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Review

Psychosocial-Stress, Liver Regeneration and Weight Gain: a Conspicuous Pathophysiological Triad

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Key Words
Stress • Glucocorticoids • Liver pathophysiology • Regeneration • Weight gain • Obesity

Abstract
Psychosocial stress alters several physiological parameters resulting in multiple disorders, particularly compromising the immune system thereby provoking various diseases including liver disorders. However, the plausible underlying mechanisms remain elusive. Recent literature provides mechanistic evidences of detrimental effects of psychosocial stress on physiology of different body organs including liver. The data of stress-induced pathophysiological changes in liver functions and obesity were systematically collected from PubMed, ScienceDirect and the Web of Science Databases published in English. Stress and glucocorticoids (GCs) control food intake and energy expenditure through appetite stimulators neuropeptide Y (NYP) and agouti-related protein (AgRP) in hypothalamus. Principle effectors of the activated hypothalamic-pituitary-adrenal (HPA) axis in response to psychosocial stress are proopiomelanocortin (POMC)-derived adrenocorticotropic hormone (ACTH) and GCs. Stress-induced GCs hyper-secretion triggers glucocorticoid receptor (GR)-dependent transcriptional factor, nuclear factor kappa B (NFκB), which interferes TNFα-IL6 and keap1-Nrf2 pathways in liver regeneration and obesity through fine-tuning of TNFα, IL6 and Nrf2 signaling. In this review, it is contrived upon existing evidence to put forward a model whereby exposure to life-stress has a prominent impact over weight gain and can alter the regenerative mode of a damaged liver through Keap1-Nrf2 and TNFa-IL6 pathways.

Introduction

Liver is a vital organ with a central role in maintaining metabolic homeostasis [1]. Despite of being a detoxifying organ, the liver has a great capability to regenerate [2]. The liver is comprised of liver parenchymal cells and liver non-parenchymal cells. Liver non-parenchymal cells consist of hepatic oval cells, Kupffer cells, and other cell types. Hepatic oval cells in rodents and adult hepatic stem/progenitor cells, termed as hepatic progenitor cells (HPCs) in humans [3], are a kind of stem cells with the potential to differentiate into

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liver cells including hepatocytes that help in liver regeneration process [4]. Normally, most of adult liver oval cells is in the quiescent state. After an injury or partial hepatectomy they can rapidly enter the cell cycle and play a complementary role in the hepatocytes proliferation [5, 6].

Accumulating evidence indicate an association between psychosocial stress and liver diseases [7, 8], markers of inflammation as well as liver disease risks [9]. In recent years, the role of stress mediators in the liver pathophysiology has gained a new dimension [8, 10, 11]. Deviant increase in glucocorticoids following stress-arousal influences both food consumption and energy expenditure [12, 13]. Studies in human subjects strongly suggest a correlation between prolonged elevation of circulating glucocorticoids and weight gain [14]. It has been acknowledged for years that, subsequent to chemical or surgical insult, the liver undergoes repairs processes to regenerate tissue possessing anatomical or functional characteristics of hepatocytes [15]. During this phenomenon, several types of liver cells comprising hepatocytes, fibroblasts, dendritic cells (DCs), liver sinusoidal epithelial cells (LSECs), vascular endothelial cells (VEC) [5, 16] and signaling molecules including cytokines; interleukin 6 (IL6), tumor necrosis factor alpha (TNFα) and growth factors; transforming growth factor alpha (TGFα), transforming growth factor beta (TGFβ), hepatocyte growth factor alpha (HGFα) contribute to regenerate the damaged liver [2] followed by controlled inhibition through feedback mechanisms [17]. Hepatic stimulatory substance, hepatopoietin, also known as augmenter of liver regeneration (ALR), is a protein specifically produced and secreted from hepatocytes [18]. The ALR has immunoregulatory and cytoprotective effects of liver injury [19]. The ALR stimulates synthesis of TNFα, IL6 and nitric oxide in Kupffer cells [18, 20] which play important roles in repairing processes. Previous studies regarding hepatic recovery following partial hepatectomy and liver injuries strongly describe the involvement of various active growth factors such as HGF [21, 22], TGF-α [16], tumor necrosis factor alpha (TNFα) and epidermal growth factor (EGF). It has been reported that the cytokines TNFα, IL6 [21], transcription factor NFκB [23] and immediate early response genes [6] are involved in liver regeneration process. Also during early stage of liver regeneration [2, 21], increased cortisol secretion in response to stressful conditions mobilizes the metabolic energy to prepare the body for emergency situations. Persistent stress is also accompanied by an increase in cytokines [10, 11], oxidative stress, reactive oxygen species (ROS) [24] and increased reactive nitrogen species (RNS) production [25] which are known to interfere the regulatory mechanisms of liver regeneration.

