

Review

The function of serotonin within the liver[☆]

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Serotonin or 5-hydroxytryptamine (5-HT) is known to regulate several key aspects of liver biology and these functions include hepatic blood flow, innervation and wound healing. Given the importance of these functions it is surprising that relatively little time has been dedicated to studying the precise function and mechanisms of serotonin within the liver. Here we describe what is known about serotonin and the liver and those receptor types that mediate the observed effects with an aim to stimulating new interest in the field of serotonin and liver biology.

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1. Introduction

Serotonin also known as 5-hydroxytryptamine (5-HT) is a biogenic amine that functions as a ligand for a large family of 5-HT receptors [1]. The majority of serotonin in the body (90%) is synthesised by enterochromaffin cells of the gastrointestinal (GI) tract and from here it is exported to various sites around the body. Serotonin plays a major role in neurotransmission within the central nervous system (CNS) and the autonomic nervous system (ANS). It is often the expression patterns of the various serotonin receptors within the CNS and ANS that determine the systems controlled by serotonin. In the CNS serotonin is known to control

mood, behaviour, learning, sleep and anxiety to name but a few. Peripherally, serotonin is able to mediate vascular contraction and relaxation, gastrointestinal motility, cell proliferation, apoptosis and platelet aggregation. Serotonin is actively taken up by cells expressing the Na⁺/Cl[−] dependent serotonin transporter (SERT) where it is stored in intracellular vesicles and released in response to various stimuli. Once bound to target receptors or taken up by the SERT, internalised serotonin can be metabolised by monoamine oxidase (MAO) leading to the generation of 5-hydroxyindoleacetaldehyde (5-HIAA). Concentrations of 5-HIAA can be readily measured in the urine and are often used to detect changes in whole body serotonin levels [2]. Fig. 1 gives an overview of the intermediate compounds and enzymes involved in serotonin synthesis and metabolism. The family of receptors that bind serotonin is subdivided into seven subgroups and where appropriate these subgroups are again divided. Table 1 summarises the characteristics associated with each member of the human serotonin receptor family. These receptors have been grouped according to their genetic and structural similarities and also according to the intracellular signalling pathways associated with each receptor. All members of the serotonin receptor family are linked to G-proteins, except the 5-HT₃ receptor which is a ligand gated Na⁺/K⁺ channel. The authors direct any readers

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetaldehyde; 5-HT, 5-hydroxytryptamine; ANS, autonomic nervous system; BDEC, bile duct epithelial cell; CNS, central nervous system; ECM, extracellular matrix; ERK1/2, extracellular regulated kinase 1/2; GI, gastrointestinal; HSC, hepatic stellate cell; HCC, hepatocellular carcinoma; MAO, monoamine oxidase; PHx, partial hepatectomy; SEC, sinusoidal endothelial cell; SERT, serotonin transporter; SMV, superior mesenteric vein; SSRI, selective serotonin reuptake inhibitor.

