

Portal and Biliary Hypertension as the Cells Proliferation Trigger (Landmarks for Future Investigations)

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ABSTRACT. The outcomes of the study demonstrated that the violent activation of cellular proliferation in liver tissue can be triggered by partial hepatectomy (PH), as well as by common bile duct ligation (BDL). However, the causes of the mentioned activation are not still clearly defined. 54 white Wistar male rats of II postpubertal age with weight 200-220 g were included in PH or BDL models. In PH setting, pressure in portal vein was measured before and immediately after PH, as well as at 6th, 24th, 48th, and 144th hours past the operation. Mitotic bodies were counted immediately after PH, and at 6th, 32nd, 72nd and 144th hours after the operation. In BDL setting, the pressure in common bile duct was measured before and at 1st, 3rd, 72nd, 96th and 120th and 144th hours after its ligation, and pressure in portal vein in this same setting was measured at 1st, 6th, 24th, 72nd, 144th hours past the operation. Mitotic bodies were counted at 24th, 48th, 72nd, 96th and 144th hours after BDL. On the basis of data obtained and analyzed the following conclusions are made: portal and biliary hypertension appeared to serve as a trigger for cellular proliferative activity in PH and BDL settings. The comprehensive evaluation of the processes involving liver regeneration following partial hepatectomy and post-BDL biliary ductular proliferation, hence requires not only the reduction of intervals between experimental data and refinement of the morphological and/or molecular/biological techniques of the study, but also the development of new experimental models with novel approaches. © 2009 Bull. Georg. Natl. Acad. Sci.

Key words: *portal hypertension, biliary hypertension, ductular reaction, hepatocyte, mitosis*

Introduction

Liver regeneration belongs to the most broad studied phenomena in general. Involving augmented proliferation of liver cells, it has been established to be triggered by the loss or injury of large liver mass as it occurs in partial hepatectomy (PH) setting, ligation of one or two lobular branches of portal vein and/or treating with CCl₄ etc. have also been evidenced to yield the same effect [1-7].

PH is conventionally accepted as the best model for liver regeneration, for two reasons:

a) PH is quite frequently encountered case in surgical practice and therefore, is a subject of considerable interest;

b) PH is readily available for performance on small laboratory animals, which facilitates the organizational and financial provision of the experiment.

Due to all above mentioned, a considerable number of studies referring to liver regeneration keep constantly being issued. PH has already been established as an initiator of powerful mitotic proliferation of hepatocytes, leading to virtually complete restoration of liver mass in

1-2 weeks after intervention [2,8]. Activation of early response genes (ERG), which is followed by “switching” of late response genes, has been determined as the top triggering mechanism for launching mitotic activity [9-12]. This process is considered to be completely dependent on the presence of growth factors (GF). The subtle relationship mechanisms between GF and ERG activation remain still unclear, though their influence on mitotic wave induction is fairly evidenced [2,3,8,13,14].

Liver regeneration (LR) following PH requires proliferation of all other non-hepatocyte cells as well (otherwise liver mass and volume regain would be inconvenient). However, this subject is covered in only few studies [15-17].

Bile congestion (cholestasis), resulted from bile duct occlusion appears to be a subject of vast interest for investigators due to the same two reasons, highlighted above with respect to PH: it is quite frequently encountered in surgical practice and its modeling through applying common bile duct ligation [BDL] technique is also readily available on small laboratory animals.

BDL as well as PH, induces the proliferative processes in liver tissue [18, 19]. However, in this setting, the focus is shifted on biliary epithelium [15]. Numerous studies have evidenced about proliferation of biliary epitheliocytes and bile ducts themselves, emerging soon after several hours of BDL and continuing during several weeks [20, 21, 58]. Drastic increase in mitotic activity of hepatocytes has also been documented in BDL setting, however, neither activation of ERG [9,10], nor increase in growth factor levels were evidenced.

Objective

Comparable evaluation of triggers of cells proliferative activity in PH and BDL models and determining landmarks for future investigations in this direction.

Material and methods

54 white Wistar male rats of II postpubertal age, whose weight ranged between 200-220 grammes, were

Table 1.

