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Evolution of Viral Hepatitis: Role of Psychosocial Stress

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1. Introduction

Psychological stress, as defined by modern science, appears when an individual balances existing threats, being real or imaginary, and after confronting them with his or hers current resources, and finds the later to be inadequate. In practice, this occurs when experiences are judged to be exceeding adaptive capacities by an individual, therefore over-soliciting the mental defense mechanisms and coping capabilities. The above definition and context excludes psychiatric disorders that may impair the integration capacities of an individual. In the following chapter, psychiatric disorders resulting from stressful events are also excluded. Chronic psychosocial stress is possibly the most complex and powerful harming agent, as its repetitive nature enables it to constantly follow a patient during the onset and the course of chronic disease.

The idea that stressful events in a life of a person can influence his or hers response to illness is an idea that appeared from ancient times, despite a lack of scientific evidence. However, recent advances in the field of psychoneuroimmunology led to a new perspective on the issue. The scientific community devoted its attention to designing experiments and studies in order to document the effects and interactions between psychological and physical stress, and the well-being of a living organism.

Within the last two decades, several studies revealed new interactions between endocrine response systems, such as the hypothalamic-pituitary-adrenal axis (HPA) or the sympathetic-adrenal-medullary (SAM) system, and various pathologies. Moreover, it has been proven that the central nervous system and especially the autonomous component exert regulatory effects on the immunity of the organism. The two regulatory bodies are deeply interconnected, numerous links at various levels critically determining the end function and outcome of the immune response.

Liver disease was demonstrated to be heavily influenced by perceived chronic stress during several human and animal studies. The effects of chronic viral hepatitis on liver parenchyma are well known, however the idea that real-life events, independent from the disease itself, can influence the course of this disease, is relatively new.

2. Historical background

From ancient times, the idea of the mind-body union has been deeply rooted into human beliefs. Religion as well as empiric medicine documented the relationship between the state

of mind and the organic well-being of an individual. Hippocrates (460-377 BC) identified a link between negative emotions and incidents and somatic disorders, introducing the concept of psychosomatics. Socrates (469-399 BC) proclaimed as well that in order to cure an individual, the physician should take into account the physical illness or defect, as well as the spiritual, or as we would call it in modern times, the psychic component. Galen (AD 129-199) further implemented the concept of negative emotions, such as anger, discontent or grief, as being "diseases".

However, this conceptual unity was contested during later years, the dispute being irrevocably solved by Rene Descartes (1596-1650) who proposed that the body is simply a machine that obeys the laws of physics, while the soul, which he placed in the pineal gland, was completely separated, and governed the mind of an individual. For the following 300 years all philosophical and medical writings approached the mind-body dichotomy from the same perspective.

Early twentieth century experiments, pioneered by Ivan Pavlov, William Beaumont and Steward Wolf, began to elucidate the relationship between the nervous system and different organs and their respective pathologies.

The last three decades of scientific research were crucial in the understanding of the intricate relationships between the

3. The anatomical foundation and the mechanisms of the organic response to stress

3.1 The central stress mechanism

Currently, it is widely acknowledged that a central stress mechanism exists, composed of different brain structures such as the lateral prefrontal cortex and the medial prefrontal structures, which in turn are connected with the amygdala and the paraventricular nucleus of the hypothalamus.

Output from these structures is projected onto the pontomedullary nuclei and the pituitary gland. The signals from this central system are conveyed to the sympathetic nervous system components regulated through autonomic neurotransmitters (epinephrine and norepinephrine). (Glaser R, 2005;)

The neuroendocrine component is represented by the functional axis composed from the hypothalamus, the pituitary and the adrenal glands (the HPA axis), regulated through circulating glucocorticoids. (Chrousos GP, 1992; Kemeny ME and Schedlowski M, 2007)

Pituitary hormones (prolactine and growth hormone) are released along with the adrenocorticotrophic hormone (ACTH), neuropeptide Y (NPY) and opioids are actively released during stressful events. They directly influence antibody as well as cellular mediated immune response. ((Malarkey and Mills, 2007; Blalock and Smith, 2007)

