Journal of Pharmacology and Toxicology

ISSN 1816-496X

Academic Journals Inc.

www.academicjournals.com

Journal of Pharmacology and Toxicology 6 (1): 24-29, 2011
ISSN 1816-496X / DOI: 10.3923/jpt.2011.24.29

Pathways of Hepatic Regeneration and Pharmacological Approaches for Hepatoprotection: A Brief Approach

J.A. Ansari and M. Jamil
Faculty of Pharmacy, Hamdard University, New Delhi-110062, Delhi, India

Corresponding Author: Javed Akhtar Ansari, Department of Pharmacology, Faculty of Pharmacy, Hamdard University, New Delhi-110062, Delhi, India

ABSTRACT

Liver is one of the most important organs in the metabolism of food, drugs, endogenous and exogenous substances. Problems related to liver such as acute or chronic inflammation, toxin-/drug-induced hepatitis, cirrhosis and hepatitis are well-known nowadays due to our exposure to different environmental pollutants like chemicals, toxins, viruses etc. Liver disease can result from dosage-dependent hepatotoxicity or from adverse reactions to drugs used in therapeutic dosage. The anatomical structures of a liver that has undergone partial hepatectomy are therefore distinctly different from those of the original liver. The restoration process of liver volume in humans is initiated by the replication of various types of intra hepatic cells, followed by an increase in cell size. Efforts to develop pharmacologic means for liver protection from damage during regeneration have identified a few molecular targets.

Key words: Microanatomy, regeneration pathway, hepatic dysfunctions, pharmacological hepatoprotection

INTRODUCTION

It is well recognized that liver is one of the most important organs in the metabolism of food, drugs, endogenous and exogenous substances. Profuse supply of blood and the presence of many redox systems (e.g., cytochromes and various enzymes) causes liver to convert these substances into different kinds of inactive, active or even toxic metabolites. Problems related to liver such as acute or chronic inflammation, toxin-/drug-induced hepatitis, cirrhosis and hepatitis are well-known nowadays due to our exposure to different environmental pollutants like chemicals, toxins, viruses etc. (Dhiman and Chawla, 2005).

Liver: Liver is the largest organ in the body weighing 1200-1500 g. It is a key organ in regulating homeostasis within the body. The liver is one of the few organs which can regenerate after injury or disease. Total liver blood flow is about 1300 mL min^{-1} (Roger and Edwards, 2003).

Structure of liver: The liver consists of four sections, or lobes. There are two main lobes-the right lobe, which is by far the larger and the left lobe. Two small lobes lie behind the right lobe (Fig. 1).

Microanatomy of liver: Liver essentially made up of a series of channels or sinusoids, running between plates of hepatocytes. These are lined by endothelial cells. Specialised phagocytic (reticulo