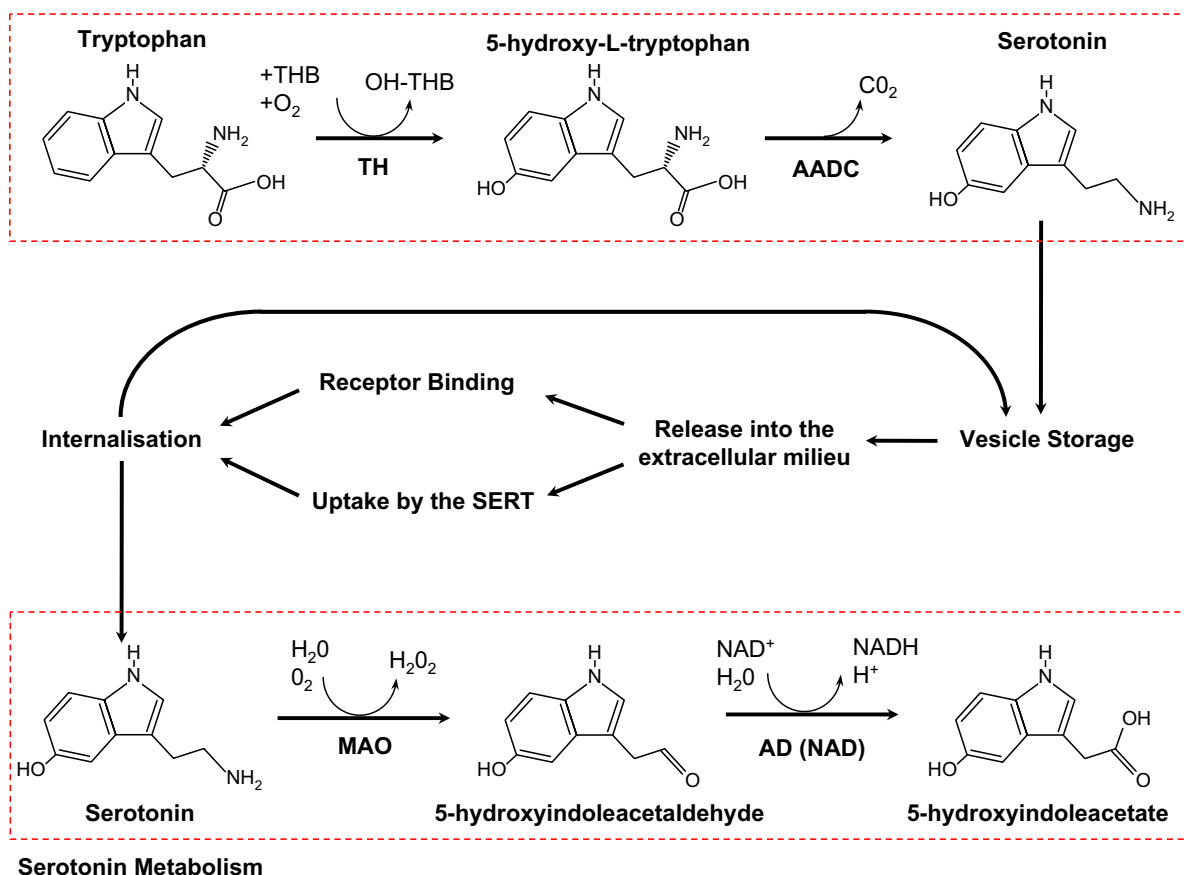
Serotonin Synthesis

Fig. 1. Serotonin synthesis and metabolism. The majority of whole body serotonin is synthesised from tryptophan by enterochromaffin cells in the gastrointestinal tract and exported around the body. The liver is known to be an important site of serotonin metabolism leading to the generation of breakdown products such as 5-hydroxyindoleacetaldehyde (5-HIAA). Outlined in this figure are the biochemical pathways that lead to the anabolism and catabolism of serotonin and also the pathways of storage and cellular uptake. AADC, aromatic amino acid decarboxylase; AD (NAD), NAD-dependent aldehyde dehydrogenase; MAO, monoamine oxidase; OH-THB, hydroxytetrahydrobiopterin; TH, tryptophan hydroxylase; THB, tetrahydrobiopterin.

interested in more detailed information of serotonin receptor families and their associated signalling pathways to the review by Raymond and colleagues [3].

A considerable array of specific/non-specific agonists and antagonists exists that allows the researcher to target serotonin receptors expressed by cells in specific tissues/organs either in healthy individuals or in various disease conditions. Many of these compounds are also able to bind to a number of other receptor types (for example, dopaminergic, adrenergic and cholinergic) and are thus described as “dirty compounds”. The list of extra-hepatic diseases that involve a role for serotonin is large, but they can be divided into diseases that mainly affect brain or peripheral function. The most clinically important diseases of the brain where serotonin has been implicated include migraine [4], depression [5], schizophrenia [6] and Alzheimer’s disease [7]. Perhaps the most clinically important peripheral diseases associated with serotonin are cardiovascular disease [8] and GI disorders such as irritable bowel syndrome [9]. The off-target effects of compounds used to treat these disor-

ders are as complex as the disease they are used to treat, but can include akathisia, insomnia, seizure, anxiety, low blood pressure and sexual dysfunction.

This review, however, will focus on what is known about the basic functions of serotonin within the liver, on the vessels supplying the liver with blood and within the nerve connections that regulate liver function. The review will also focus on the translational and clinical aspects of serotonin biology in terms of pathophysiology and the therapeutic applications of serotonin and relevant antagonists in human liver disease (summarised in Fig. 2).

2. Serotonergic innervation of the liver

2.1. Experimental evidence

Both the sympathetic [10] and parasympathetic [11] branches of the autonomic nervous system are known to regulate several human hepatic metabolic functions

