

# The emerging role of serotonin in liver regeneration

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## Summary

Serotonin has a multifunctional role in many different organs serving either as a neurotransmitter in the central nervous system or a paracrine factor in the gastrointestinal tract. Over 90% of serotonin is synthesised in the enterochromaffin cells of the intestine and subsequently taken up by platelets. The involvement of platelet-derived serotonin in liver mass restoration after partial hepatectomy or toxic injury has been greatly investigated during the last decade. There is a growing body of evidence implicating serotonin in hepatic regeneration through altered expression of serotonin receptor subtypes in the liver. This review article provides a brief overview on the current knowledge about the actions of serotonin in liver regeneration.

**Key words:** *liver regeneration; serotonin; partial hepatectomy*

## Introduction

The amazing ability of the liver to regenerate following partial resection or injury is unique, especially because the highly differentiated functions of the organ are totally maintained. Partial hepatectomy (PH) has been widely used for long as an experimental model in order to gain a deeper understanding of the underlying mechanisms of liver regeneration. The presence of numerous diverse ligands in the initiation, propagation and termination of the mitotic stimulus, such as priming factors, co-mitogens, growth factors and their suppressors, is necessary for the successful and complete restoration of hepatic mass [1, 4]. Neurotransmitters have from long attracted the scientific interest about their possible role in liver regeneration after either PH or toxic liver injury. Catecholamines are now well known comitogens for hepatocytes and their plasma levels have been shown to increase significantly within the first two hours after PH [5, 7].

Although the possible involvement of serotonin (5-hydroxytryptamine, 5HT) in liver regeneration has been hypothesised some decades ago, it was only quite recently extensively investigated in a variety of animal models. The

aim of this mini-review is to briefly summarise the interesting relationship between serotonergic system and liver regeneration and provide knowledge about the recent scientific evidence on the role of serotonin in liver regeneration.

## Serotonin physiology

Serotonin is an evolutionarily conserved biogenic monoamine neurotransmitter with variable effects on many different target organs. It can be classified among neurotransmitters participating in appetite modulation, circadian rhythm regulation, and platelet contraction among others or may be partly considered a hormone modulating gastrointestinal tract motility [8, 9]. It is derived from the aminoacid L-tryptophan, which is hydroxylated to 5-hydroxy-L-tryptophan (5-HTP) by tryptophan hydroxylase (Tph), the rate-limiting step in serotonin biosynthesis. 5-HTP is then converted to serotonin, which can not cross the blood-brain barrier contrary to its precursor molecules L-tryptophan and 5-HTP [10, 11]. As a consequence serotonin is required to be synthesised de novo within the serotonergic neurons of the central nervous system, where it participates in the modulation of variable actions, such as mood, sleep and appetite [12, 14].

More than 90% of the total body serotonin is located in the enterochromaffin cells in the gut, where it regulates intestinal motility [15]. The secretion of serotonin from the intestinal enterochromaffin cells is followed by its platelet uptake which is dependent on the serotonin transporter (SERT). Platelets do not synthesise serotonin, but store and release it in sites of injury where it contributes to platelet recruitment and thrombus propagation [16, 17]. In the absence of an extracellular enzyme to catabolise serotonin in brain and gut, SERT has the important role in terminating its action. The enzymes monoamine oxidase and aldehyde dehydrogenase can convert serotonin to 5-hydroxyindoleacetic acid (5-HIAA) excreted in urine. The 5-HIAA urine concentration can be measured and reflects changes in whole body serotonin levels [18, 20].

### Serotonin receptors

Seven families of 5-HT receptors (5-HT1-7), comprising a total of 14 subtypes with structural and functional diversities, have been identified. Of these 5-HT receptor subtypes all but 5-HT3 receptor are metabotropic. 5-HT3 receptor is a ligand-gated, postsynaptically located nonspecific cation channel, which is modulating ion flux. The other 5-HT receptors are G-protein-coupled causing either hyperpolarisation or depolarisation of the cell membrane. 5-HT1A, 5-HT1B and 5-HT1D subtypes are presynaptic autoreceptors that inhibit serotonin release by a direct action of their associated G protein by opening  $K^+$  channels and hyperpolarising the cell membrane. 5-HT2A and 5-HT4 are postsynaptically located receptors, which belong to the G-protein receptor superfamily and along with 5-HT3 receptors, cause the depolarisation of the cell membrane. The expression and distribution of 5-HT receptors in different brain areas and in the periphery as well, is variable. As a paradigm, there is little evidence for expression of 5-HT2C receptors outside the central nervous system, while some others are located on the membrane of many different cellular populations, playing a pivotal role in the peripheral serotonergic neurotransmission [18, 21].

