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MORPHOFUNCTIONAL CORRELATION OF DETOXIFICATION ENZYME ACTIVITY IN LIVER TISSUE AND HEPATOCYTE APOPTOSIS IN EXPERIMENTAL GASTRIC ULCER

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Abstract

Objective: Experimental gastric ulcer is known to cause systemic metabolic disturbances affecting distant organs, including the liver. This study aimed to evaluate the morphofunctional relationship between the activity of hepatic detoxification enzymes and the development of hepatocyte apoptosis in an experimental model of gastric ulcer.

Materials and Methods: The experiment was performed on 48 adult male Wistar rats divided into control, sham-operated, and experimental groups with gastric ulcers examined on days 3, 7, and 14 after ulcer induction. Gastric ulcers were produced using the acetic acid method. Liver tissue samples were analyzed biochemically to determine the activity of cytochrome P450 2E1 (CYP2E1), glutathione-S-transferase (GST), and malondialdehyde (MDA). Histological examination included hematoxylin–eosin staining, TUNEL assay for apoptosis detection, and immunohistochemical analysis for Caspase-3 and Ki-67 expression.

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Results: The induction of gastric ulcer resulted in significant changes in hepatic detoxification enzyme activity. CYP2E1 activity increased by approximately 45% on day 7 compared with controls, indicating enhanced oxidative metabolism. In contrast, GST activity showed an initial increase followed by a marked decrease by day 14 (38% below control). Oxidative stress marker MDA was significantly elevated. These biochemical changes correlated with increased hepatocyte apoptosis, confirmed by TUNEL assay and elevated Caspase-3 expression. A strong negative correlation ($r = -0.72$) was observed between GST activity and Caspase-3 positive hepatocytes.

Conclusion: Experimental gastric ulcer induces oxidative stress and disrupts hepatic detoxification systems, leading to activation of apoptotic pathways in hepatocytes. These findings support the concept of a functional hepato-gastric axis where gastric pathology contributes to secondary liver injury.

Keywords: Experimental gastric ulcer, liver detoxification, cytochrome P450 2E1, glutathione-S-transferase, apoptosis, hepatocytes, Caspase-3, TUNEL assay.

Introduction

Peptic ulcer disease remains a widespread gastrointestinal disorder and continues to represent an important clinical problem worldwide. Although ulcer formation primarily affects the gastric mucosa, increasing evidence suggests that gastric lesions may produce systemic metabolic and inflammatory responses that influence the function of other organs. The liver plays a crucial role in maintaining metabolic homeostasis and detoxification. Hepatic detoxification processes involve two major enzymatic phases. Phase I reactions are mainly mediated by cytochrome P450 enzymes, which oxidize xenobiotics and endogenous metabolites. Among them, the CYP2E1 isoenzyme is particularly important due to its ability to metabolize small molecular compounds and generate reactive oxygen species during oxidative reactions.

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Phase II detoxification reactions are primarily mediated by conjugating enzymes such as glutathione-S-transferase. GST neutralizes reactive metabolites by conjugating them with glutathione, thereby protecting hepatocytes from oxidative injury. An imbalance between these enzymatic systems may lead to excessive production of reactive oxygen species and oxidative stress. Recent studies emphasize the importance of the so-called gut-liver axis, which describes the functional interaction between the gastrointestinal tract and the liver. Gastric injury may lead to the release of inflammatory mediators and toxic metabolites that reach the liver via the portal circulation and alter hepatic metabolic activity.

One of the important consequences of oxidative stress in hepatocytes is apoptosis, or programmed cell death. Apoptosis is regulated by complex intracellular signaling pathways, including activation of caspases. Caspase-3 is considered a key executioner enzyme responsible for the final stages of apoptotic cell death. The detection of apoptotic hepatocytes using TUNEL staining and caspase-3 immunohistochemistry provides reliable morphological evidence of liver injury.

Despite growing interest in systemic consequences of gastric pathology, the relationship between gastric ulcer formation, hepatic detoxification enzyme activity, and hepatocyte apoptosis remains insufficiently investigated. Understanding these interactions is essential for clarifying mechanisms of liver injury associated with gastrointestinal diseases.