All structures of the immune system receive sympathetic noradrenergic innervation, while B and T cellular lines express beta and alpha adrenoreceptors. (Kelley et al., 2007) The production and release of various cytokines and the circulation of leukocytes are also influenced by adrenaline and noradrenaline, neuromediators which are increasingly secreted during stress response. This increased sympathetic response stimulates the functions of the next major component in the stress response mechanism, the HPA axis, which in turn secretes elevated quantities of glucocorticoids, thus impairing the immune response. (Glaser and Kiecolt-Glaser, 2005)

3.2 The hypothalamic-pituitary-adrenal axis, glucocorticoids and the sympathetic nervous system

The HPA axis represents, as stated above, the functional and anatomical system that regulates glucocorticoid secretion, playing a major role in the adaptive response of a normally-functioning organism. It is under direct neural control, receiving sympathetic innervation through short and long feedback circuits from the hypothalamus and other central structures.

Hence, it is deeply interconnected with the systemic and sympathetic adrenomedullary systems, both key components of the stress system, collaborating for the maintenance of basal homeostasis. The corticotrophin-releasing hormone (CRH) and noradrenergic neurons of the central stress system are in close relation through a two-way feedback mechanism (Sanders VM and Kavelaars A, 2007) that assures inter-regulated levels of production of norepinephrine and CRH. (Sawchenko PE et al, 1993)

The hypothalamus represents the main regulatory structure of the HPA axis. It balances glucocorticoid secretion through the release of CRH and arginine vasopressin (AVP), with proinflammatory effects. These mediators are released in inflammation areas, while plasmatic concentrations remain low, thus proving their local effect in the inflammatory process. (Karalis K et al, 1991) The hypothalamic activity is up-regulated by the serotonergic and cholinergic systems, and its activity is inhibited by the opioid-peptide and the gamma-aminobutyric acid-benzodiazepine systems existing at cerebral level. Substance P stimulates the central noradrenergic system, while inhibiting hypothalamic CRH-secreting neurons. (Culman J et al, 1993; Larsen PJ et al, 1993; Jessop DS et al, 1992)

Hormones secreted by the adrenal medulla, such as corticotrophin, are the most important factors that regulate the secretion of glucocorticoids by the HPA. (Hinson JP. 1990; Calogero AE et al, 1992)

Secreted glucocorticoids regulate T-helper-1 and 2 responses to viral infection by inhibiting the production of Interleukin 12 (IL-12) and Tumor Necrosis Factor Alpha (TNF Alpha). Several other interleukines (IL), such as IL-2 and cytokines IL-10 and IL-4 are stimulated through their actions. All these exert a pro-inflammatory role and occur under the influence of stress-related mechanisms. (Glaser and Kiecolt-Glaser, 2005).

Glucocorticoids also cause resistance to cytokines and stimulate eosinophil apoptosis, inhibit adhesion molecules and their specific receptors expressions (Cronstein BN et al, 1992) and exacerbate the acute phase reaction (Hirano T et al, 1990). Pituitary hormones such as corticotrophin and especially beta-endorphin increase the immune response level and facilitate local inflammatory activity, (Bateman A et al, 1989) along with having analgesic effects (Schafer M et al, 1994).

3.3 The HPA axis role in acute and chronic liver inflammation

As already stated above, the activation of the HPA axis represents a key element of the normal response to stressor factors. The end result of this stimulation is the active secretion of glucocorticoids from the adrenal cortex, which is a natural process designed to improve survival chances in a fight-or-run scenario, usually associated with the notion of "exterior stress". This process, however, is involved in the control of the inflammatory response, which, in turn, can also interact by stimulation of the vagal afferents and thus activation of the HPA axis.

Patients with chronic liver diseases, such as viral hepatitis, express delayed cortisol clearance and altered cortisol binding at plasma level. Elevated plasma cytokine levels are common in chronic inflammatory diseases, and chronic exposure to high levels of circulating cytokines is associated with HPA axis failure or dysfunction. (Turnbull AV and Rivier CL, 1999)

Experimental data suggest that chronic liver injury results in elevated TNF-alpha and IL-6 levels, as well as more specific cellular alterations at hypothalamic level, such as mRNA depletion and impaired protein expression resulting in decreased levels of secreted CRH, which in turn impairs the activation of HPA axis mechanisms. (Swain MG et al, 1993) Thus, lower levels of circulating hormones, consecutive to the independent action of an exterior stressor, may be a promoter of hepatic inflammation, concomitant to the usual viral effects.

