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THE ROLE OF THE LIVER AS AN ENDOCRINE GLAND

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Abstract: The liver, in addition to being the body's principal metabolic organ, plays an important role in endocrine regulatory processes. Its endocrine activity is manifested through the synthesis of biologically active substances and hepatokines, the metabolism of hormones, and the production of plasma proteins responsible for hormone transport. The liver synthesizes substances such as insulin-like growth factor 1 (IGF-1), hepcidin, thrombopoietin, angiotensinogen, and fibroblast growth factor 21 (FGF21). These substances participate in the regulation of growth, iron metabolism, hematopoiesis, blood pressure, and glucose and lipid homeostasis. This article analyzes the anatomical and histological foundations of the liver's endocrine activity, the molecular mechanisms of action of major hepatokines, hormonal disturbances associated with liver pathologies, and modern pharmacological approaches, based on scientific literature.

Keywords: liver, endocrine function, hepatocyte, hepatokine, IGF-1, hepcidin, thrombopoietin, FGF21, angiotensinogen, fetuin-A, hormone metabolism, liver cirrhosis.

INTRODUCTION. The endocrine system is a complex regulatory system that ensures the growth, development, metabolism, and maintenance of homeostasis in the body. Traditionally, the pituitary gland, thyroid gland, parathyroid glands, and adrenal glands are regarded as classical endocrine glands. However, modern physiological and molecular studies have demonstrated that certain parenchymal organs also actively participate in endocrine regulation.

The liver is one such organ. It is the largest internal organ of the human body and performs essential functions in metabolism, protein synthesis, detoxification, bile production, and immune defense. In addition, the liver synthesizes numerous biologically active substances, metabolizes hormones produced by other endocrine glands, and regulates their biological effects.

The endocrine activity of the liver is manifested through the following major mechanisms:
- synthesis and secretion of hormones and hepatokines into the bloodstream;
- participation in the activation, inactivation, and degradation of hormones;
- production of plasma proteins responsible for hormone transport;
- regulation of glucose, lipid, and amino acid metabolism through hormonal signaling;
- endocrine communication with the intestine, pancreas, pituitary gland, and other organs.

Therefore, the liver should be studied not merely as a metabolic and detoxifying organ, but also as an important regulatory center responsible for maintaining the body's metabolic and endocrine homeostasis.

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The following cell types play important roles in the endocrine activity of the liver:

- Hepatocytes are the primary source of IGF-1, hepcidin, angiotensinogen, thrombopoietin, FGF21, and numerous plasma proteins.

- Kupffer cells are resident macrophages located in the hepatic sinusoids. They may influence hepcidin synthesis through the production of inflammatory mediators, particularly interleukin-6 (IL-6).

- Sinusoidal endothelial cells facilitate the exchange of substances between the blood and hepatocytes. They participate in the regulation of hepcidin synthesis through BMP6 signaling, which is involved in iron homeostasis.

- Ito cells are located in the space of Disse and normally store retinoids. In response to chronic liver injury, they become activated and differentiate into collagen-producing cells, thereby contributing to the development of hepatic fibrosis.

Thus, the endocrine activity of the liver is not exclusively dependent on hepatocytes. Interactions among different hepatic cell types constitute an important basis for hormonal and metabolic regulation.

MATERIALS AND METHODS

This article is a narrative literature review aimed at examining the liver's function as an endocrine organ. The primary objective of the study is to analyze the physiological significance of hormones and hepatokines synthesized in the liver, their molecular mechanisms of action, endocrine alterations associated with liver pathologies, and the possibilities for pharmacological regulation of these processes.

In preparing this article, national and international scientific literature related to liver physiology, biochemistry, endocrinology, and hepatology was reviewed. The main sources of information included original research articles, scientific reviews, and findings from randomized clinical trials published in the PubMed, PubMed Central, and Google Scholar scientific databases.

The analysis focused on the following areas:

1. The physiological functions of the major hormones and hepatokines synthesized in the liver.
2. Their receptors and intracellular signal transduction mechanisms.
3. Interactions between the liver and other endocrine organs.
4. Changes in hormonal homeostasis associated with liver pathologies.
5. Mechanisms of action and safety profiles of modern pharmacological agents.

RESULTS AND DISCUSSION

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Biologically active substances produced by the liver affect various physiological systems of the body. Some of these substances are classified as classical hormones, whereas others are known as hepatokines. Hepatokines are biologically active proteins synthesized primarily in the liver that exert their effects on other tissues and organs through the bloodstream.

Insulin-like growth factor 1 (IGF-1). IGF-1 is synthesized mainly in hepatocytes under the influence of growth hormone (GH). It plays an important role in body growth, cell differentiation, and protein synthesis. Once synthesized, IGF-1 is released into the bloodstream and exerts its effects primarily through the IGF-1 receptor. In liver failure, IGF-1 synthesis may decrease, resulting in loss of muscle mass, sarcopenia, and impaired growth processes.