This article reviews the current literature related to psychosocial stress and its effects on liver regeneration and body weight. It is hypothesized that cellular responses initiated because of chronic stressful events may interfere hepatic regeneration mechanisms by disrupting normal physiology either promoting or inhibiting feedback mechanisms following partial hepatectomy and liver injuries. Therefore, the goal of this review is to discuss psychological stimuli, which trigger excessive body weight gain and interfere liver regeneration processes.

The impact of psychosocial stress and glucocorticoids on body weight and liver physiology

Stress related factors in response to psychosocial distress have been the focus of study for contemporary sciences [11, 26]. Various stressful life events are reflected as “stressor” [11] which adversely affect the physiological processes. High intensity and/or long term exposure to circulating GCs are capable of showing the profound effects on intake of “comfort food” (fat and sugar, enriched food) that in turn cause a relative increase in body weight and subsequent obesity [14]. Once exposure to stressor, specific pathways within the brain lead to activation of the hypothalamo-pituitary-adrenal (HPA) axis as well as central sympathetic outflow. This constitutes the stress response with the release of key peripheral mediators

"glucocorticoids and catecholamines" [25]. In response to activation of the HPA axis, POMC-derived ACTH stimulates adrenal cortex to release GCs. Moreover, POMC influences synaptic inputs for appetite stimulators NPY and AgRP. It stimulates the nexus in the hypothalamus that controls food intake which may lead to weight gain [14]. The normal physiology of food intake and energy expenditure is managed by functioning of POMC cells as well as the number of excitatory inputs to neuroendocrine systems [27, 28]. There is a strong nexus among endocrine system and the stress response controlled by the nervous system. The arcuate nucleus of the hypothalamus contains distinct populations of neurons, which contain appetite stimulators NPY and AgRP. This linkage of systems is highly influenced by long-term stress resulting in altered physiological parameters and causes excessive weight gain leading to obesity [29–35].

The GCs play important role in restoration of homeostasis in response to psychological stress by mediating their effects via GR [36]. The GR, a nuclear receptor, is abundantly expressed in hepatocytes and other liver cells [37] and plays diverse roles in many cellular functions including cell proliferation [38]. The GCs act either via modulation of GR-independent cell membrane components (involving GCs-physiochemical interactions with components of cell membrane), cell membrane-bound GR (involving a MAPK pathway) or cytoplasmic GR to initiate rapid non-genomic cell signaling events [39–41]. The functioning of cytoplasmic GR involves a conformational change upon ligand binding, dissociation of heat shock proteins (chaperones) complex and nuclear localization of the ligand-bound receptor. The ligand-GR complex invokes transcriptional effects, either positive or negative through interactions with distinct liver specific transcriptional co-regulators and transcription factors [42] such as *CCAAT/enhancer binding protein (*c/EBP) [43], hepatic nuclear factor (Hnf4) [44, 45], Forkhead factor A2 (FoxA2) [46] and Forkhead factor O1 (FoxO1) [47]. Anti-inflammatory activity of GR is mediated at least partially by interactions with transcriptional co-repressors inhibiting the expression of several inflammatory mediator genes. The transcription of NFκB, one of the nuclear factors which control the expression of inflammatory cytokines, is repressed by GCs action [48, 49]. Interestingly, in a recent report, GR-prompted leucine zipper (GILZ) pathway in Kupffer cells is shown to be associated with obesity due to down regulation of GR [50] and it promotes the liver proliferation by activation of NFκB [51]. At the cellular level, GCs target several cellular functions to affect liver regeneration. Noticeable rise in ROS production, because of excessive glucocorticoids secretion during prolonged stress, activates liver degenerative processes through extrinsic and intrinsic pathways of cell death. Alongside these detrimental effects of the glucocorticoids, "The Kelch ECH associated protein 1 (Keap1) -Nrf2 pathway" which promotes liver regeneration [14, 52] is also activated by the glucocorticoids. Thus, both apoptosis and regenerative pathways are fine-tuned by the glucocorticoids signaling and the outcome would be determined by alteration in any of the two mechanisms.

Pathways linking psychosocial stress to liver regeneration

Psychological stressors are often linked to social environment, natural or man-made disasters, socioeconomic conditions and lifestyle. The stresses or even the memory of the stressful events impacts the individuals over an extended period, thereby constituting chronic psychosocial stress [53]. The HPA axis and adrenomedullary system are key components of the stress system. Their main function is to maintain the basal and stress-related homeostasis. All key hormones secreted by HPA components play different roles in modulation of immune response. Hepatic cellular functions are influenced by GCs, as they suppress cytokine immune activation by inhibiting the production of other cytokines and inflammatory mediators [11, 26] (Fig. 1).