### Serotonin in liver regeneration

#### Brief overview of liver regeneration after partial hepatectomy in the rat

Hepatocytes are resting cells under normal conditions, but they are the first cells to divide after 60–70% PH with a peak in DNA synthesis at around 22–24h in young adult rats. Nonparenchymal liver cells, such as biliary ductal cells, Kupffer cells, stellate cells and endothelial cells divide 24h after hepatocytes [1-4, 22, 23]. Although rat liver regeneration continues up to 10 days after 60–70% PH, the major restoration of liver tissue has already been completed on the third postsurgical day. The regeneration process can be viewed as a sequence of events starting from an initial signal and comprises a priming phase, followed by a progression phase, a cell cycle phase and finally a termination signal [4, 24, 25]. The increase of portal vein pressure and liver tissue perfusion and the extracellular matrix remodeling may be considered as the initial events after PH [3, 4, 25, 26]. Shortly after, a great number of genes are activated (primed) and some of them encode transcrip-

tional factors, essential for the propagation of the mitotic stimulus. Priming phase urge hepatocytes from quiescence to G1 phase of the cell cycle [4, 22]. Gene expression during priming phase is not capable by itself to promote liver regeneration after hepatectomy and a subsequent increase in growth factor levels is also necessary. Hepatocytes overcome the G1/S restriction point of the cell cycle only in the presence of growth factors and after this milestone they become committed to divide [22, 25, 27]. At least two intracellular signalling pathways, the MAPK and JAK-STAT, involved in liver regeneration have been identified. The MAPK (mitogen-activated protein kinase) pathway is activated after the binding of growth factors on specific cell membrane receptors leading to activation of Ras, Raf, MEK and ERK1/2 [28]. Early induction of MEK/ERK cascade is restricted to primed hepatocytes, distinguishing them from those returning to quiescence. On the other hand, the MAPK pathway activation at the late G1 phase of the cell cycle is mainly associated with cyclin D1 accumulation [29]. Expression of cyclin D1 highlights the point of G1/S transition point after which hepatocytes, independently of mitogens, can progress into the S phase of DNA synthesis [22, 29]. The activation of JAK-STAT pathway depends on the binding of cytokines to their receptors, which in turn results in the translocation of the transcription factor STAT3 into nucleus and the subsequent transcription of genes essential for the regenerative process [28].

#### Serotonin in liver regeneration

The involvement of serotonin in the induction of hepatocyte DNA synthesis was first investigated in primary cultures of adult rat hepatocytes by Balasubramanian et al. [30], which showed that 5-HT could significantly induce hepatocyte proliferation in the presence of insulin and EGF (epidermal growth factor). On the other hand, ketanserin, a 5-HT2 receptor antagonist [31], caused a significant displacement of [ $^3H$ ] 5-HT in the regenerating rat liver when administered at 24h after PH, the peak point of DNA synthesis, implying an increased involvement of the hepatic 5-HT2 receptor during the regenerative response [30]. In a more recent study by Liu et al. quipazine, a selective 5-HT receptor agonist with a high affinity for the 5-HT1D, 5-HT2B and 5-HT2C receptors led to a substantial improvement of proliferation rate in L-02 cell, a human hepatocyte strain, further supporting the mitogenic activity of serotonin [32].