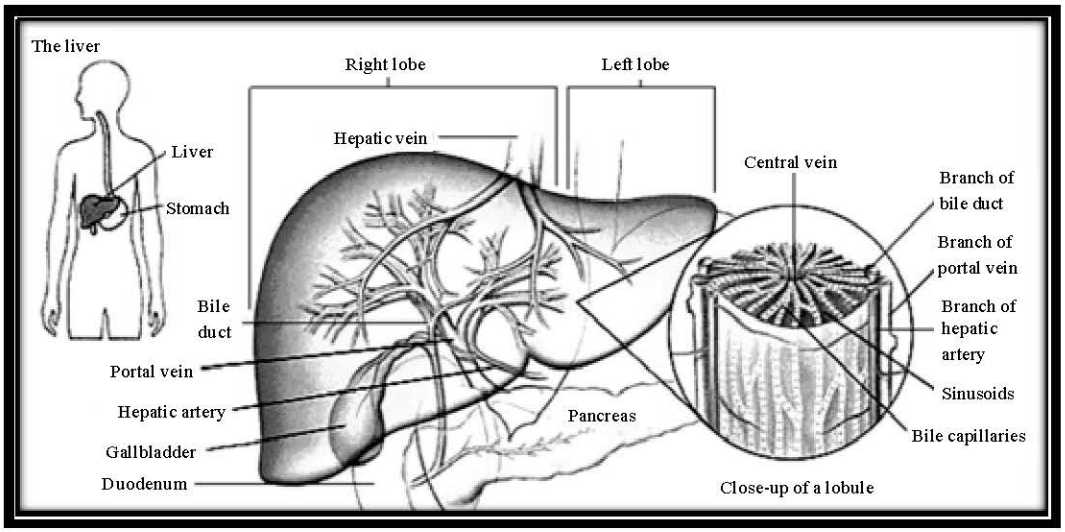

Fig. 1: Structure of liver

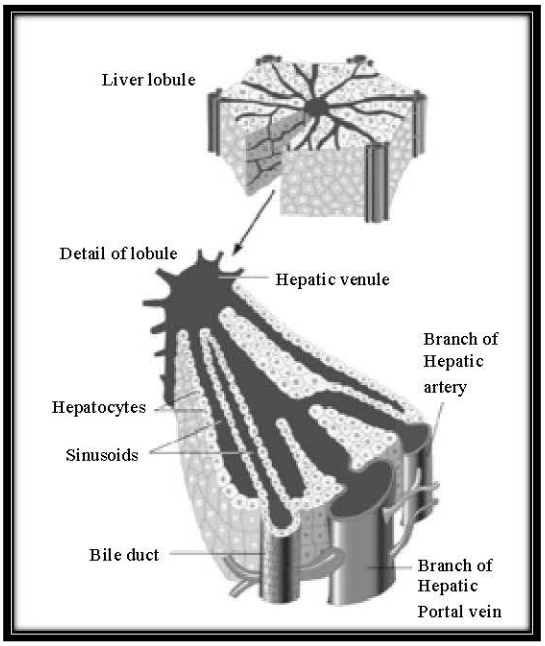

Fig. 2: Microanatomy of liver

endothelial) cells (Kupffer cells) are also present in sinusoids. Each lobe is consisting of multisided units called lobules. Most livers have between 50,000 and 100,000 lobules. Each lobule consists of a central vein surrounded by tiny liver cells grouped in sheets or bundles. These cells perform the work of the liver. Cavities known as sinusoids separate the groups of cells within a lobule. The sinusoids give the liver a spongy texture and enable it to hold large amounts of blood (Fig. 2) (Cunningham and Van Horn, 2003). The liver consists of four systems:

- Hepatocyte (liver cell) system
- Biliary tract system
- Blood circulatory system
  - Dual blood circulatory system:

  The blood in the liver is supplied by two sets of blood circulatory systems:

    - Systemic circulation
    - Portal circulation
  - Blood flow of the liver: 1,300 cc of blood flow into the liver every minute, it is about 1/4 of the cardiac output
  - 3/4 of the blood in the liver is supplied by the portal system and the remaining 1/4 is supplied by hepatic artery from systemic circulation
  - The liver receives blood from both the intestine and the heart. The blood then flows through a latticework of tiny channels inside the liver. Blood from the intestine and heart then mix together and flow back to the heart through the hepatic vein
- Reticulo-endothelial system
  - Kupffer cells: highly mobile macrophages, attached to the endothelium, phagocytic
  - Lipocytes (Ito cells): fat-storing cells in the sinusoids
  - Pit cells: highly mobile, natural killer lymphocytes attached to the endothelium
  - Endothelial cells (Cunningham and Van Horn, 2003)

Hepatic dysfunctions: Liver disease can result from dosage-dependent hepatotoxicity or from adverse reactions to drugs used in therapeutic dosage. The idiosyncratic hepatotoxins can cause clinical syndromes that mimic all known liver diseases, so that drugs must be considered as the possible causal agent for all unexplained cases of liver disease (Javed *et al*., 2009).

Many hepatic dysfunctions are accompanied by jaundice caused by increased levels of bilirubin in the system. The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile.