	Control	PH							BDL								
		Just after PH	6 h	24 h	32 h	48 h	72 h	120 h	Initial	3 h	6 h	24 h	48 h	72 h	96 h	120 h	144 h
	6	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total	6	21							27								

subjected to the experiments. Animals were housed in individual cages at a standard temperature of 24°C and a 12 hour light/dark cycle and fed ad libitum on standard rat chow, with free access to water.

Distribution of animals by the experimental models is given in Table 1.

PH was performed through resection of left lateral and medial lobes, with preliminary ligation of their portal complexes and hepatic veins, without affecting the remaining liver tissue.

Bile congestion was induced via BDL (transection of common bile duct between two ligatures).

The pressure in portal vein before and after PH and in common bile duct – before BDL was measured by applying hydrostatic manometry technique, which implied the registration of fluid level in catheter, inserted in mentioned tubular structures. For measuring pressure in portal vein, the catheter was inserted distally in it, in the direction of bloodstream (“to liver”). Biliary pressure in control animals was measured via distal insertion of the catheter (“to major duodenal” papilla). The level of 0.9% NaCl in tube, at which it begun to leak into proximal part of small intestine of the rat was considered as the index of biliary pressure (22).

At 1st and 3rd hours after BDL, the biliary pressure was measured again, only via proximal inserton of the catheter (“to liver”).

At 96th, 120th and 144th hours after BDL, the biliary pressure was measured by modified optic (membranous) tonometer; such manometry was obtainable only in case if the diameter of congested common bile duct stump exceeded 4 mm.

Histological study of liver tissue was performed on haematoxylin-eosin stained, parafin-embedded sections.

Mitotic activity was evaluated on serial sections on 30 optic fields, in terms of 480-fold magnification, without applying the method of “preliminary accumulation of mitoses”.

All operations were performed with keeping sterile conditions, under general anesthesia via intraperitoneal injection of Nembutal.

Results and discussion

Results of the study are shown in Table 2 and Figures 1-4.

The presented data confirm the results we have previously demonstrated, namely: PH results in increased transcriptional activity in hepatocyte nuclei, which reach the first peak at 6th hour [3] followed by the peak for hepatocyte mitoses at 30-32nd hour after operation [9, 10].

Rise in mitotic wave is supposed to be resulted from increase in hepatocyte growth factor (HGF) level. Different considerations arise over the possible causes of the latter [23]. Furthermore, there are discrepancies about whether HGF increase is the cause or the consequence of the hepatocyte proliferation [2,3]. Admitting the latter conception, the focus should be made on other factors, possibly accounting for mitotic activity in hepatocytes, involving: endotheliocyte growth factor (EGF), transforming growth factor (TGF), tumor necrosing factor- α (TNF- α) etc. [2, 12, 14].

The release of growth factors and their passage into circulation is thought to be resulted from the damage to liver tissue, occurring at the time of LR [2, 24]. However, in case of PH model performed by us [25], the causes of cellular and tissular damage were not clearly identified and hence, remain obscure. The results of the studies, evidencing that ligation of lobular portal veins in rats, without resection of these lobes, leads to the same regenerative-proliferative processes in the intact

lobes as well as in PH, still remain to be clarified as well [26]. In addition, it also should be taken into account that HGF, or even EGF and/or TGF injection in intact rats though actually results in DNA synthesis and mitoses activation in hepatocytes, but this effect is yet very scarcely manifested, compared to the PH case [2, 8, 27,28,29]. However, infusion of growth factors, following the previous single injection of cytokine – tumor necrosing factor (TNF) - has been shown to result in replication of 40% of hepatocytes. Moreover, replication in 30% of hepatocyte population has been shown to be triggered by simultaneous injection of EGF and TNF. TNF is considered to activate matrix metalloproteinases (MMPs), resulting in sequential progressive damage to extracellular matrix, which in turn, paves the way for hepatocyte proliferation [8, 29].