Purpose of the Study

The aim of this study was to investigate the morphofunctional correlation between hepatic detoxification enzyme activity and hepatocyte apoptosis in an experimental model of gastric ulcer.

Materials and Methods

The study was conducted at the laboratories of Tashkent State Medical University in accordance with ethical standards for animal research. Forty-eight adult male

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Wistar rats weighing 200–220 g were used in the experiment. Animals were maintained under standard laboratory conditions with free access to food and water. The rats were randomly divided into experimental groups: control, sham-operated, and gastric ulcer groups evaluated on days 3, 7, and 14 following ulcer induction.

Experimental gastric ulcers were induced using the acetic acid model. Under general anesthesia with ketamine and xylazine, a midline laparotomy was performed and the stomach was exposed. A filter paper soaked in glacial acetic acid was applied to the serosal surface of the stomach for one minute, after which the area was rinsed with saline and the abdomen was closed.

At predetermined time points the animals were euthanized and liver tissue samples were collected. Portions of liver tissue were homogenized for biochemical analysis. The activity of CYP2E1 was determined spectrophotometrically by measuring oxidation of p-nitrophenol. Glutathione-S-transferase activity was evaluated using 1-chloro-2,4-dinitrobenzene as a substrate. Malondialdehyde levels were measured as an indicator of lipid peroxidation and oxidative stress.

For morphological examination, liver tissues were fixed in formalin, embedded in paraffin, and sectioned. Hematoxylin–eosin staining was used to assess general histological structure. Apoptosis was evaluated using the TUNEL assay, and the apoptotic index was calculated as the percentage of TUNEL-positive hepatocytes. Immunohistochemical staining was performed using antibodies against Caspase-3 and Ki-67 to evaluate apoptosis and cellular proliferation. Positive cells were counted in multiple microscopic fields.

Statistical analysis was performed using one-way analysis of variance with significance accepted at $p < 0.05$.

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Results

Macroscopic examination confirmed the successful induction of gastric ulcers in experimental animals. Liver tissue appeared grossly normal in all groups. Biochemical analysis revealed significant alterations in hepatic detoxification enzyme activity following ulcer induction. CYP2E1 activity showed a moderate increase on day 3 and reached its maximum on day 7, rising by approximately 45% compared with control animals. This increase indicates enhanced oxidative metabolic activity in hepatocytes. In contrast, GST activity demonstrated a biphasic pattern. A slight increase was observed during the early stage of ulcer formation, suggesting an adaptive protective response. However, by days 7 and 14 GST activity decreased significantly, indicating exhaustion of the detoxification system.

The level of malondialdehyde increased progressively throughout the experimental period, confirming the development of oxidative stress in liver tissue.

Histological examination revealed structural alterations in hepatocytes. Mild sinusoidal dilation and hydropic degeneration were observed in early stages. By day 7, more pronounced pathological changes appeared, including ballooning degeneration of hepatocytes and inflammatory infiltration. Apoptotic hepatocytes with condensed nuclei and apoptotic bodies were frequently detected.

The TUNEL assay confirmed a significant increase in apoptotic cells in the liver of ulcer-bearing animals. The apoptotic index increased markedly on day 7, corresponding to the peak of oxidative stress and enzymatic imbalance.

Immunohistochemical analysis demonstrated increased Caspase-3 expression, confirming activation of apoptotic pathways. At the same time, Ki-67 expression increased at later stages, indicating activation of regenerative processes in the liver.

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Correlation analysis revealed a strong negative relationship between GST activity and the number of Caspase-3 positive hepatocytes, indicating that depletion of detoxification enzymes contributes to hepatocyte apoptosis.

Conclusion

The results of this study demonstrate that experimental gastric ulcer induces significant morphofunctional changes in the liver. The development of gastric lesions leads to disruption of hepatic detoxification systems, characterized by increased activity of CYP2E1 and depletion of glutathione-S-transferase.

These biochemical disturbances result in oxidative stress and activation of apoptotic pathways in hepatocytes, confirmed by increased Caspase-3 expression and TUNEL-positive cells. The findings support the existence of a functional hepato-gastric axis in which gastric pathology may cause secondary liver injury.

Understanding these mechanisms is important for improving the management of gastrointestinal diseases and preventing systemic complications associated with gastric ulceration.

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