Table 1
Summary of human 5-HT receptor characteristics

Human receptor	Agonists	Antagonists	G protein coupling	Common signalling linkage	Functions
5-HT _{1A}	8-OH-DPAT, buspirone, 5-CT	WAY 100635, methiothepin, spiperone	G _{i/o}	Inhibits AC Activates K ⁺ channels Stimulates ERK	CNS: neuronal hyperpolarisation
5-HT _{1B}	5-CT, CP 93129, sumatriptan	SDZ 21009, methiothepin, yohimbine	G _{i/o}	Inhibits AC Stimulates ERK	CNS: inhibition of neurotransmitter release
5-HT _{1D}	Sumatriptan, L 694247, 5-CT	Metergoline, methiothepin, GR 127935	G _{i/o}	Inhibits AC	CNS: inhibition of neurotransmitter release
5-HT _{1E}	5-HT	Methiothepin	G _{i/o}	Inhibits AC	Not yet characterised
5-HT _{1F}	5-HT	Methiothepin	G _{i/o}	Inhibits AC	Not yet characterised
5-HT _{2A}	α -Methyl-5-HT, DOI	Ketanserin, ritanserin, pirenperone	G _q	Activates PLC & PKC Stimulates ERK Activates PLA2	CNS: neuronal excitation Periphery: smooth muscle contraction, platelet aggregation
5-HT _{2B}	α -Methyl-5-HT, DOI	SB 200646, LY 53857	G _q	Similar to 5-HT _{2A}	Periphery: GI motility
5-HT _{2C}	α -Methyl-5-HT, DOI	Mesulergine, ritanserin, LY 53857	G _q	Similar to 5-HT _{2A}	CNS: cerebrospinal fluid secretion.
5-HT ₃	2-Methyl-5-HT, <i>m</i> -chlorophenyl-biguanide	Ondansetron, tropisetron	N/A		Peripheral and central neurons: depolarisation
5-HT ₄	Metoclopramide, renzapride	GR 113808, SB 204070, tropisetron	G _s	Activates AC & PKA	CNS: neuronal excitation Periphery: GI tract motility, tachycardia
5-HT _{5A}	5-HT, 5-CT	Methiothepin	Unknown	Unknown	Not yet characterised
5-HT _{5B}	5-HT	Methiothepin	Unknown	Unknown	Not yet characterised
5-HT ₆	5-HT, LSD	SB 271046	G _s	Activates AC & PKA	CNS: unknown
5-HT ₇	5-HT, LSD, 5-CT	Methiothepin	G _s	Activates AC & PKA	CNS: unknown Periphery: unknown

5-CT, 5-carboxamidotryptamine; 5-HT, 5-hydroxytryptamine; 8-OH-DPAT, 8-hydroxy-2-di-*n*-propylamino-tetralin; AC, adenylate cyclase; CNS, central nervous system; DOI (\pm)-([1-(2,5-Dimethoxy-4-iodophenyl)-aminopropane]-hydrochloride); ERK, extracellular regulated kinase; GI, gastrointestinal; LSD, lysergic acid diethylamide; PKA, protein kinase A; PKC, protein kinase C; PLA, phospholipase A; PLC, phospholipase C.

and also the response of the liver to injury [12]. Serotonergic nerve fibres are included in the peptidergic family of the ANS and have been previously shown in man to be localised to the tunica media on branches of the hepatic artery and portal vein as well as bile ducts and the connective tissue of the interlobular septa [13]. In addition the presence of serotonin positive nerve fibres in portal tracts and that of fibrous septa within rat hepatic lobules have also been demonstrated [14].

Recent experimental work has shown an increase in 5-HT_{2C} receptor expression in the brain stem and cerebral cortex during liver regeneration following partial hepatectomy (PHx) and *N*-nitrosodiethylamine-triggered hepatic neoplasia in rats. Brain stem serotonin was also significantly elevated in rats following both PHx and *N*-nitrosodiethylamine treatment [15]. In addition spontaneously hypertensive Wistar–Kyoto rats subjected to CCl₄ treatment, also demonstrate a significant increase and rearrangement of both serotonin particles and mast cells (a source of serotonin) within the fibrous septum of the repairing liver [12].

2.2. Serotonergic innervation of the human liver

The importance of serotonergic innervation to human liver regeneration remains relatively unexplored. Experimental animal data and preliminary experiments in human liver show the presence of serotonergic neurons would suggest it does have a role. The exact receptor subtypes that are found on nerve tissue within the human liver are an enigma. However, the availability of serotonin agonists which can specifically bind to various members of the serotonin receptor family presents the researcher with the possibility that serotonergic innervation of the liver can be modulated with resultant beneficial effects on regeneration.

3. Serotonin and the hepatic vasculature

The ability of serotonin to regulate blood flow and vascular tone has been known since 1868, however, it was not until 1948 that serotonin was isolated and characterised [16]. This led to the logical question—can serotonin also regulate the flow of blood within the liver?

