

The Influence of Mechanic Jaundice on Liver Regeneration after Partial Hepatectomy

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Abstract

The present study was aimed to detect the molecular mechanisms of early response genes expression inactivation under influence of cholestasis in hepatocytes stimulated towards proliferation. Has been revealed, that occlusion of common bile duct affects the expression of early response genes in hepatocytes stimulated towards proliferation. Suppressive effect of cholestasis upon liver regeneration is realized only at the level of expression of cell proliferation controlling genes. Corticosterone (signal molecule) causes suppression of expression of early response genes controlling proliferation. After adrenal gland extirpation, the proliferative stimuli result in acceleration of mentioned gene expression in hepatocytes. Increased concentration of bile acid, as a result of cholestasis, causes inactivation of 11 β -hydroxysteroid dehydrogenase, providing increase in corticosterone concentration. In resected liver hepatocytes, due to corticosterone, early response gene partial suppression occurs, and processes related to reparative regeneration is delayed correspondingly.

Keywords: *cholestasis, early gene expression, liver regeneration, partial hepatectomy*

Introduction

The problem of mechanical jaundice, despite of thorough and versatile investigations, remains as one of the topical question of modern surgery. Of particular interest is the reparative regeneration ability of liver in case of common bile duct occlusion since, nowadays occurrence of organ's resection on the background of common bile duct occlusion does not belong to casuistry, the more so, that this sphere is less investigated. [10, 11]

According to literature, cholestasis induces apoptosis and causes suppression of post-resection regeneration of liver at the expense of early response genes conservation however, the exact mechanism of conservation determined by the cholestasis is not clear. [1]

In patients with obstructive jaundice, the delayed regeneration after liver resection may become as a reason of liver malfunction conditioned by the organ mass insufficiency and thereby the reason of lethal outcome. Aforesaid once more emphasizes topicality of our investigations.

The aim of our investigations was to study the molecular mechanisms of early response genes expression inactivation under influence of cholestasis in hepatocytes stimulated towards proliferation.

Material and Methods

Total of 132 white rats of mixed population (body mass 120 g.) and several experimental models - Occlusion of common bile duct, partial hepatectomy, and bilateral adrenalectomy were used for investigations. Isolation of

hepatocytes' nucleus was achieved by the method of Chauveau [2] modified by Georgiev et al. Transcription activity of isolated nucleus was assessed by the previously described method [5].

Results and Discussions

Has been shown that over 6 hour after operation due to occlusion of common bile duct and partial hepatectomy the transcription activity of nucleus isolated from hepatocytes is suppressed by 39% compared to control data (Fig.1).

Results of present study have shown, that occlusion of common bile duct affects the expression of early response genes in hepatocytes stimulated towards proliferation. The good evidence of it is decreased transcription activity of delayed response genes 6 hour later after operation.

According to literary data, in rats at the early stage of hepatocytes proliferation, the increased activity of delayed transcription of early response genes over 6 hour after operation is determined by the products of immediate early response genes expression [8,9].

Occlusion of common bile duct without proliferative stimulation does not result in suppression of transcription activity of nucleus in hepatocytes.

During the first 8 hour after bile congestion, in hepatocytes' nucleus intensity of RNA synthesis remains unchanged (Fig.2) indicating, that suppressive effect of cholestasis upon liver regeneration is realized only at the level of expression of cell proliferation controlling genes.

Has been stated that, at different periods (0, 1 and 5 hour) occlusion of common bile duct exerts the same affect on transcription activity of nucleus in hepatocytes. Despite, at what time the common bile duct occlusion is performed, over 6 hour after operation RNA synthesis is decreased in all cases by 40% compared to control (Fig.3).

According to received data, occlusion of common bile duct results in disorder of transduction of signal in hepatocytes stimulated towards proliferation.

Has been stated, that corticosterone in cells of white rats (signal molecule) causes suppression of expression of early response genes controlling proliferation [9]. Has been shown, that after adrenal gland extirpation, the proliferative stimuli results in acceleration of mentioned gene expression in hepatocytes.

Early appearance of the first pick of delayed early response gene transcription activity by 3 hour is realized via the non-corticosterone-dependent mechanism [3].

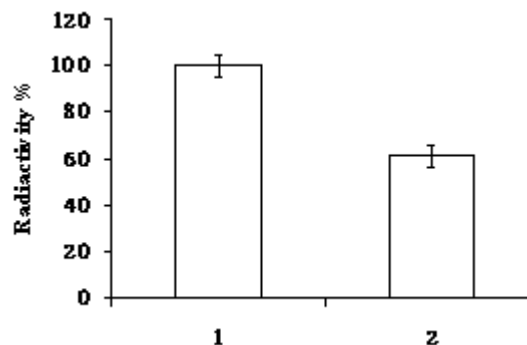
Coming from the aforesaid, on the next stage of investigation, the effect of cholestasis on expression of early response genes in the presence of hormonal disbalances (bilateral adrenalectomy) was studied.

Has been revealed that on the 4th day after bilateral adrenalectomy at the early stage of post-hepatectomic rehabilitative growth, occlusion of common bile duct does not affect on expression of genes controlling hepatocytes' proliferation. On the 4th day after adrenalectomy in white rats' hepatocytes, stimulated towards proliferation, the decreased transcription activity of nucleus has not detected (Fig.4) that could be explained by decreased concentration of corticosterone.

According to literary data, enzyme 11 β -hydroxysteroid dehydrogenase, presented in many tissue controls intracellular concentration of glucocorticoids. In renal cells, due to conversion of 11 β -hydroxycorticoid (corticosterone) into 11 β -ketosteroid (11 β -dihydrocorticosterone), prevention of binding of glucocorticoids to mineralocorticoid receptors occurs. [6]. At the same time it is determined that in contrast to renal tissue, in liver, the less active 11 β -hydroxysteroid dehydrogenase owing to high lability inactivates readily [7].