It is shown, that in the setting of uniting two rats circulations by special porto-portal shunts, PH performed in one rat results in enlargement of liver size in another (through mitotic activations), and complete removal of the liver in one rat significantly increases the liver growth rate in another [2,30,31]. This fact allegedly confirms the inevitable role of humoral factors (growth factors) in this process. On the other hand, it is unclear, where could possibly these growth factors take origin when the liver is totally removed. The facts, that liver transplantation from small-sized donor to large-sized recipient inevitably is followed by transplantat enlargement, but liver transplantation from large-sized animal to small-sized one contrarily results in decreasing

Table 2

Indexes of portal and biliary pressures and mitotic activity of hepatocytes and cholangiocytes in control and on different stages after PH and BDL

METHODS	GROUPS	Control	PH							BDL								
			Just after PH	6 h	24 h	32 h	48 h	72 h	144 h	1 h	3 h	6 h	24 h	48 h	72 h	96 h	120 h	144 h
Biliary Pressure (mmH ₂ O)		169.67 ±4.16								205.0 ±1.0	213.67 ±3.06				252.67 ±3.51	270.67 ±2.52	277.33 ±3.21	285.67 ±2.52
Portal Pressure		103.67 ±3.51	194.33 ±13.87	196.67 ±8.08	197.00 ±6.56		162.00 ±5.29		111.00 ±2.00	107.33 ±4.16		123.33 ±2.08	158.00 ±1.73		172.00 ±3.61			190.67 ±4.93
Mitotic Activity	Hepatocyte	0,5 ±0,2	0,5 ±0,1		5.5 ±1.2	15.6 ±2.1			11.1 ±1.4	4.4 ±1.1				4.2 ±0.6	7.2 ±1.4	31.5 ±2.1	4.2 ±0.8	-
	Biliary epitheliocyte	-												4.1 ±0.6	18.0 ±1.3	14.4 ±2.0	4.3 ±1.2	1.1 ±0.4

subjects undergoing PH without shunting. The lower levels of growth factor, ERG expression and mitotic activity, manifested in shunted group, compared to control group, will evidence our suggestion.

b) Lumens of hepatic veins (inferior vena cava inflows) should be experimentally reduced so that portal hypertension would develop in liver tissue [42], or high pressure portal perfusion must be performed in isolated liver perfusion model. Increase in growth factors concentrations and induction of ERG expression and mitoses in these settings will also prove our suggestion.

In addition, we may consider, that decreased portal pressure in liver (in case of transplanting the liver from big-sized donor to small-sized recipient) actually accounts for diminution of liver mass, through triggering apoptotic mechanisms.

Validity of this consideration could be tested by evaluation of apoptotic index in the setting of orthotopic liver transplantation from big-sized dogs to small-sized puppies.

Thus, the widely accepted suggestion that liver regeneration is triggered by loss of functioning cell masses, and stopped by restoration of this mass [2,3,8,43], can be postulated as follows: compensative liver hyperplasia (regeneration) as well as its involution are portal-pressure dependent events. Liver regeneration is triggered by portal pressure increase, and ceased by normalization of this pressure. A contrary picture is revealed in case of decreased portal pressure, which results in liver tissue involution, which persists until portal pressure is normalized.

Most authors in their works focus on hepatocyte proliferation in PH settings [5,44], though, studies concerning other cell populations are apparently scarce and non-systematized [3,8]. However, there are some works, demonstrating the activation of DNA synthesis in all cell types of liver in PH setting, only at different stages following intervention [2, 5, 8, 17, 45].

Obviously, it is impossible to consider about liver tissue regeneration at PH, without regarding the respective proliferative activity of all cell types [8, 46, 47]. At the same time, the questions listed below still remain unanswered in current literature:

- Whether liver regeneration, demonstrated in PH setting, occurs only due to cellular hyperplasia (activation of mitotic processes), or is there hypertrophy involved too? [48].

- Whether the growth of remaining tissue (regeneration) is provided by building up of new lobulae or enlargement of “old” lobulae, or does the reconstruction in specific lobular architecture take place? [3, 46, 47].