Acute inflammatory injury of the liver in a rodent model resulted in the rapid activation of the HPA axis, with consecutive rises in circulating glucocorticoid (GC) levels. When the physiological effects of GCs are inhibited, the inflammatory response is enhanced, resulting in an increase mortality rate. (Swain MG et al, 1999) This in turn can be prevented by the administration of exogenous GCs. (Swain MG, 2000) The protective effect of GCs can partially be attributed to the fact that they mediate the synthesis and release of IL-10 at hepatic level, specifically by the liver-specific macrophage system, the Kupffer cells. They also produce a number of inflammatory mediators, such as IL-1, IL-6, TNF-alpha and the nitric oxide (NO), all of them up-regulated during liver inflammation. These effects are attributed to indirect mechanisms, as they interfere with the production of proinflammatory transcription factors such as (NF)-kB and the activator protein AP-1, or to direct mechanisms which operate at the level of mRNA stability and gene transcription.

Liao et al (Liao et al, 1995) studied the effects of corticosterone, at both normal and stress levels, on an isolated perfused rat liver. He observed that the GC increased the release of TNF-alpha and IL-6. Later studies provided evidence that psychological stress itself can have the exact effect, possibly by following the same pathways. (Tjandra K et al, 2001) The hepatic levels of inflammatory cytokines and compounds are differently influenced by GCs, as TNF-alpha seems to be the first to be altered, followed by IL 1 and IL 6.

The hepatitis C virus was directly linked to the recruitment of cellular effectors implicated in liver inflammation, during viral disease. Chemokines, being important mediators of liver inflammation, experience an increased expression during HCV infection. As dexamethasone, synthetic GC is routinely used in pretreatment phases, and was shown to attenuate endotoxins and cytokine expression of chemokines in immune cells during liver inflammation, we can suggest a theoretical link between stress-levels of endogenous GCs and chemokine levels during viral hepatitis.

Another critical component of the immune system is represented by T cells. In the liver, they are actively involved in the initiation, propagation and maintenance of the inflammatory disease. GCs were proven to specifically interact with T-cell proliferation in the liver, adrenal steroids being regulators of the T helper (Th) lymphocyte cytokine secretion. Many hormones that circulate in plasma as inactive forms are transformed into their active forms within the liver. Activation of the HPA axis under stress impairs the release of Th1 cytokines, thus shifting the profile towards Th2 dominance, as documented by Iwakabe et al (Iwakabe K et al, 1998) in a restrain-stress study on a rodent model.

Circulating GCs induce T cell apoptosis. During the course of viral hepatitis, increased GCs levels at a hepatic level, following HPA activation, correlate with lower levels of activated T-cells at the same level.

Tamada et al (Tamada K et al, 1998) proved that administration of dexamethasone increases production of IL-4 hepatic natural killer (NK) 1.11-positive T cells, demonstrating that this cellular line is resistant to apoptosis induced by GCs. This study comes to support the theory that HPA may actively regulate the Th1/Th2 balance during acute or chronic stress exposure.

Proliferation of liver natural killer T (NKT) cells and the up-regulation of the Fas antigen on hepatocytes follow the increased GC production by the HPA axis. This conclusion is supported by research conducted by Chida and his team (Chida Y et al, 2004; Chida Y et al, 2006), who induced physical and psychological stress to rats by inescapable foot-shock.

Restrain stress, another standardized method of assessing psychophysical stress in animal studies, was found to increase the proportion of NK cells in the mouse liver through increased HPA activity and higher than normal GC concentrations. (Shimizu et al, 2000) Recent studies shown that monocyte chemotactic protein (MCP 1) and macrophage inflammatory protein (MIP 2) distribute NK cells along with other chemokines, thus suggesting that GCs may influence this sub-population through down-regulation of these substances (Kawakami K et al, 2001; Faunce DE et al, 2000)

Neutrophils are important in the early phases of hepatic inflammation. Circulating GCs have an inhibitory effect on neutrophil recruitment, as they down-regulate the expression of adhesion molecules, thus impairing chemotaxis.