Liver regeneration is a compensatory mechanism of hepatic mass proliferation in response to tissue resection or injuries caused by toxins, drugs or viral infections [54, 55].

Detailed studies of the mechanisms that regulate liver growth have been done in animals subjected to partial hepatectomy or chemical injury [6]. Hepatocytes priming by the cytokines TNFα and IL6 along with other agents is required for the optimal regenerative potential in response to growth factors; HGF, TGFα, and EGF [56]. The proliferative or apoptotic effect of TNF is influenced and determined by the ROS and glutathione contents in hepatocytes. In addition to growth factors, at least four transcription factors, NFκB, STAT3 (which are strongly induced by TNFα), AP-1 and C/EBPβ play important roles in the initiation of liver regeneration [57]. In addition, extensive remodeling of the hepatic extracellular matrix involving matrix metalloproteinases (MMPs) occurs shortly after partial hepatectomy [57]. Hepatic stellate cells (HSCs) are the central effector of fibrosis in liver injury. Normally HSCs are quiescent, but in liver injury, undergo a myofibroblastic differentiation or activation, leading to accumulation of extracellular matrix. As the liver injury resolves, the number of activated stellate cells decreases either by spontaneous reversion or clearance by apoptosis [58].

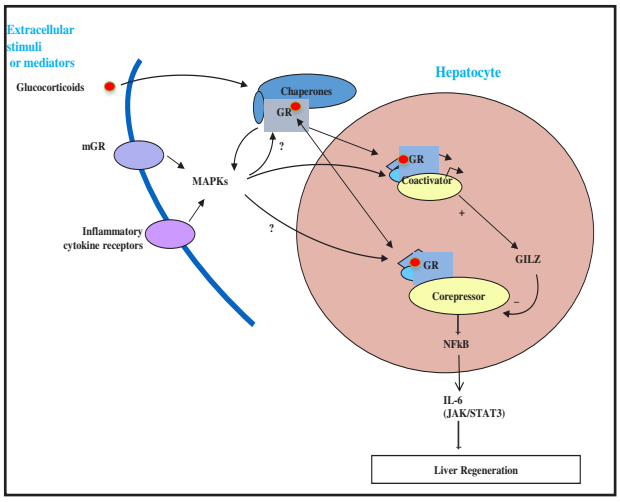

Fig. 1. Glucocorticoids cross talk with inflammatory cytokines affecting liver regeneration. Glucocorticoids (GCs) released from the hypothalamus-pituitary-adrenal (HPA) axis in response to psychosocial stress can either bind to major (membrane bound GR) or cytosolic GR to trigger immediate non-genomic pathways through activation of mitogen-activated protein kinases (MAPK). Nuclear translocation of GR is followed by GR interaction with transcriptional co-regulators at distinct target gene promoters. GR interaction with transcriptional coactivators increases the expression of GILZ. Interaction of GR with transcriptional corepressors inhibits the expression of NFκB and subsequently IL-6 which influence liver regeneration through JAK/STAT3 pathway.

The TNFα-IL6 signaling for liver regeneration appears to be a crucial pathway in early stages of liver injury [59–61]. Following cytokine activation, many other transcriptional factors and signal transduction pathways are activated [6, 61]. Recently, it has been reported that Nrf2 pathway has been shown to regulate the cellular antioxidant response and improve the process of liver regeneration. It was shown that Nrf2/antioxidant response element (ARE) system is an effective way to control ALR expression necessary for hepatic regeneration [20]. Another study showed that ROS-induced Nrf2 is capable of triggering transcription of proteins that play vital role in cell redox homeostasis function [52]. Taken together, these studies provide evidence that the stress factors or mediators play an important role in the regulation of liver regeneration pathways.

Stress-induced GCs affect TNFα-IL6 signaling during liver regeneration

Liver macrophages are key components involved in homeostasis and regression of hepatic disorder [62]. A pro-inflammatory cytokine TNFα (released from macrophages) signaling is a prominent pathway in course of NFκB-prompted a liver cell proliferation. It has been shown that the NFκB signaling pathway regulate the proliferation of hepatic oval cells during liver regeneration. TNFα induces up-regulation of NFκB [51] which activates transcription of IL6 [6]. The IL6 is a critical mediator in liver, acute phase response and compensatory liver regeneration. In addition, animal model studies have proven the significance of IL6 in stimulating normal cell cycle progression and liver regeneration after partial hepatectomy

[1, 63]. Psychosocial stress-released GCs interaction with GR in Kupffer cells to increase GILZ expression and inhibit NFκB [50]. The GCs also inhibit IL6 via suppressing NFκB activation (Fig. 1).