There is no unilateral answer to these questions, especially as DNA synthesis is interrupted after 72 hours past PH, and histological alterations are ceased too, thereafter [2,49]. Nevertheless, some authors stand for hyperplasia and enlargement of “old” lobulae [3]; there are some works claiming the unity and simultaneity of all above mentioned events [46]. At the same time, possible alternation of these events in time should not be excluded: implying, that degenerative/apoptotic processes could develop due to imperfection of integrative communications of neo-structures resulted from hyperplastic (mitotic) activity of the cells, with ensuing diminution of hepatocyte number, simultaneously, cellular hypertrophy could arise too and as a result, the volume of “regenerated” organ would be in sum sustained after PH. This suggestion is acceptable, considering that multiple repetitive (subsequential) liver PHs result in “depletion” of hepatic regeneration capacities and eventual death of the animal. Depletion of liver capacities is more likely to be considered with at least “co-existence” of concurrent hepatocyte hypertrophy phenomenon, than only with supposed mitotic hyperplasia.

Investigation of peculiarities of these processes require evaluation of hepatocyte, lobular and portal zone sizes, also assessment of mitotic and apoptotic indices in long-term dynamics after PH including post periods of repeated PHs [50].

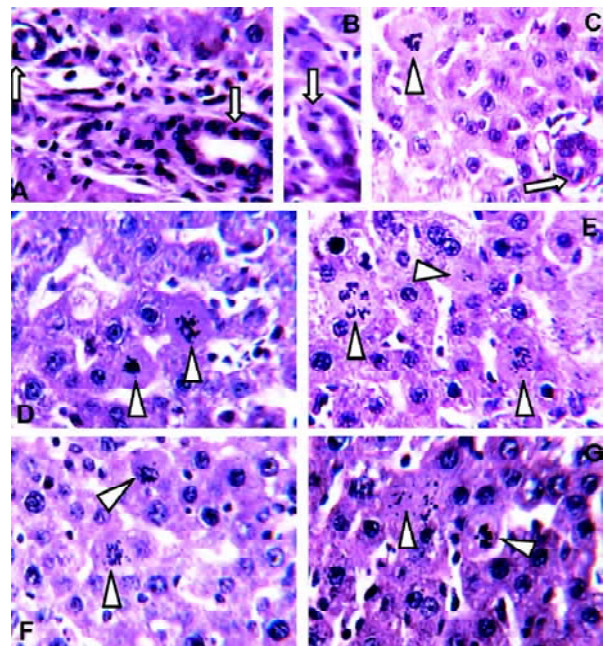


Fig. 5.
A, B, C – Mitoses of bile-duct epitheliocytes (arrows) and hepatocytes (arrowheads) on 72 hours after BDL.
D,E,F,G - Mitoses of hepatocytes (arrowheads) on 96 hours after BDL.

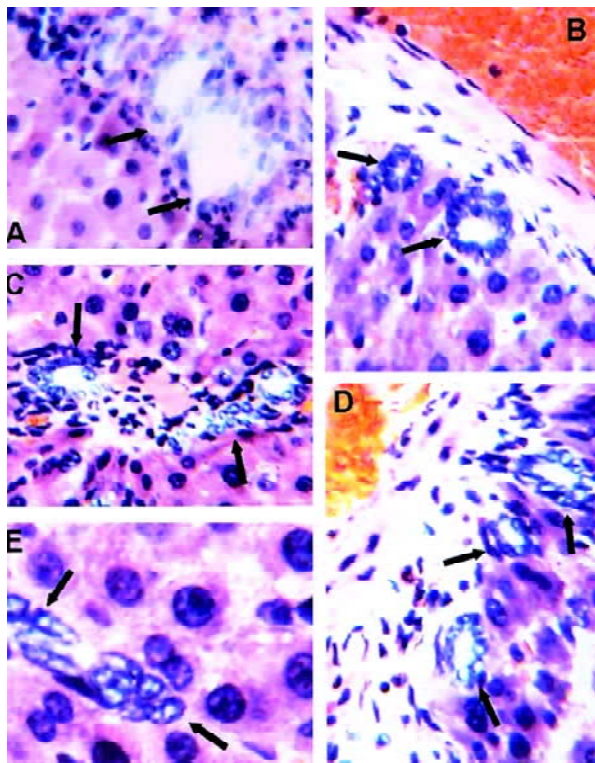


Fig. 6.
A,B,C,D,E – Ductular reaction in 6 hours after BDL.
Duct-like structures built up by epitheliocyte-type-cells with light cytoplasm (arrows).

