-, α2- and β1-adrenergic receptors, leading to an increased production of pro-inflammatory cytokines.

Nakajima et al. 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. 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. Cancers with a strong immune-mediation component, such as HBV-related HCC are believed to be the most appropriate

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

By using this knowledge, psychological intervention was used as a tool to improve immune functioning and to reduce progression. 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.

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, in turn influencing the activity of NKT cells. 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.

Liu et al 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. Sivonova et al 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 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.

In a study regarding psychological stress, Tomei et al found that cellular death decreased during examination compared with a control group, after phorbol ester (tumor promoter through activation of protein kinase C) 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.

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