The Role of the Liver in the Metabolism of Other Hormones

The liver not only produces hormones but also regulates the metabolism and biological activity of hormones secreted by other endocrine glands.

Insulin. Insulin is produced by the β-cells of the pancreas and reaches the liver through the portal circulation. By binding to hepatic insulin receptors, it stimulates glycogen synthesis, suppresses gluconeogenesis, and influences lipid metabolism. A substantial proportion of insulin undergoes metabolism in the liver during its first pass.

Glucagon. Glucagon is synthesized by the α-cells of the pancreas. It binds to glucagon receptors in the liver and activates the adenylate cyclase–cAMP–PKA signaling pathway. Consequently, glycogenolysis and gluconeogenesis are enhanced, leading to an increase in blood glucose levels.

Thyroid hormones. The liver participates in the conversion of a proportion of thyroxine (T4) into the biologically active form triiodothyronine (T3), as well as in their metabolism and elimination. In addition, the liver synthesizes thyroxine-binding globulin (TBG).

Steroid hormones. The liver plays an important role in the metabolism of cortisol, estrogens, and androgens. Through hydroxylation and conjugation reactions, these hormones are converted into more water-soluble forms, facilitating their subsequent excretion through bile or urine. The liver also produces sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG).

Vitamin D. The liver carries out the 25-hydroxylation of vitamin D, resulting in the formation of 25-hydroxyvitamin D (calcidiol). Its subsequent activation occurs primarily in the kidneys.

The liver influences circulating hormone concentrations, their transport, biological activity, and rate of degradation.

Endocrine Disorders in Liver Diseases

Chronic injury to hepatic tissue disrupts hormone synthesis, metabolism, and transport. This may lead to various endocrine and metabolic complications.

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Liver cirrhosis. In cirrhosis, normal hepatic parenchyma is replaced by fibrous tissue and regenerative nodules. The functional mass of hepatocytes decreases, portal blood flow is disrupted, and hormonal regulation is altered.

The major consequences include:

- Decreased IGF-1 synthesis;
- Insulin resistance and impaired glucose tolerance;
- Alterations in sex hormone metabolism;
- Hypogonadism and decreased testosterone levels in men;
- Reduced thrombopoietin synthesis;
- Impaired vitamin D metabolism and bone metabolism;
- Alterations in thyroid hormone metabolism.

Metabolic dysfunction-associated steatotic liver disease (MASLD). This condition is characterized by lipid accumulation in hepatocytes, insulin resistance, oxidative stress, and inflammatory processes. Changes may occur in the levels of hepatokines such as FGF21 and fetuin-A. Although these substances are associated with metabolic processes, neither should be considered the sole cause of the disease.

Chronic hepatitis. In chronic hepatitis of viral or other etiologies, inflammatory mediators, particularly interleukin-6 (IL-6), may influence hepcidin synthesis. Increased hepcidin levels restrict the transfer of iron from the intestine into the bloodstream, thereby contributing to functional iron deficiency and anemia.

Cholestasis. When bile flow is impaired, bile acids accumulate in hepatocytes. Protective mechanisms are activated through receptors such as the farnesoid X receptor (FXR). If these mechanisms are insufficient, hepatocellular injury and inflammation may intensify.

Endocrine disturbances observed in liver cirrhosis are multisystem in nature and cannot be explained solely by changes in the level of a single hormone.

CONCLUSION

In addition to being the body's principal metabolic organ, the liver plays an important role in endocrine regulation. Its endocrine activity is mediated through the synthesis of biologically active substances and hepatokines, hormone metabolism, the production of plasma carrier proteins, and interorgan signaling interactions with other endocrine organs. IGF-1 contributes to the regulation of body growth and development; hepcidin regulates iron metabolism; thrombopoietin is involved in platelet production; angiotensinogen participates in blood pressure regulation; and FGF21 and fetuin-A contribute to the regulation of energy balance and metabolic processes.

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Disruption of these mechanisms in liver diseases may lead to anemia, thrombocytopenia, insulin resistance, sarcopenia, sex hormone disturbances, and alterations in bone metabolism.

Contemporary pharmacological research is expanding the therapeutic possibilities for liver-related metabolic disorders through agents targeting glucagon-like peptide-1 (GLP-1) receptors, thyroid hormone receptors, and thrombopoietin receptors. However, the use of each drug must be guided by clinical indications, contraindications, and established safety criteria.

Overall, an in-depth understanding of the liver's endocrine activity is of considerable scientific and practical importance in the fields of endocrinology, gastroenterology, hematology, and clinical pharmacology.

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