- Hepatitis, inflammation of the liver, caused mainly by various viruses but also by some poisons, autoimmunity or hereditary conditions
- Cirrhosis is the formation of fibrous tissue in the liver, replacing dead liver cells. The death of the hepatic cells can for example be caused by viral hepatitis, alcoholism or contact with other liver-toxic chemicals
- Hemochromatosis, a hereditary disease causing the accumulation of iron in the body, eventually leading to liver damage
- Cancer of the liver (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the gastrointestinal tract)
- Wilson's disease, a hereditary disease which causes the body to retain copper
- Primary sclerosing cholangitis, an inflammatory disease of the bile duct, autoimmune in nature.
- Primary biliary cirrhosis, autoimmune disease of small bile ducts
- Budd-Chiari syndrome, obstruction of the hepatic vein
- Gilbert's syndrome, a genetic disorder of bilirubin metabolism, found in about 5% of the population (David and Thomas, 2003)

Liver regeneration: The human body acts to partial hepatectomy not by regenerating lost segments but by inducing hyperplasia in the liver remnant. The anatomical structures of a liver that has undergone partial hepatectomy are therefore distinctly different from those of the original liver. The restoration process of liver volume in humans is initiated by the replication of various types of intra hepatic cells, followed by an increase in cell size. The onset and peak of hepatocyte replication vary among species. In humans, replication of hepatocytes generally starts within 1 day after a major resection. Non parenchymal cells, such as endothelial cells, Kupffer cells (macrophages resident in the liver) and biliary-duct cells, replicate in a delayed fashion. After completion of replication, growth consisting of an increase in cell size occurs over several additional days (Taub, 2004; Michalopoulos and DeFrances, 2005; Fausto *et al*., 2006). The initiation and synchronization of replication in different types of hepatic cells depend on the degree of the resection, tissue damage, or both. Low-grade tissue damage (e.g., toxic or ischemic injury) or a comparatively small resection (removal of less than 30% of the liver) substantially reduces the replication rate, which also appears to be less synchronized than after a large resection (removal of 70% of the liver) (Taub, 2004; Fausto *et al*., 2006; Nocito *et al*., 2007). After a massive resection, up to 90% of the hepatocytes appear to replicate (Taub, 2004).

Molecular basis of liver regeneration: Liver regeneration has been studied in murine models, an approach that permits the determination of cellular events and the analysis of the molecular triggers governing regeneration (Taub, 2004; Michalopoulos and DeFrances, 2005; Fausto *et al*., 2006). In short, the process of liver regeneration involves mediators similar to those found in acute inflammation. Usually, hepatocytes are in the quiescent G0 phase. After resection, the remaining hepatocytes enter the G1 phase. Cytokines derived predominantly from Kupffer cells prime hepatocytes; tumor necrosis factor α (TNF-α) and, then, interleukin-6 are released, contributing to the initiation of the cell cycle (Cressman *et al*., 1996; Yamada *et al*., 1997). Mitogenic factors are needed for the regenerative process to enter the S phase, primarily growth factors such as epidermal growth factor, hepatocyte growth factor and transforming growth factor α (TGF-α) (Mead and Fausto, 1989; Pediaditakis *et al*., 2001). Integration of these signals induces full and synchronized regeneration. Failure to activate this signal cascade can result in a delay in the onset of regeneration, inadequate recovery of liver volume and finally clinical signs of liver failure (Tian *et al*., 2006).

Termination of the regenerative steps appears to be controlled by the action of transforming growth factor α (TGF-β) and other members of the activ in family (Strain *et al*., 1987). Two newer reports shed further light on the mechanisms of regeneration. In one report from our group, platelets (thrombocytes) were shown to be critically involved in regeneration (Lesurtel *et al*., 2006). Serotonin, a neurotransmitter transported within the peripheral circulation by platelets, appears to be a co-mitogen that is essential for liver regeneration. Mice deficient in tryptophan hydroxylase (Taub, 2004), which lack peripheral serotonin, have diminished hepatocyte proliferation after partial hepatectomy (Lesurtel *et al*., 2006).