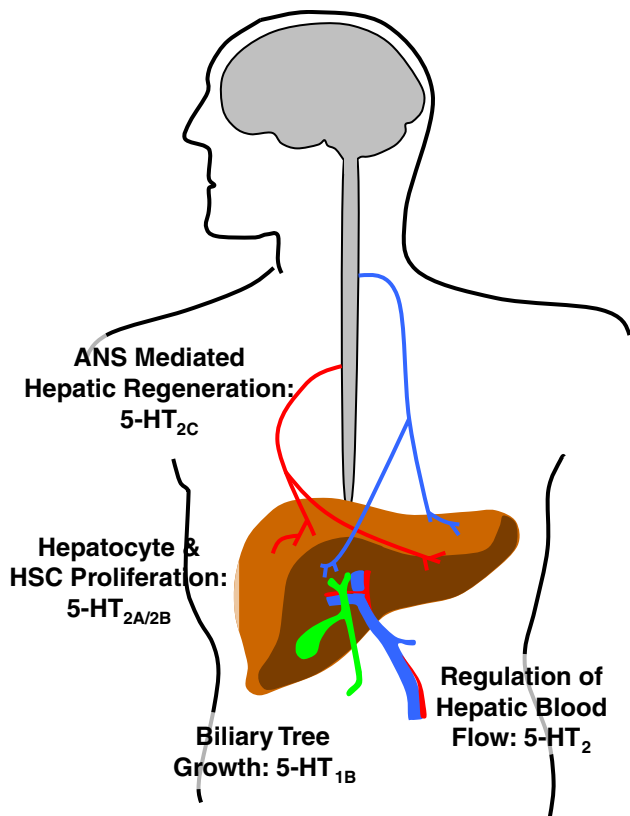


Fig. 2. A summary of the major liver processes influenced by serotonin and the proposed receptors that mediate those events. 5-HT, 5-hydroxytryptamine; HSC, hepatic stellate cell.

The effects of serotonin and antagonists of the 5-HT₂ receptor family on hepatic blood flow and other aspects of vascular function have been studied in both animal models of liver disease and in humans. What is known about the ability of serotonin to regulate hepatic blood flow at both the portal and sinusoidal levels, and also the various experimental attempts to regulate normal and diseased hepatic blood flow will be discussed.

3.1. Experimental regulation of portal blood flow by serotonin

Preliminary experiments have shown an increase in portal resistance elicited by serotonin in normal healthy dogs [17]. Subsequent experiments performed by Cummings and colleagues further defined the role of serotonin in regulating rat portal venous pressure. Their data demonstrated that the isolated superior mesenteric vein (SMV) of portal hypertensive rats was significantly more sensitive to serotonin administration than non-hypertensive rats [18]. The effects of serotonin on the isolated SMV were blocked by the known 5-HT₂ receptor antagonist, ketanserin, suggesting the involvement of the 5-HT₂ receptor. Similarly intraportal injections of serotonin were found to significantly increase portal

pressure, events that were antagonised by ketanserin in portal hypertensive rats but not normal rats. The effects of ketanserin were found to be due to a decrease in portal inflow which followed a decrease in cardiac output, consistent with venous dilation and pooling of blood within the portal system, leading to the proposition that ketanserin should be explored for the treatment of patients with portal hypertension [18].

Both α and β adrenoceptors are also known to regulate portal pressure [19] which is important when one considers that ketanserin also has a lower affinity for the α_1 -adrenoceptor [20]. Experiments that compared and contrasted the actions of prazosin (α_1 -adrenoceptor antagonist) and ketanserin demonstrated that α_1 -adrenoceptor blockade had no effect on the portal pressure of hypertensive rats [20]. Other studies have investigated the role of the selective 5-HT₂ antagonist ritanserin in reducing portal pressure in experimentally hypertensive rats with [21] or without [22] cirrhosis and in dogs with portal hypertension and cirrhosis [23]. In all cases significant reductions in hepatic portal vein pressures were achieved without causing systemic haemodynamic changes.

3.2. Experimental regulation of sinusoidal blood flow by serotonin

Various studies have also investigated the effects of serotonin and the 5-HT₂ receptor antagonist LY53857 on the blood flow of the hepatic sinusoid. Reduced flow at the inlet of the periportal and outlet of the centrilobular sinusoids induced by serotonin was completely antagonised by 1 mg/kg LY53857 [24]. It could be concluded that 5-HT₂ receptors were localised on hepatic sinusoids and that it was this subtype of receptor that mediated the hypoperfusion of the hepatic sinusoid elicited by serotonin [24]. One resident of the hepatic sinusoid that is postulated to regulate blood flow is the hepatic stellate cell (HSC). The HSC is known to undergo an activation process acquiring a smooth muscle cell-like phenotype with enhanced contractile capabilities in response to liver injury. The HSC has recently been demonstrated to express functional 5-HT_{2A} and 5-HT_{2B} receptors [25] and it is therefore possible that the HSC is able to regulate sinusoidal blood flow. Contrary to this hypothesis experimental data from Rockey and colleagues failed to demonstrate cellular contraction of HSC invoked by serotonin on collagen lattices [26]. However, it should be noted that the HSCs in these experiments were activated and therefore a role for quiescent HSC in regulating sinusoidal blood flow cannot be ruled out.

Sinusoidal endothelial cells (SECs) are also known to respond to serotonin incubation [27,28]. Serotonin is able to induce the contraction of fenestrae which is achieved via a rapid influx of extracellular Ca²⁺

leading to activation of the myosin light chain [28]. In these cells serotonin also inhibits cAMP production, and activates phospholipase A2, causing the release of arachidonic acid [28]. The exact significance of these findings has not been fully qualified, it is, however, well established that SEC fenestrae play an important role in the exchange of fluid, solutes and particles between the parenchyma and the blood. Serotonin may therefore play a role in regulating the exchange of various fluids, solutes and particles across the space of Disse. Serotonin in these cells may also exert complex control over various aspects of inflammation and immunity since arachidonic acid is a precursor of various prostaglandins, prostacyclin, and thromboxane.

