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PHYSIOLOGICAL AND BIOCHEMICAL CHANGES IN THE LIVER UNDER THE INFLUENCE OF STRESS FACTORS

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Abstract: The liver is a central organ affected by various stressors including environmental toxins, psychological pressure, and poor dietary habits. These stressors activate complex physiological and biochemical pathways leading to oxidative stress, mitochondrial dysfunction, inflammation, and metabolic disruptions. Psychological stress affects the liver through hormonal and nervous system responses, while unhealthy diets exacerbate liver damage via increased lipid accumulation and insulin resistance. The synergistic effects of these stressors contribute to liver diseases such as MASLD and NASH. Protective interventions, including antioxidant-rich diets, are essential to mitigate stress-induced liver damage.
Keywords: liver, stress, oxidative stress, psychological stress, fatty liver disease.

Introduction

The human liver undergoes significant physiological and biochemical changes when exposed to various environmental stressors, psychological stress, and dietary influences. Environmental stressors, such as climate change, can exacerbate liver diseases by altering food availability, increasing substance abuse, and promoting waterborne infections, which collectively impact liver health and disease progression[3]. Psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased glucocorticoid levels that facilitate hepatic inflammation and may increase the risk of hepatocellular carcinoma[2]. This stress also affects the liver through the sympathetic nervous system, which exacerbates liver diseases via catecholamines, while the parasympathetic system may inhibit hepatic inflammation[2]. Chronic psychological stress, particularly when combined with a high-fat, high-fructose diet, disrupts metabolic and inflammatory gene networks in the liver, promoting insulin resistance and lipid metabolism alterations[8]. This combination can lead to metabolic syndrome-related conditions, further impacting liver function[8]. Additionally, oxidative stress, a common consequence of environmental toxins, drugs, and alcohol, disrupts redox balance in the liver, contributing to inflammation and progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma[6]. In metabolic dysfunction-associated steatotic liver disease (MASLD), chronic stress is a significant risk factor, promoting systemic low-grade inflammation through the gut-liver-brain axis, which exacerbates liver damage[5]. The liver's response to acute stressors, such as fasting or exposure to extreme temperatures, includes ultrastructural changes like rough endoplasmic reticulum fragmentation and increased autophagic vacuoles, which may represent an adaptive response to maintain cellular homeostasis[9]. Furthermore, anxiety-like states in animal models have been shown to impair liver function through the EGFR/PI3K/AKT/NF-κB pathway, highlighting the impact of psychological distress on liver health[10]. Collectively, these studies underscore the complex interplay between stressors and liver physiology, emphasizing the need for integrated therapeutic strategies to mitigate liver disease progression under stress conditions.

Environmental Stressors and Liver Health

Oxidative Stress and Mitochondrial Dysfunction

Environmental stressors, such as exposure to air pollutants (e.g., PM2.5), heavy metals (e.g., arsenic), and pesticides, can induce oxidative stress in the liver. Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) and antioxidants, leading to lipid

peroxidation and mitochondrial dysfunction. This imbalance disrupts normal lipid metabolism, promoting hepatic fat accumulation and inflammation [9] [10].

Role of Mitochondria in Liver Damage

Mitochondria are central to energy production and lipid metabolism in hepatocytes. Environmental toxins, such as arsenic, impair mitochondrial function, reducing ATP production and increasing ROS levels. This dysfunction exacerbates lipid accumulation and inflammation, contributing to the progression of fatty liver disease [10].

Epigenetic Modifications and Liver Injury

Environmental stressors can also induce epigenetic changes, such as DNA methylation and histone modifications, which alter gene expression. These changes can impair the liver's ability to detoxify harmful substances and regulate metabolism, increasing susceptibility to liver damage [4].

Psychological Stress and Liver Pathophysiology

The Role of the Psychoneuroendocrineimmunological (PNEI) Network

Chronic psychological stress activates the PNEI network, leading to the release of cortisol and other stress hormones. Elevated cortisol levels promote visceral fat accumulation and insulin resistance, which are key contributors to MAFLD development [6].

Cortisol and Lipid Metabolism

Cortisol increases the release of free fatty acids from adipose tissue, which are subsequently taken up by hepatocytes. This process exacerbates hepatic steatosis and inflammation, creating a vicious cycle that worsens liver damage [6].

Gut-Liver Axis and Dysbiosis

Psychological stress disrupts the gut microbiota, leading to dysbiosis. An imbalanced gut microbiome can increase the translocation of bacterial products (e.g., lipopolysaccharides) into the liver, triggering inflammation and oxidative stress [6] [16].