According to another recent report, bile acids also seem to influence regeneration. In experiments in animal models in which bile-acid pools were high, regeneration was complete, whereas low bile flow was associated with reduced hepatocyte replication. The signal responsible for this feedback mechanism of regeneration is a nuclear bile receptor, the farnesoid X receptor. This mechanism may be important in integrating the metabolic load of the liver and may have a direct action on regeneration (Huang *et al*., 2006). The integration of all these signals is important for full and synchronized regeneration.

Pharmacological approaches for hepatoprotection: Efforts to develop pharmacologic means for liver protection from damage during regeneration have identified a few molecular targets. It has recently been shown that pentoxifylline (Trental, Hoechst-Roussel), an inhibitor of TNF-α synthesis in Kupffer cells that has other properties such as vasodilatation and induction of the interleukin-6 pathway, decreases the likelihood of inadequate liver function in the liver remnant in a murine model of partial liver transplantation (Tian *et al*., 2006). Pretreatment of a small graft (30% of the total liver volume) and of the recipient with pentoxifylline prevents lethal outcomes and fully restores regeneration (Cressman *et al*., 1996). Acetylcysteine, a precursor of glutathione, has been widely explored as a protective molecule. Clinical trials of its use in the perioperative treatment of patients undergoing liver transplantation showed reduced levels of circulating selectins (Weigand *et al*., 2001) and a reduction in the severity of rejection in pediatric patients undergoing hepatic transplantation (Bucuvalas *et al*.,2001), but neither study showed an overt benefit for the patient.

Other molecules, such as cardiotrophin-1, a member of the interleukin-6 cytokine family, have shown a hepatoprotective potential in preventing regeneration and in animal survival after 90% hepatectomy in rats (Bustos *et al*., 2003). Drugs with a reduction in portal pressure, such as somatostatin (Xu *et al*., 2006), fingolimod (FTY720, Novartis Pharma) (Zhao *et al*., 2004), or the low-dose nitric oxide donor FK 409 provided significant protection in animal models of smallgraft transplantation. These drugs have additional activities that might contribute to protection, such as down-regulation of endothelin-1, up-regulation of heme oxygenase-195 or interleukin-10, (Man *et al*., 2004) and activation of Akt signaling, which has been shown to be related to cell survival (Zhao *et al*., 2004). An immunosuppressive agent, sirolimus (Rapamune, Wyeth-Ayerst), has also been shown to reduce injury and improve survival-effects that may be related to suppression of the activation of hepatic stellate cells in a model of partial graft transplantation in cirrhotic rats (Man *et al*., 2006). Although, these strategies have been successful in animal models, their usefulness in humans remains to be demonstrated in clinical trials.

REFERENCES

Bucuvalas, J.C., F.C. Ryckman, S. Krug, M.H. Alonso, W.F. Balistreri and U. Kotagal, 2001. Effect of treatment with prostaglandin E1 and N-acetylcysteine on pediatric liver transplant recipients: A single-center study. Pediatr Transplant., 5: 274-278.

Bustos, M., N. Beraza, J.J. Lasarte, E. Baixeras, P. Alzuguren, T. Bordet and J. Prieto, 2003. Protection against liver damage by cardiotrophin-1: A hepatocyte survival factor upregulated in the regenerating liver in rats. Gastroenterology, 125: 192-201.

Cressman, D.E., L.E. Greenbaum, R.A. De Angelis, G. Ciliberto, E.E. Furth and V. Poli 1996. Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. Science, 274: 1379-1383.

Cunningham, C.C. and C.G. Van Horn, 2003. Energy availability and alcohol-related liver pathology. Alcohol Res. Health, 27: 281-299.

David, Z. and D.B. Thomas, 2003. Hepatology: A Textbook of Liver Disease. 4th Edn., W. B. Saunders Co., Philadelphia, ISBN: 0-7216-9051-3.

Dhiman, R.K. and Y.K. Chawla, 2005. Herbal Medicines for liver diseases. Digestive Dis. Sci., 10: 1807-1812.

Fausto, N., J.S. Campbell and K.J. Riehle, 2006. Liver regeneration. Hepatology, 43: S45-S53.

Huang, W., K. Ma, J. Zhang, M. Qatanani and J. Cuvillier *et al*., 2006. Nuclear receptor-dependent bile acid signaling is required for normal liver regeneration. Science, 312: 233-236.