3.3. Role of serotonin in human hepatic vasculature

A number of studies have demonstrated the responsiveness of the human hepatic vasculature to serotonin and the 5-HT₂ antagonist ketanserin [29–32]. Serotonin is known to stimulate the contraction of the human hepatic artery and in patients with liver cirrhosis this contractility is moderately enhanced [31]. Administration of 10 mg i.v. ketanserin to cirrhotic patients was found to decrease mean arterial pressure, the hepatic venous pressure gradient and azygos blood flow, with hepatic blood flow remaining unchanged [29]. These findings would suggest that serotonergic mechanisms may contribute to maintaining portal hypertension in patients with cirrhosis [29]. The role of β -adrenergic blockade (propranolol) in conjunction with serotonergic blockade (ketanserin) in patients with alcoholic cirrhosis has also been defined [30]. Results demonstrated an independent and additive decrease in wedged hepatic venous pressure, hepatic venous pressure gradient and azygos blood flow [30]. Investigations into the benefits of long-term treatment using a 5-HT₂ receptor antagonist (51 mg ketanserin per day for 32 days) on patients with portal hypertension also demonstrated a significant decrease in portal pressure. However, 50% of patients in the study developed significant side effects which included reversible portosystemic encephalopathy [32]. The frequency of the side effects ruled out further investigations into the beneficial effects of 5-HT₂ receptor antagonism on portal hypertension at least until the development of more selective agents.

3.4. Altered peripheral serotonin and platelet function in patients with cirrhosis

Patients with advanced liver disease often present with variceal haemorrhage and a more generalised “bleeding tendency” [33]. These additional symptoms linked to hepatic cirrhosis are thought in part to be

due to impaired platelet aggregation, with deficiencies identified in several aggregating agents in the platelet-rich plasma of cirrhotic patients [33]. Under normal conditions platelets are activated in response to a variety of different stimuli, releasing various aggregating factors including serotonin, and following this they become exhausted. Patients with cirrhosis are known to have significantly lower peripheral blood serotonin and intraplatelet serotonin concentrations when compared to healthy individuals [34]. Platelet storage pool defects have been shown in cirrhotic patients which prevent the storage of a number of factors including serotonin [33]. It is therefore tempting to propose that the reduced blood serotonin concentration and platelet serotonin storage ability were in part responsible for the haemorrhagic tendency of cirrhotic patients. The reasons for the decreased intraplatelet and peripheral blood serotonin levels in patients with cirrhosis are unclear. A number of studies have now described a role for platelet serotonin in mediating hepatic regeneration. Whether this leads to depleted platelet serotonin remains to be determined, it has, however, been suggested that these findings might justify platelet transfusion in patients with low platelet counts when they bleed spontaneously or before undergoing surgery or liver biopsy [35]. To date no controlled clinical trials have been performed to test this hypothesis.

4. Serotonin and hepatic wound healing

The liver demonstrates a remarkable capacity for regeneration and following 70% PHx in rodents is able to almost completely restore its lost mass within 14 days [36]. The hepatic regenerative and wound healing processes are tightly regulated and known to involve many hepatic and extra-hepatic cell types. While much work has been done in understanding rodent liver regeneration and its response to injury many important questions regarding human liver regeneration remain unanswered. The concept that serotonin may play a role in hepatic regeneration is gaining interest with several recent papers highlighting the importance of serotonin in rodent hepatic wound healing. The hypothesised events mediated by various cell types in response to serotonin at the sinusoidal level are summarised in Fig. 3 and Table 2. With the development of a considerable array of knockout mice lacking specific serotonin receptors and the SERT, new opportunities exist to further study the role of specific components of the serotonin signalling cascade within the normal and diseased liver. Armed with this knowledge, translational research into the mechanisms that underlie human liver regeneration following injury may lead to new and novel therapeutic targets.