5-HT2 receptor has been cloned from human liver and has a great homology with that of mouse and rat liver [33]. The expression of 5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT3A and 5-HT3B receptors has been identified in naïve mouse liver and the mRNA expression of 5-HT2A and 2B receptors, which are well known to mediate mitogenic and developmental effects, has been shown to increase after PH, while their antagonists inhibited liver regeneration [18, 34]. Our group investigated the effect of 5-HT2 blockage by ketanserin after 60–70% PH in rats and we found that its administration can arrest liver regeneration only when administrated close to the G1/S transition point implying that serotonin may be a cofactor for DNA synthesis. In the same study, we also measured the concentration of liver serotonin which started to increase

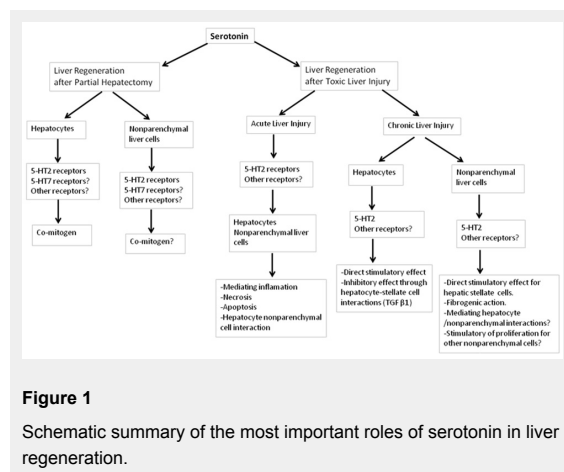


Figure 1

Schematic summary of the most important roles of serotonin in liver regeneration.

around the G1/S transition point and culminated at the time of maximal hepatic proliferative activity [35]. These data were in accordance with the study by Sulaiman et al. [36] which also showed that hepatic serotonin content significantly increased during hepatocyte DNA synthesis in rats after PH. The above similar findings strongly support a possible correlation between hepatic serotonin content and the rate of cell proliferation.

The mitogenic activity of serotonin has been also confirmed in a rat model of cirrhotic liver, where splenectomy-induced thrombocytosis led to an increase of serotonin content in the damaged liver with an acceleration of liver regeneration. Nevertheless, platelet content and plasma serotonin levels were not significantly affected indicating that the serotonin increase in the damaged liver might be attributed to modulation of hepatic hemodynamics after splenectomy. The subsequent ketanserin administration nullified the beneficial effect of splenectomy though without influencing the hepatic serotonin levels [37]. The effect of thrombopoietin-induced thrombocytosis or antiplatelet-antibody-induced thrombocytopenia on the hepatic regenerative process has also been investigated in a mouse model after 70% PH, where the number of platelets seemed to strongly correlate with hepatocyte proliferative capacity [38].

The importance of serotonin has also been shown by the failure of liver regeneration after PH in tryptophan hydroxylase 1 knockout mice lacking peripheral serotonin due to the absence of the rate limiting enzyme in 5-HT biosynthesis. However, the injection of the serotonin precursor 5-HTP restored the unimpeded progression of liver regeneration [39]. In the same study by Lesurtel et al. the administration of clopidogrel, an inhibitor of platelet aggregation, prevented hepatocyte proliferation after 70% PH emphasizing the role of platelet-derived serotonin [39]. However, in a more recent study the regenerative process has not been influenced in SERT-deficient rats where 5-HT was almost completely diminished in platelets indicating that its active platelet release is not possibly essential and only very low serotonin levels may be finally required [40].

The activation of 5-HT<sub>2B</sub> receptor has been also associated with improved survival rate in mice transplanted with a small, otherwise nonviable graft by enhancing liver regeneration and hepatic microcirculation. This finding may possibly be used to develop strategies for preventing liver failure, since the small-for-size syndrome is the single most important limiting factor in liver surgery and transplantation [41].

In a recent study in our laboratory, 5-HT<sub>7</sub> receptor blockade with competitive inhibitors greatly attenuated liver regeneration after 60–70% PH only when applied close to the G1/S transition point and this reveals an additional type of serotonin receptor mediating the proliferating action of the monoamine (work in process to be submitted for publication).