Dietary Influences on Liver Health

High-Fat and High-Fructose Diets

High-fat diets (HFDs) and high-fructose diets are major contributors to liver damage. These diets induce oxidative stress, insulin resistance, and mitochondrial dysfunction, leading to hepatic steatosis and inflammation. The combination of HFD and environmental stressors, such as PM2.5 exposure, exacerbates these effects, promoting the progression to NASH [9] [16].

Role of Saturated Fats and Fructose

Saturated fats and fructose disrupt lipid metabolism by upregulating the expression of lipogenic genes, such as sterol regulatory element-binding protein-1c (SREBP-1c), and enzymes like fatty acid synthase (FAS). This results in increased hepatic lipid synthesis and accumulation [9] [20].

Protective Effects of Antioxidant-Rich Diets

Diets rich in antioxidants, such as the Mediterranean Diet (MD) and extra virgin olive oil (EVOO), can mitigate liver damage by reducing oxidative stress. Polyphenols in EVOO, such as hydroxytyrosol and tyrosol, have been shown to improve lipid metabolism and reduce inflammation in MAFLD patients [1] [2].

Role of Polyphenols

Polyphenols, found in foods like berries, green tea, and turmeric, exert anti-inflammatory and antioxidant effects. They reduce the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and improve insulin sensitivity, thereby protecting against liver damage [2] [13].

Interplay Between Environmental, Psychological, and Dietary Factors

Synergistic Effects on Liver Damage

The combined effects of environmental stressors, psychological stress, and unhealthy diets create a synergistic impact on liver health. For example, chronic psychological stress amplifies the

harmful effects of a high-fat diet by increasing visceral fat accumulation and insulin resistance [6] [16].

Gene-Environment Interactions

Genetic predisposition and environmental factors interact to influence liver disease progression. For instance, polymorphisms in genes involved in lipid metabolism and antioxidant defense can modulate the impact of environmental stressors and dietary habits on liver health [15].

The findings discussed in this review highlight the multifactorial impact of stress on liver physiology and biochemistry. Environmental stressors, such as air pollution and chemical toxins, provoke oxidative stress by increasing the production of reactive oxygen species (ROS), which disrupt the mitochondrial function and lipid metabolism of hepatocytes. Mitochondrial dysfunction, in turn, impairs ATP production and exacerbates hepatocellular injury, contributing to the development of hepatic steatosis and inflammation. Epigenetic modifications triggered by these stressors further influence gene expression profiles associated with detoxification and metabolic regulation. These alterations not only affect liver function in the short term but also predispose individuals to chronic liver diseases such as MASLD and non-alcoholic steatohepatitis (NASH).

Psychological stress acts synergistically with environmental and dietary factors by activating the hypothalamic-pituitary-adrenal (HPA) axis and releasing cortisol, which increases visceral adiposity and insulin resistance. This leads to increased hepatic uptake of free fatty acids, promoting lipid accumulation and inflammatory responses. Additionally, gut microbiota dysbiosis associated with chronic stress may enhance the translocation of endotoxins to the liver via the gut-liver axis, triggering immune activation and further oxidative damage. These findings underscore the importance of considering the combined impact of psychological, environmental, and nutritional stress in understanding liver pathophysiology. Targeted interventions, such as antioxidant-rich diets and stress management strategies, may offer therapeutic benefit by attenuating the progression of liver damage under chronic stress conditions.

Table: Physiological and biochemical changes in the liver under different stressors

Stressor Type	Physiological/Biochemical Changes	Citation
Environmental Stressors	Induce oxidative stress, mitochondrial dysfunction, and epigenetic modifications leading to hepatic steatosis	[4] [9] [10]
Psychological Stress	Activates the PNEI network, increases cortisol levels, and promotes visceral fat accumulation and insulin resistance	[6] [16]
High-Fat Diets	Upregulate lipogenic genes (e.g., SREBP-1c), increase lipid synthesis, and induce hepatic inflammation	[9] [20]
Antioxidant-Rich Diets	Reduce oxidative stress, improve lipid metabolism, and decrease inflammation	[1] [2] [13]

Conclusion

The liver is highly sensitive to environmental, psychological, and dietary stressors, which induce physiological and biochemical changes that can lead to liver diseases such as MAFLD and NASH. Oxidative stress, mitochondrial dysfunction, and inflammation are central mechanisms underlying these changes. While unhealthy diets and environmental toxins exacerbate liver damage,

antioxidant-rich diets and lifestyle modifications offer promising therapeutic strategies. Understanding the interplay between these factors is crucial for developing targeted interventions to prevent and manage liver diseases.

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