3.4 The parasympathetic nervous system and hepatic inflammation

Recently, the main component of the parasympathetic feedback loop-mechanism that regulates liver inflammation was identified to be the "cholinergic anti-inflammatory pathway", this theory stating that efferent nerve fibers exist, supplementing the normal afferent pathways that sent information to the central nervous system from the hepatic site. Several cytokines such as IL-1 beta and TNF alpha seem to be implicated in the transduction process. In an in vivo macrophage culture, efferent vagus nerve was found to inhibit TNF alpha by releasing acetylcholine, when stimulated by endotoxins. This effect was proven to be dependent to nicotine acetylcholine receptor alpha 7 subunit (Borovikova LV et al, 2000; Wang H et al, 2003; Chida et al, 2006).

Several studies on transplanted and denervated livers show that inflammatory and immune components are severely impaired by the lack of sympathetic and parasympathetic innervations.

Growing evidence that anti-stress therapies known in traditional and standard medicine seem to stimulate the vagal influence on the liver, thus decreasing the immune response. (Zachariae R et al, 2001; Lux G et al, 1994)

4. The influence of psychosocial stress on viral hepatitis

Not many clinical studies evaluate the relationship between viral hepatitis B or C and stress response in a real-life setting. A number of studies did however underline the different mechanisms between the primary anatomical and functional systems in the human body and the intrinsic mechanisms regulating hepatic inflammation, the main morphological change encountered during the course of viral liver infection.

Nagano et al (Nagano J et al, 2004) indicated in a clinical trial that a possible correlation exists between psychosocial stress and the severity of chronic hepatitis C. His team assessed levels of perceived stressor events through standardized stress questionnaires specifically designed to also provide information regarding personality types. Type 1 personality subjects are prone to disease due to the nature of their personal traits, being likely to be affected throughout chronic stress. Both type 1 personality traits as well as psychosocial stress positively correlated with the severity of chronic hepatitis C. Stress levels were assessed using items from the Grossarth-Maticek theory, which states that type-1 personality subjects are prone to developing chronic diseases. The severity of chronic hepatitis C was assessed through the levels of ALAT, platelet counts, albumin and total bilirubin levels, resulting two hepatitis groups and one cirrhosis group, containing those patients that exhibited signs of this pathology. Platelet count and serum albumin levels were positively correlated with levels of stress, and also proved to be good assessors for the severity of chronic hepatitis. ASAT values were strongly correlated with stress levels and type 1 personality types, thus establishing a connection between stress and the severity of chronic hepatitis C.

A link between chronic hepatitis B and depression scores and psychosocial stressors were assessed in a group of 50 HbsAg-positive Korean immigrants. (Kunkel et al, 2000). Depression scores, psychosocial factors and social support were evaluated and compared with biological markers of liver dysfunction, including hepatic transaminases, albumin levels and prothrombin times. These routine clinic follow-up values were correlated with scores obtained from short form Beck Depression Inventory questionnaires. Higher scores were significantly associated with elevated levels of transaminases; however albumin and PT levels did not correlate with stress scores.

Psychological implications of hepatitis C virus diagnosis were evaluated by a number of studies. Muzaffar et al (Muzaffar L et al, 2005) proved that the diagnosis of HCV is considered more stressful than divorce or material loss or house relocation. His study of 98 patients infected with hepatitis C and 100 controls compared stress and anxiety levels regarding the diagnosis of HCV with other life-changing events including death of a close relative, loss of marital or material status or move to another city.

A study performed by Laurent Castera (Castera L et al, 2006) concluded that the psychological impact of chronic hepatitis C and emotional burden of such diagnoses are considerable, even when liver disease is insignificant.