Javed, A., A.M. Khan and M.B. Anwar, 2009. Liver toxicity caused by synthetic drugs. J. Chem. Pharm. Sci., 2: 265-269.

Lesurtel, M., R. Graf, B. Aleil, D.J. Walther and Y. Tian *et al.*, 2006. Platelet-derived serotonin mediates liver regeneration. Science, 312: 104-107.

Man, K., T.K. Lee, T.B. Liang, C.M. Lo, P.C. Fung and S.H. Tsui, 2004. FK 409 ameliorates small-for-size liver graft injury by attenuation of portal hypertension and down-regulation of Egr-1 pathway. Ann. Surg., 240: 159-168.

Man, K., M. Su, K.T. Ng, C.M. Lo and Y. Zhao *et al.*, 2006. Rapamycin attenuates liver graft injury in cirrhotic recipient: The significance of downregulation of Rho-ROCK-VEGF pathway. Am. J. Transplant., 6: 697-704.

Mead, J.E. and N. Fausto, 1989. Transforming growth factor alpha may be a physiological regulator of liver regeneration by means of an autocrine mechanism. Proc. Natl. Acad. Sci. USA., 86: 1558-1562.

Michalopoulos, G.K. and M. DeFrances, 2005. Liver regeneration. Adv. Biochem. Eng. Biotechnol., 93: 101-34.

Nocito, A., P. Georgiev, F. Dahm, W. Jochum, M. Bader, R. Graf and P.A. Clavien, 2007. Platelets and platelet-derived serotonin promote tissue repair after normothermic hepatic ischemia in mice. Hepatology, 45: 369-376.

Pediaditakis, P., J.C. Lopez-Talavera, B. Petersen, S.P. Monga and G.K. Michalopoulos, 2001. The processing and utilization of hepatocyte growth factor/scatter factor following partial hepatectomy in the rat. Hepatology, 34: 688-693.

Roger, W. and C. Edwards, 2003. Clinical Pharmacy and Therapeutics. 3rd Edn., Churchill Livingstone: Elsevier Publication, Canada, pp: 209-210, 214, 226.

Strain, A.J., A. Frazer, D.J. Hill and R.D. Milner, 1987. Transforming growth factor beta inhibits DNA synthesis in hepatocytes isolated from normal and regenerating rat liver. Biochem. Biophys. Res. Commun., 145: 436-442.

Taub, R., 2004. Liver regeneration: From myth to mechanism. Nat. Rev. Mol. Cell. Biol., 5: 836-847.

Tian, Y., W. Jochum, P. Georgiev, W. Moritz, R. Graf and P.A. Clavien, 2006. Kupffer cell-dependent TNF-alpha signaling mediates injury in the arterialized small-for-size liver transplantation in the mouse. Proc. Natl. Acad. Sci. USA., 103: 4598-4603.

Weigand, M.A., J. Plachky, J.C. Thies, D. Spies-Martin, G. Otto and E. Martin, 2001. N-acetylcysteine attenuates the increase in alpha-glutathione S-transferase and circulating ICAM-1 and VCAM-1 after reperfusion in humans undergoing liver trans-plantation. Transplantation, 72: 694-698.

Xu, X., K. Man, S.S. Zheng, T.B. Liang, T.K. Lee and K.T. Ng, 2006. Attenuation of acute phase shear stress by somatostatin improves small-for-size liver graft survival. Liver Transplant., 12: 621-627.

Yamada, Y., I. Kirillova, J.J. Peschon and N. Fausto, 1997. Initiation of liver growth by tumor necrosis factor: Deficient liver regeneration in mice lacking type I tumor necrosis factor receptor. Proc. Natl. Acad. Sci. USA., 94: 1441-1446.

Zhao, Y., K. Man, C.M. Lo, K.T. Ng and X.L. Li *et al.*, 2004. Attenuation of small-for-size liver graft injury by FTY720: Significance of cell-survival Akt signaling pathway. Am. J. Transplant., 4: 1399-1407.