The effect of serotonin on liver regeneration has been investigated mainly regarding hepatocytes while less is known about possible proliferative effect of the monoamine on other liver cell subpopulations. Endothelial cells comprise the second most abundant cell type in the liver after hepatocytes and they have been reported to express

5-HT<sub>1D</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors at least in human umbilical veins [42, 43]. Previously published work has been controversial towards a ubiquitous mitogenic effect of serotonin on endothelial cells and this has also been confirmed in a recent study [44, 45]. At this point a possible angiogenic effect of serotonin during liver regeneration remains unknown. Finally and interestingly 5-HT<sub>7</sub> receptor has been very recently shown to be expressed in bovine corneal endothelial cells while its possible expression and up-regulation in hepatic endothelial cells in quiescent and regenerating liver has not been investigated [46]. Serotonin has also been reported to exert a proliferative effect on cholangiocytes and to promote cholangiocarcinoma growth [47, 48] while there are no data available regarding its role as a mitogen for cholangiocytes during liver regeneration. Hepatic stellate cells (HSCs) in humans and rats express 5-HT<sub>1B</sub>, 5-HT<sub>1F</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>7</sub> receptors with increased expression of 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> upon their activation [45, 49]. Among serotonin receptors 5-HT<sub>2B</sub> receptor has been strongly associated with increased HSC proliferation and liver fibrosis [49].

The interactions between hepatocytes and nonparenchymal cells during liver regeneration and disease have been partly investigated for HSCs and the contribution of HSCs in the regulation of hepatocyte proliferation has not been established [50]. HSCs have been reported to secrete numerous factors that influence hepatocyte proliferation, such as hepatocyte growth factor (HGF), transforming growth factor  $\beta$ 1 (TGF $\beta$ 1) and interleukin-6 [50, 53] with both stimulatory and inhibitory effects. The role of serotonin as a mitogen for HSCs during liver regeneration remains hugely unknown today. The same also applies for possible interactions between hepatocytes and HSCs during the regenerative process.

Additionally, there is evidence that serotonin may also play a role in liver regeneration at the cerebral level. This observation came from Pyroja et al. which showed that the exclusively centrally located 5-HT<sub>2C</sub> receptor in the brainstem and cerebral cortex may be up-regulated during liver regeneration after PH and in hepatic neoplasia resulting in hepatocyte proliferation probably through sympathetic stimulation [54]. The above data reflect the activation of multiple mechanisms both in CNS and in the periphery.

Apart from receptor-dependent signaling, serotonin also acts through receptor-independent signaling pathways by posttranslational modification of intracellular proteins. This process constitutes serotonylation and is mediated by the enzyme transglutaminase that creates glutamyl-amide bonds by attachment of serotonin to glutamine residues of intracellular proteins [55]. Serotonylation of small GTPases mediates exocytosis of platelet alpha granules [55] and insulin release from pancreatic beta cells [56] while the same covalent modification of vascular proteins is important for vascular contraction [57]. More recently serotonylation has been found to mediate serotonin-induced proliferation and migration of pulmonary artery smooth muscle cells [58]. No data are available today in relation to the role of serotonylation during liver regeneration after partial hepatectomy or toxic liver injury.

Figure 1 summarises the known effects of serotonin on liver regeneration.

### The controversial role of serotonin in the pathogenesis of liver diseases

Serotonin has been recently shown to mediate the pathology of many liver diseases, such as steatohepatitis, chronic cholestasis and liver cirrhosis, although the exact mechanisms still remain unclear [18, 48, 49, 59, 60]. Serotonin signalling seems to play a pivotal role in determining the balance between regeneration and fibrogenesis in chronic liver disease and recently it has been reported that activation of 5-HT<sub>2B</sub> receptor on fibrogenic HSCs suppresses hepatocyte proliferation through augmented production of TGFβ1 [61]. At the severe end of the spectrum, 5-HT has been involved in the pathogenesis of human hepatocellular carcinoma through increased 5-HT<sub>2B</sub> expression, which seems to facilitate the survival of carcinoma cells and to inhibit autophagy [62]. There are also some interesting reports suggesting that serotonin can potentially contribute to liver tissue hypoperfusion following hepatic ischemia and reperfusion in canines raising new dilemmas about its effects on hepatic regeneration [20, 63].