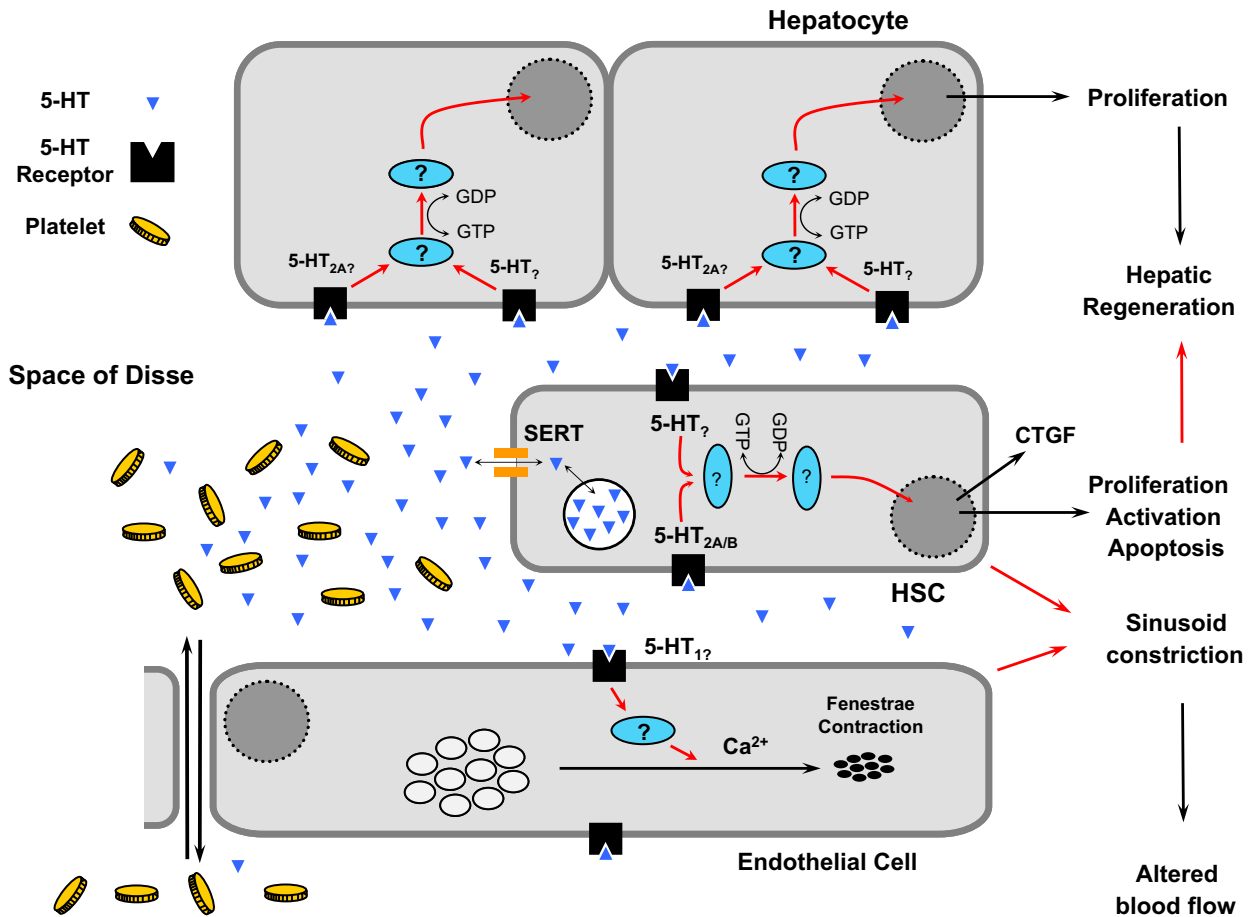


Fig. 3. Known and hypothesised functions of serotonin on cells of the hepatic sinusoid. Contraction of sinusoidal endothelial cell fenestrae is triggered by serotonin in a Ca^{2+} dependant manner. Simultaneous inhibition of cAMP production in these cells would suggest that a serotonin receptor subtype (possibly 5-HT₁) negatively coupled to adenylate cyclase may be mediating the observed changes. Platelets are known to be the major source of sinusoidal serotonin in times of liver injury and have also been shown to adhere to sinusoidal endothelial cells and also to translocate to the space of Disse in response to various proinflammatory mediators where serotonin mobilisation occurs. Serotonin within the space of Disse is then free to bind serotonin receptors expressed by both quiescent and activated HSC as well as hepatocytes. In response to serotonin both cell types are known to proliferate and experimental data indicate that serotonin is able to prevent HSC apoptosis and regulate gene expression. HSCs are also able to traffic serotonin to an internal compartment from which it can be released thereby initiating a possible feedback loop sustaining both hepatocyte and activated HSC proliferation. Both cell types are known to contribute to the regeneration of hepatic mass following liver injury. Serotonin has also been shown to regulate sinusoidal blood flow. The fact that both endothelial cells and HSC express serotonin receptors and are contractile gives rise to the possibility that both cell types can regulate sinusoidal blood flow in response to serotonin. Red arrows represent plausible but as-yet untested pathways. 5-HT, 5-hydroxytryptamine; CTGF, connective tissue growth factor; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HSC, hepatic stellate cell; SERT, serotonin transporter.

The involvement of serotonin in hepatic regeneration is by no means new information, with many studies in existence from at least the early 1980s. However, these publications were often not originally published in English and were difficult to obtain until quite recently, thus keeping them relatively unknown.