5. Psychosocial stress and vaccination against hepatitis B

Hepatitis B currently represents a major health burden in many areas around the globe. The possibility of an effective vaccination is vital for controlling the effects hepatitis B viruses may have on exposed populations. Current studies estimate that a proportion of over 90% of the healthy subjects respond well to vaccination; however, the remaining 10% may not possess protective antibody titers at the end of the vaccination period. (Zajac BA et al, 1986)

Chronic environmental stress exposure is common in several social settings, such as academic mediums which require extensive examination periods, unfulfilled marriages or job-related distress. These situations were shown to have a negative impact on all components of the immune response. This relationship can best be described by studying the effects stressors have on vaccination outcome, as this procedure clearly reflects the efficiency of the innate immune system against disease.

Clinical studies which take into account stress exposure when assessing vaccination protection against hepatitis B are especially useful both for quantifying the effects of psychological stress on the immune response, and naturally for determining the optimum clinical settings for a successful vaccination campaign.

Burns et al (Burns VE et al, 2002) evaluated the stress and coping level of 265 first-year medical school undergraduates who completed the standard three-dose recombinant hepatitis B vaccination program. Test questionnaires were given to the participants, assessing life events of the past 12 months as well as coping types through the brief cope questionnaire and a short survey on individual health behaviors. Then their serum antibody levels were determined quantitatively. They found significant relations between stress questionnaire scores and antibody titers, while determining that coping and acceptance coping are significant predictors for antibody status. Life events exposure, sleep duration and physical exercises also proved to significantly improve antibody status post-vaccination.

Another study (Marsland AL et al, 2006) examined 84 graduate students who received standard hepatitis B vaccination series. Subjects underwent a battery of questionnaires, and blood samples were evaluated. Their results showed that higher scores, measuring a positive dispositional affect (thus a sense of well-being and fulfillment), positively correlated with greater antibody response to hepatitis B vaccination. Physical activity also proved to provide a protective role.

The general consensus of these studies is that further studies should overcome obvious limitations such as retrospective design or small cohorts, and that experimental models can be devised in order to assess antibody status after hepatitis B vaccination.

6. Conclusion

Current evidence proves a definite link between psychosocial stress levels and the status of liver hepatitis. The effects on the immune response ultimately lead to an exacerbation of the inflammatory response at hepatic level.

Recent advances were made in understanding the complete interactions between stress, neuroimmunomodulation and ultimately the onset and progress of viral infections.

Clinical implications are profound, as translational studies deciphering intrinsic cellular mechanisms and pathways lead the way to a better understanding of viral liver infection, thus improving the standard of care in this pathology.

Further studies are needed in order to fully understand the complex interactions between the social environment and chronic viral hepatitis.

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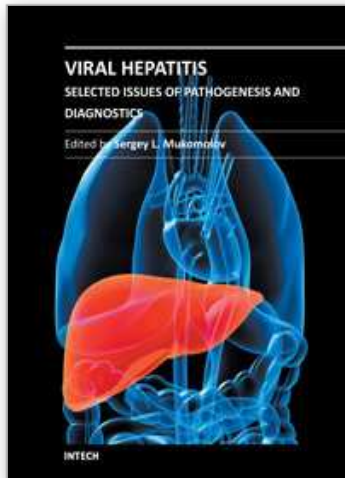
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There are a lot of important issues related to viral hepatitis studies: molecular biology of viruses, laboratory diagnostics, epidemiology, treatment etc. However, there is a number of special textbooks and monographs on the subject. Considering this fact and rather fast progress in our understanding of the problem this book focuses on the important sections of the problem immune pathogenesis of parenterally transmitted viral hepatitis and some aspects of hepatitis diagnostics. Seven chapters were prepared by several groups of researchers to share information and results of studies with specialists working in the field and persons who are interested to learn about the viral hepatitis issue. The Nobel Prize Committee (the field of physiology and medicine, 2011) awarded Bruce A. Beutler and Jules A. Hoffmann for their discoveries concerning the activation of innate immunity whilst Ralph M. Steinman was awarded for his discovery of the dendritic cell and its role in adaptive immunity. We are proud to say that our book is in line with these discoveries, because 3 chapters cover the problems of innate and adaptive immune response in case of viral hepatitis.

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