Another subject of study is the possible involvement of stem (progenitor) cells in post-PH liver regeneration process [2,3,8,51-53]. In case of demonstrating such fact, the possible role of increased portal pressure in progenitor cell proliferation may be contemplated too [51,54].

What about the proliferative activity of the cells in BDL setting:

A significantly increased proliferative activity in common bile duct cells on the 2nd day after BDL has been reported [18]. It was accompanied by 3-4 fold activation of hepatocyte mitoses and endotheliocyte proliferation [55]. The results of our study revealed that increasing biliary pressure in BDL setting is accompanied by portal pressure increment. This kind of correlation between portal and biliary pressures, as well as structural changes in biliary and vascular compartments, as the backgrounds for this correlation, LSO have been described previously [56, 57].

Table 2 displays, that epitheliocyte mitoses reach the peak on the 3rd day, whereas the peak of hepatocyte mitoses develops on the 4th day after operation, in case of increased biliary/portal pressure. The latter peculiarity has been as well reported by us in previous works [10]. We have also demonstrated that pressure increase

in common bile duct results in proliferation of biliary epitheliocytes just in several hours. Moreover, we demonstrated that yet completely underdeveloped, duct-like structures may be found in periportal zones, built up by light-coloured cytoplasm epitheliocytes. It should be underlined, that no mitotic bodies were found in any of these structures [58].

The given study actually evidences that pressure rise in common bile duct already in the first hours results in “ductular reaction”. Regardless of what could be considered as a reason for creation of such “neoductules” – implying the proliferation/differentiation of already existing cholangiocytes or stem (oval, progenitor) cells [20,59-65], or other cells – the absence of mitotic bodies at this site still has to be clarified anyway.

We admit the established role of biliary hypertension in triggering of epitheliocyte proliferation, as reported by other authors too [66]. We may suggest, that biliary hypertension alters the time and regimen of ERG expression “schedule” in “ductular cells” (this concept was previously verified by us on hepatocyte model, in the setting of simultaneous BDL and PH [8,9,23] and leads to their active proliferation in the very first hours. (Unfortunately, the study of ERG expression in cholangiocytes, which would be able to confirm or cancel this suggestion, was complicated due to their small amount and difficulty of isolation).

Subsequently, when biliary pressure begins to rise in bile capillaries (that is, in spaces enclosed by hepatocytes), ERG expression in hepatocytes is initiated too. Previously we have shown that ERG expression in hepatocytes does not commence until first 8 hours after BDL. It may be suggested that it begins after more than 8 hours past BDL, e.g. on 10th, 12th, 14th etc. hours, which later on is followed by mitotic activity, e.g. on 2nd day after BDL. Thus, it is quite probable, that the biliary pressure rise in BDL setting appears to be the trigger for hepatocyte genes expression, with subsequent DNA synthesis and mitosis activation.

In PH setting, portal pressure alteration applies a direct effect to hepatocytes and non-parenchymal cells (NPC), without affecting cholangiocytes. Consequently, proliferation begins in hepatocytes, but mitotic wave in biliary epitheliocytes become activated later, by the influence of humoral factors (including growth factors and others), secreted by proliferating hepatocytes and NPCs.

Different scene comes up in BDL setting, when biliary pressure primarily acts on cholangiocytes with progressive intensity and later on, applies effect to hepato-

cytes and NPCs, thereby resulting in similarly progressive proliferating activity in these cells. It is also likely, that triggering of hepatocyte and NPC proliferation is supported by the factors released by proliferating cholangiocytes.

It also should be denoted that on the 4th day after BDL, when significant activation in hepatocyte mitoses is revealed, ERG expression still can't be found. The following suggestions can be made with regard to this concern:

1) ERG expression could develop on 10th, 12th, 14th etc. hours after BDL (as already indicated above), might have reached the peak and returned to normal level by the 4th day. Yet for this time, mitoses "triggered" by it would still be persisting;

2) In the setting of cholestasis, unusual, alternative mechanisms for hepatocyte and biliary epitheliocyte proliferation may be developing [67,68] with participation of primary mitogen, e.g. TNF- α , induced by BDL [13]. Stimulation of hepatocyte proliferation is induced by binding of TNF- α to respective TNF1 receptor. This chemical binding promotes the prolonged activation of NF- κ B, which is followed by transcription of immediate early genes (except c-foc), activation of cycline genes and transition of the cell in S-phase of cellular cycle. It should be underlined, that levels of HGF and TNF- α remain unchanged at this time. This kind of mitogen-provided hepatocyte proliferation (hepatocyte DNA synthesis) is considered to be mediated by activation (proliferation) of NPCs of the liver (including Kupfer cells, sinusoidal endotheliocytes, Ito cells etc.).