4.1. In vivo studies investigating the role of serotonin in hepatic regeneration

Kulinskii and colleagues were the first to describe the effects of serotonin and various serotonin antagonists on mouse liver regeneration following

Table 2

Outline of the cell-specific expression of various components of the 5-HT dependent signalling pathways and those functions regulated

Cell type	5-HT components expressed	Functions
Hepatocyte	5-HT _{2A} , SERT, MAO	Proliferation, oxidant stress, mitochondrial toxicity
Bile duct epithelial cell	5-HT _{1A} , 5-HT _{1B} , SERT	Proliferation, biliary tree growth
Hepatic stellate cell	5-HT _{1B} , 5-HT _{1F} , 5-HT _{2A} , 5-HT _{2B} , 5-HT ₇ , SERT	Proliferation, growth factor expression, apoptosis, contraction?
Endothelial cell	Unknown	Fenestra contraction

SERT, serotonin transporter; MAO, monoamine oxidase; 5-HT, 5-hydroxytryptamine.

PHx [37–39]. They observed a mobilisation of intestinal serotonin and accumulation in the liver and spleen following PHx [39]. Subsequent work showed enhanced hepatocyte proliferation following low-dose administration of serotonin also to mice subjected to PHx [38]. The role of serotonin agonists, 5-methoxytryptamine and α -naphthylbiguanide (a 5-HT₃ receptor agonist) and that of the antagonist Lisuride on regeneration following PHx were also investigated. 5-methoxytryptamine was found to mimic serotonin and the effects of serotonin were blocked by Lisuride which is known to antagonise the 5-HT_{1A/1B} and 5-HT_{2B} receptors whereas α -naphthylbiguanide had no effect. Subsequent work demonstrated that serotonin was able to elevate cAMP and cGMP within rat hepatocytes exposed to X irradiation and cycloheximide [40] and also enhance hepatic poly-(A) RNA synthesis in normal healthy Wistar rats [41]. It should be noted that these early studies into the effects of serotonin on liver regeneration were done at a time with limited availability of specific pharmacological agents and incomplete knowledge of serotonin receptor biology.

More recently a number of studies have reinvestigated the role of serotonin, however, this time against a background of knockout technology, advances in serotonin receptor ligand design and advances in receptor characterisation. [42–44]. Ketanserin is now known to be a potent inhibitor of liver regeneration and more specifically hepatocyte proliferation following PHx [43]. Hepatic stimulator substance, which is known to be a potent hepatocyte growth factor, is also unable to overcome the blockade of liver regeneration by ketanserin following PHx [44]. Recent elegant studies by Lesurtel et al. identified platelets as the major source of serotonin that drives liver regeneration in PHx mice [42]. They found that liver regeneration in thrombocytopenic mice following PHx was restored by supplementing the mice with platelet-rich plasma containing near WT levels of serotonin [42]. These effects were mimicked by the 5-HT₂ agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) and antagonised by ketanserin and to a lesser degree SB 206553 (5-HT_{2B/2C} receptor antagonist). These results again suggest a key role for the 5-HT₂ family of receptors in mediating hepatic regeneration.

4.2. *In vitro* studies investigating the role of serotonin in hepatic regeneration

Similarly advances in serotonin receptor cloning and characterisation in conjunction with the development of serotonin receptor ligand-binding profiles allowed for more detailed studies of serotonin receptors expressed by hepatocytes *in vitro*. Balasubramanian and Paulose were the first to publish data on the stimulation of DNA synthesis in hepatocytes by one of the 5-HT₂ receptor family members [45]. Using pri-

mary rat hepatocytes Balasubramanian and Paulose showed serotonin was able to induce a dose-dependent increase in [³H]thymidine incorporation into DNA in the presence of epidermal growth factor and insulin [45]. The 5-HT₂ antagonists ketanserin and spiperone were able to displace [³H]serotonin binding from crude liver-membrane preparations and also inhibit the stimulatory effects of serotonin on hepatocyte DNA synthesis [45]. It should be noted that these experiments were performed at a time when 5-HT₂ receptor biology was in its infancy and the existence of three separate members of the 5-HT₂ was unknown. Today the three members of the 5-HT₂ family have been fully characterised and armed with this knowledge new insight into the exact function and expression patterns of the 5-HT₂ receptor family on hepatocytes can be more fully explored.

4.3. *Serotonin and the hepatic stellate cell*

As previously mentioned the HSC is an important component in the response of the liver to injury in terms of both wound healing and scar formation in cases of extended liver insult. Interestingly, activation of the HSC has also been demonstrated in response to PHx in rats [36]. This finding indicates that HSC activation is not only important in examples of extended liver injury but also in hepatic regeneration with little or no fibrosis present. Serotonin is now known to regulate several key facets of HSC biology with regard to their involvement in wound healing [25]. Five members of the serotonin receptor family have been identified in HSC including 5-HT_{1B}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B} and 5-HT₇ receptors. It has been demonstrated that both the 5-HT_{2A} and 5-HT_{2B} receptors are upregulated (~100- and 50-fold, respectively, that of quiescent HSC) in response to activation, suggesting an important role for these receptors in the function of the HSC. In the presence of PDGF-BB, serotonin was able to stimulate HSC proliferation. While on its own it was able to induce CTGF expression and protect HSC against nerve growth factor-induced apoptosis. An array of 5-HT₂ antagonists was also found to inhibit HSC proliferation and stimulate apoptosis and in addition activated HSCs also expressed the SERT and were able to internalise serotonin [25]. Considering the locality of the HSC in the liver, these findings take on added significance with the knowledge that the proinflammatory cytokines TNF α , IL-1 and LPS are known to induce translocation of platelets to the space of Disse in mice where serotonin mobilisation occurs [46]. This may represent an important mechanism by which the HSC gains access to serotonin in response to injury, thus allowing serotonin to modulate the behaviour of the HSC.