Data of recent years show, that in case of cholestasis the activity of aforementioned enzyme decreases by the influence of chenodeoxycholic acid [6].

From the above mentioned and on the basis of findings obtained by investigations, it is supposed, that in case of cholestasis, increase of bile acid concentration causes inactivation of 11 β -hydroxysteroid dehydrogenase, thereby providing increase in corticosterone concentration. That's why, in resected liver hepatocytes, due to corticosterone, early response genes partial suppression occurs, and processes related to reparative regeneration is delayed correspondingly.



1. Control: partial hepatectomy (6 hour)
2. Colestasis + partial hepatectomy (6 hour)

Fig.1 Effect of cholestasis on expression of early response genes in hepatocytes stimulated towards proliferation.

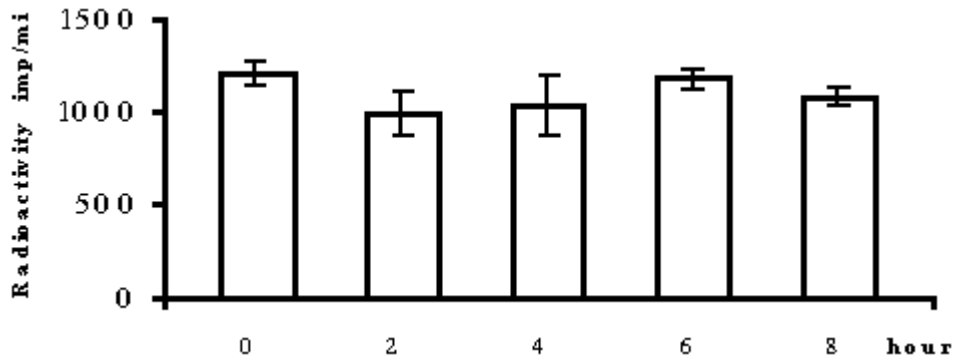
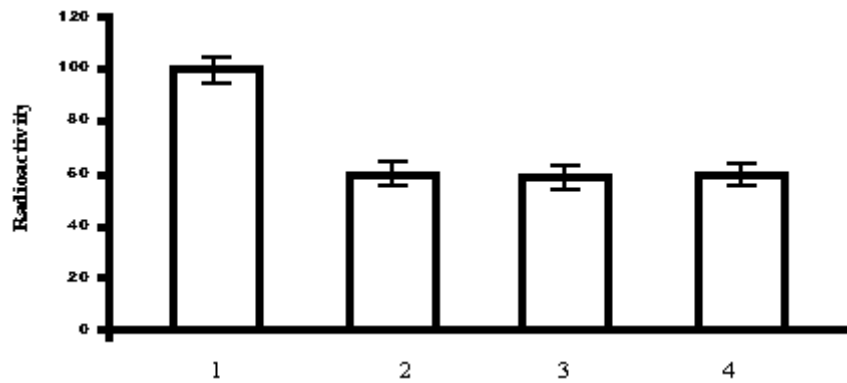
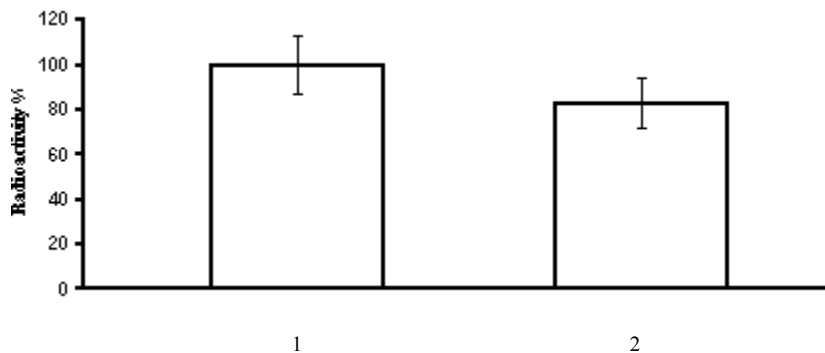


Fig.2 Changes of transcription activity of nucleus in white rats hepatocytes in case of cholestasis.



- 1. Partial hepatectomy (6 hour)
- 2. Colestasis + partial hepatectomy (6 hour)
- 3. Colestasis (1-st hour) + partial hepatectomy (6 hour)
- 4. Colestasis (5-th hour) + partial hepatectomy (6 hour)

Fig.3 Effect of cholestasis on expression of early response genes in hepatocytes stimulated towards proliferation.



- 1. Bilateral adrenalectomy (4 day)+hepatectomy (3 hours)
- 2. Bilateral adrenalectomy (4 day) + hepatectomy+cholestasis (3 hours)

Fig.4 Effect of cholestasis on expression of early response genes in hepatocytes on the background of hormonal disbalance.

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Влияние механической желтухи на регенерацию печени после частичной гепатэктомии

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РЕЗЮМЕ

Целью исследования было изучение молекулярных механизмов инактивации экспрессии генов раннего ответа в стимулированных к пролиферации гепатоцитах. Холестаз угнетает экспрессию генов раннего ответа в гепатоцитах посредством кортикостерона (сигнальной молекулы). Вызванное холестазом повышение концентрации желчных кислот инактивирует 11 β -гидроксистероиддегидрогеназу, что, в свою очередь, повышает концентрацию кортикостерона и, тем самым, инактивирует транскрипционную активность генов раннего ответа. Это является причиной понижения регенеративной способности в резецированной печени.

Ключевые слова: холестаз, экспрессия генов раннего ответа, регенерация печени, частичная гепатэктомия