Stress-induced GCs affect nuclear factor Nrf2 during liver regeneration

The keap1-Nrf2 pathway is a key regulator of cytoprotective responses to endogenous and exogenous stresses caused by ROS. Keap1, a cysteine rich cytoplasmic protein of hepatic cells, helps the quiescent Nrf2 complex formation in the cytoplasm and promotes its degradation by the ubiquitin proteasome pathway. Various stimuli trigger the detachment of this complex to initiate hepatic regeneration and oxidative stress. Liver pathologies produce greater extent of such oxidative stress. Most importantly, the stress-prompted GCs are well recognized to produce ROS [15]. Chronically released GCs increase ROS production in liver cells that causes the keap1-Nrf2 complexity of conformational changes resulting in detachment of Nrf2 from the quiescent complex and the release of the activated Nrf2 [24] which plays a role in liver regeneration. It has been reported that the absence of Nrf2 results in delayed liver regeneration after partial hepatectomy [54]. The Nrf2 regulates the expression of ALR which acts as antioxidative protein and plays an important role in liver regeneration to ensure the survival of the damaged cells [20]. Free Nrf2 translocate to the hepatic cell nucleus where it regulates the expression of several genes involved in cell proliferation (Fig. 2).

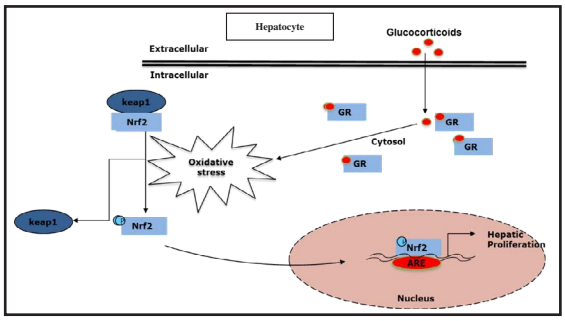

Fig. 2. GCs-induced oxidative stress regulates hepatic cell proliferation through the keap1-Nrf2 pathway. Increased GCs level causes oxidative stress due to excessive production of reactive oxygen species, which dissociate keap1-Nrf2 complex, resulting in nuclear localization of Nrf2 where it enhances the transcription of genes implicated in hepatocyte proliferation.

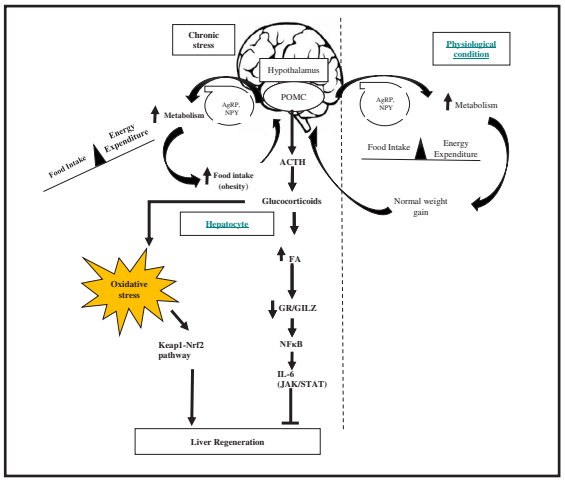

Fig. 3. Schematic illustration of the mechanism of stress-induced GCs-dependent weight gain, oxidative stress and liver generation. Under normal conditions, POMC cells, through the regulation of appetite stimulators AgRP and NPY, maintain balance between food intake and energy expenditure. In chronic stress, an increased weight gain occurs due to excessive activity of appetite stimulators and results in an imbalanced food intake and energy expenditure. Increased adrenocorticotropic hormone (ACTH) and glucocorticoids levels accompanied with obesity-linked high levels of fatty acids (FA) down regulates GILZ expression which increases NFκB and IL6 expression regulating the liver regeneration processes through JAK/STAT3 pathway.

Conclusion

This review addresses the multi - dimensional relationship of psychosocial stress involving Neuro-endocrine system, which affects liver regenerative pathways, food intake regulation and susceptibility to obesity. The schematic illustration is presented in Fig. 3. Distinct populations of neurons in the arcuate nucleus of hypothalamus contain appetite stimulators NPY and AgRP that are highly influenced by long-term stress resulting in altered physiological parameters and excessive

weight gain leading to obesity. Noticeable rise in ROS production, as a result of excessive glucocorticoids secretion during prolonged stress, activates liver degenerative processes through extrinsic and intrinsic pathways of cell death. Alongside these detrimental effects of glucocorticoids, Keap1-Nrf2 pathway, which promotes liver regeneration, is also activated by the glucocorticoids. Thus, both apoptosis and regenerative pathways are fine-tuned by the glucocorticoids signaling and the outcome would be determined by alteration in any of the two mechanisms.

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Disclosure Statement

No conflict of interests exists.

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