Another possible mechanism for immediate hyperplasia implies the following suggestion: immediate mitogenes, like peroxisome proliferators (PP) – BR931, nafenopin and retinoids (9-cis retinoic acid), without binding to transmembrane receptors, pass through the cell membrane by diffusion and bind to respective nuclear receptors, namely to PPAR (PP-activated receptor – belongs to the group of steroid hormone nuclear receptors), and PXR (retinoic X-receptor), which leads to the formation of PPAR-PXR hetero- and PXR-PXR homodimers, representing transcriptional factors themselves, which, via later effects, directly activate the cycline genes. It should be emphasized, that activation of other transcriptional factors, including NF- κ B, immediate early genes, HGF and TNF- α does not take place [13].

The concept of NPC-mediated direct hyperplasia in hepatocytes is as well supported by the fact that in the very first hours after BDL intracellular bile transport changes its direction from biliary pole towards sinusoidal pole of hepatocytes, with subsequent passage of bile

components into spaces of Disse and Mall (this phenomenon, like other authors, was evidenced by us too) [69]. The latter leads to activation of situated here NPCs (including fibroblasts), which, together with other processes, increases collagen synthesis and triggers the fibrotic alterations in liver.

On the other hand, intracellular transport of bile components is mediated by peroxisomes and lysosomes. Peroxisomes participate in the synthesis of bile acids as well. In BDL setting these processes appear deranged. In such circumstances, the expected (possible) compensatory hyperplasia of peroxisomes with supporting concentration rise in peroxisome proliferators, may become an additional argument for admitting the peroxisomal mechanism for direct hyperplasia of hepatocytes in BDL setting. This assumption can be verified by immunohistochemical method, via demonstrating the hyperexpression of peroxisomal markers in BDL setting.

However, in case of assuming the possibility of direct hepatocyte hyperplasia in BDL setting, activation of apoptosis should be expected following the transition period, after mitotic peak [13,70].

Obviously, verification or disapproval of all above mentioned statements requires further investigation. Moreover, conduction of specially designed experiments are necessitated, implying the repeated studies on every single hour at first day of BDL (for assessing DNA synthesis and mitotic activity in cholangiocytes) and with small intervals at subsequent days, for assessing the similar measures and apoptotic activity as well, in every cell populations (6-10 days are accepted as optimal period for cholestasis modelling) [69]. The study of "ductular reaction" at early stages of BDL, by application of immunohistochemical markers for cell types and proliferative features, also pertains to the subjects of primary concern.

What concerns the study of ERG expression in cholangiocytes, due to the obstacles mentioned above, it requires the inclusion of large-sized animals, like dogs, which will provide the separation of target cells in adequate amounts; Otherwise, modelling of bile influence on epitheliocyte apical membranes with certain pressure in biliary epithelial cell cultures could be contemplated.

Conclusion

Portal and biliary hypertension appear to be the major stimulating factors for cellular proliferation in PH and BDL settings;

Factors supporting post-PH liver regeneration and post-BDL ductular proliferation are released in liver tissue, subjected to the influence of increased pressure;

however, both - the dynamics and the mechanisms of this processes require further profound investigation;

Complete and accurate evaluation of post-PH liver regeneration and post-BDL biliary ductule proliferation

events require not only shortening of inter-experimental intervals and refinement of morphological or molecular-biological techniques, but also contriving of experimental models corresponding to novel approaches.