In an effort to further understand the effect of serotonergic system activation in the liver we examined the effect of 5-HT<sub>2</sub> receptor blockade in cadmium-induced acute hepatotoxicity in rats. The administration of ketanserin or ritanserin (selective 5-HT<sub>2</sub> receptor antagonist), prior and after the administration of a sublethal cadmium dose, resulted in a remarkable reduction of inflammatory and apoptotic indices [64].

Based on the above data, the development of serotonin receptor antagonists may be potentially used as therapeutic agents for the treatment of various liver diseases.

### Conclusion

Although the involvement of serotonin in liver regeneration has been initially suggested many years ago, it has only recently started being thoroughly studied. The results from many different experimental models have indisputably shown that the hepatocyte proliferative capacity can be substantially altered by the activation or blockade of the serotonergic system and especially the 5-HT<sub>2</sub> receptor subfamily. Moreover, there is increasing evidence that serotonin can be potentially associated with either beneficial or detrimental effects on liver regeneration and these actions are mediated through many different receptor subtypes located either centrally or peripherally. These observations pose a plethora of questions and provide also research opportunities, necessitating further work in the coming years.

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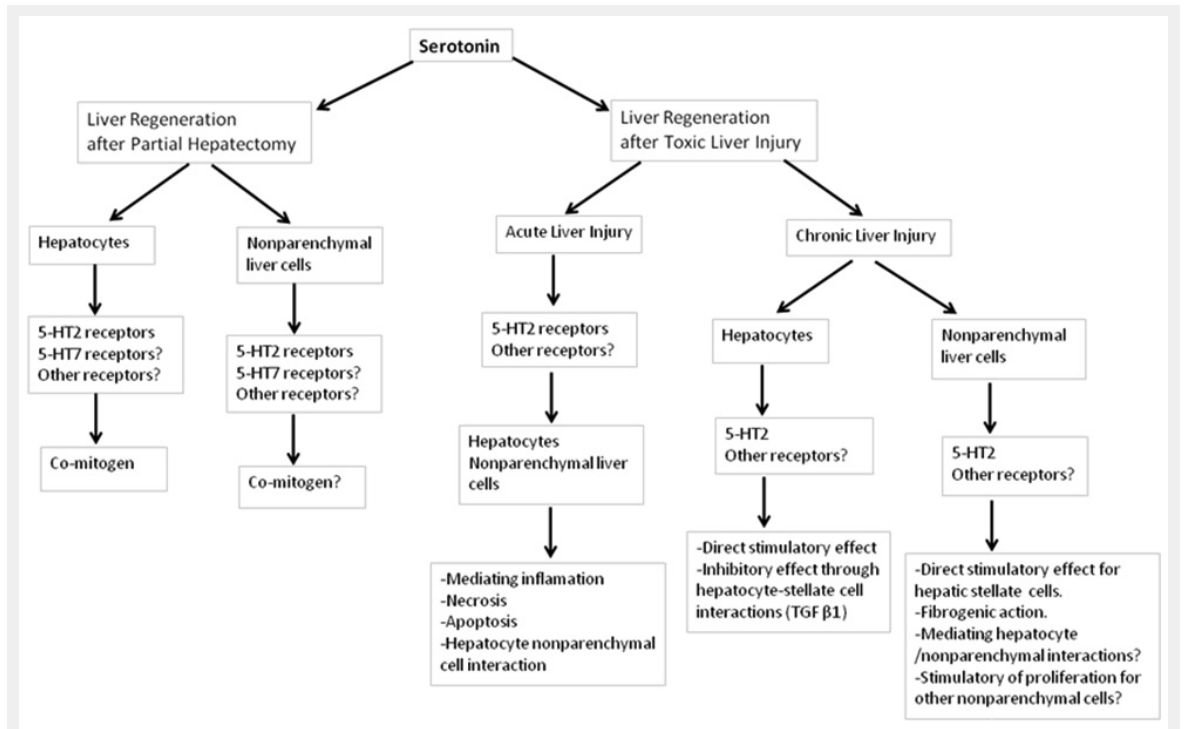
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Figures (large format)



**Figure 1**  
Schematic summary of the most important roles of serotonin in liver regeneration.