სამედიცინო მეცნიერებანი

პორტული და ბილიური ჰიპერტენზია, როგორც უჯრედთა პროლიფერაციის ინდუქტორი (მომავალ კვლევათა ორიენტირები)

დ. კორძაია

ალექსანდრე ნათიშვილის მორფოლოგიის ინსტიტუტი, თბილისი

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ცნობილია, რომ როგორც პარციული ჰეპატექტომია (პპ), ისე ნაღვლის საერთო სადინარის ოკლუზია (ნსსო) იწვევს ღვიძლის ქსოვილში უჯრედთა პროლიფერაციის მკვეთრ გააქტიურებას. ამასთანავე, აღნიშნული გააქტიურების მიზეზები საბოლოოდ დადგენილი არ არის.

კვლევის მიზანს წარმოადგენდა პპ-ისა და ნსსო-ის მოდელებში ჰეპატოციტებისა და სადინარების ეპითელიოციტების პროლიფერაციული აქტივობის შედარებითი დაზუსტება და ამ მიმართულებით მომავალი კვლევების არეალის განსაზღვრა.

ექსპერიმენტები ჩატარებულია II პოსტპუბერტული ასაკის 200-220 გრ 54 თეთრ მამრ ვირთაგვანზე. პარციულ ჰეპატექტომიას ვაზორციელებდით მარცხენა ლატერალური და მარცხენა მედიალური წილების რეზექციით, ამ წილების პორტული კომპლექსების და შესაბამისი ღვიძლის ვენების (ღრუ ვენის შენაკადის) წინასწარი გადაკვანძვით, დარჩენილი წილების დაზიანების გარეშე. ნაღვლის შეუშებას ვიწვევდით ნაღვლის საერთო სადინარის ორ ლიგატურას შორის გადაკვეთით. ღვიძლის ქსოვილის ჰისტოლოგიურ გამოკვლევას ვატარებდით პარაფინში ჩაყალიბებულ და ჰემატოქსილინ-ეოზინით შეღებულ ანათლებზე. სამიზნე უჯრედთა მიტოზურ აქტივობას ვაფასებდით სერიულ ანათლებზე 30 მხედველობის ველზე ჯამური 480 გადიდების პირობებში, მიტოზთა ე.წ. “წინასწარი დაგროვების” მეთოდის (კოლხიციანის) გამოყენების გარეშე.

პპ-ს დაქვემდებარებულ ჯგუფში წნევას კარის ვენაში ვზომავდით როგორც პპ-მდე, ისე უშუალოდ პპ-ის შემდეგ, ასევე ოპერაციიდან 6, 24, 48 და 144 საათის შემდეგ. მიტოზის ფიგურებს ვითვლიდით უშუალოდ პპ-ის შემდეგ, ასევე ოპერაციიდან 6, 32, 72 და 144 საათის შემდეგ. ნსსო-ს დაქვემდებარებულ ჯგუფში წნევას ნაღვლის საერთო სადინარში ვზომავდით – ოკლუზიამდე და ოპერაციიდან 1, 3, 72, 96, 120 და 144 საათის შემდეგ, ხოლო კარის ვენაში 1, 6, 24, 72, 144 საათის შემდეგ. მიტოზის ფიგურებს ვითვლიდით ნსსო-დან 24, 48, 72, 96, 120 და 144 საათის შემდეგ. ანალოგიური გამოკვლევები ტარდებოდა საკონტროლო ჯგუფშიც.

მიღებული მონაცემების ანალიზისა და ადრე ჩატარებული კვლევების შედეგებთან შეჯერების საფუძველზე გამოტანილია დასკვნა:

პარციული ჰეპატექტომიისა და ნაღვლის საერთო სადინარის ოკლუზიის პირობებში განვითარებულ უჯრედთა პროლიფერაციის მასტიმულირებელს წარმოადგენს პორტული და ბილიური ჰიპერტენზია;

პარციული ჰეპატექტომიის შემდგომი ღვიძლის რეგენერაციის და ნაღვლის საერთო სადინარის

ოკლუზიის შემდგომი ნაღვლის დუქტულების პროლიფერაციის პროცესის სრულად შეფასებისათვის, მნიშვნელოვანია არა მარტო ექსპერიმენტების ვადებს შორის ინტერვალების შემცირება და კვლევის მორფოლოგიური თუ მოლეკულურ-ბიოლოგიური მეთოდების დახვეწა, არამედ ახალი მიდგომების შესაბამისი ექსპერიმენტული მოდელების შემუშავება.

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