4.4. Serotonin and cholangiocyte growth

Serotonin has been proven to regulate biliary tree growth via the 5-HT_{1A} and 5-HT_{1B} receptors in the rat bile duct-ligated rat model of cholestasis [47]. Bile duct epithelial cell (BDEC) proliferation is markedly inhibited by agonist activation of the 5-HT_{1A} (8-OH-DPAT) and 5-HT_{1B} (anpirtoline). Marzoni and colleagues also showed that BDECs were able to secrete serotonin in much the same manner as HSCs and the authors postulated the existence of self governing BDEC antiproliferative loop regulated by serotonin [47]. Selective serotonin reuptake inhibitors (SSRI) such as citalopram and paroxetine have been linked with cholestasis in addition to severe acute and chronic hepatitis in humans [48–50]. The mechanisms by which SSRI contribute to cholestasis are unknown and occurrences are very rare. When one considers that BDECs express the 5-HT_{1A} and 5-HT_{1B} receptors in addition to the SERT, it is possible that serotonin may regulate bile excretion and SSRI treatment may disrupt this pathway in predisposed patients.

4.5. Deleterious effects of serotonin on hepatic regeneration

Serotonin does not always play a beneficial role in liver regeneration following injury. Indeed two animal studies have shown serotonin contributes to liver injury and hypoperfusion following ischaemia and reperfusion of the small intestine [51] and the liver [52]. Both models of ischaemia resulted in elevated serotonin levels in the portal and hepatic veins resulting in decreased hepatic blood flow and hepatic microcirculation injury, with evidence suggesting that serotonin was derived from platelets [52]. Conversely, platelet-derived serotonin has been shown to be beneficial in terms of stimulating hepatocyte proliferation following hepatic ischaemia in mice [53]. In addition over proliferation by hepatocytes can lead to hepatocellular carcinoma (HCC) and this would raise the possibility that serotonin may play a role in HCC, although to date this hypothesis has remained untested.

4.6. Studies on the role of serotonin in human liver disease

Serotonin breakdown catalysed by monoamine oxidase (MAO; see Fig. 1) is known to generate hydrogen peroxide [54]. In examples of experimentally induced NASH serotonin has been shown to elevate oxidative stress and contribute to mitochondrial damage via elevated expression of both the SERT and MAO [55]. MAO is known to be elevated in patients with NASH, suggesting serotonin may play a clinically relevant role in disease progression in humans [55].

4.7. Summary

Current data clearly indicate the importance of serotonin in mediating various facets of hepatic regeneration. The overwhelming majority of data suggest that serotonin acting mainly through the 5-HT_{2A} and 5-HT_{2B} receptors plays a key role in mediating hepatocyte proliferation and restoration of hepatic mass following injury. HSC activation is an important part of the hepatic response to injury and is as important to the regenerative arm of this response as it is to the fibrotic arm. Fig. 3 outlines known and hypothesised roles for serotonin acting at the sinusoidal level on three separate cell types. Much more information is required to fully complete this picture and the existence of other serotonin receptor subtypes on hepatocytes, SEC and HSC, cannot be ruled out. To date no attempts have been made to investigate either serotonin receptor expression or the role of serotonin in human hepatic regeneration and recovery from liver injury. Numerous studies aimed at resolving experimentally induced fibrosis in various animal models of hepatic injury have been performed. Equally, a large number of studies indicate that once the underlying causes of liver injury are treated in either humans or animals spontaneous resolution of fibrosis can occur. The effects of serotonin on the liver represent another possible point of intervention whereby the return of the liver to a normal healthy state can be enhanced.

5. Conclusion

It is apparent that serotonin plays a crucial role in regulating hepatic function and response to injury. Acting as a neurotransmitter and as a neuroendocrine hormone, it regulates ANS input to the liver, blood flow within the normal and healthy liver and also regulates the proliferation and function of a number of key resident liver cells (as can be seen in Table 2). The ability of serotonin to modulate all of these factors renders it crucial in times of hepatic injury and repair. Data are very limited regarding the function of serotonin within the human liver and this review represents the first comprehensive attempt to bring all of this information together. Due to the availability of a number of selective agonists and antagonists for the various serotonin receptor subtypes (some of which were covered here) and knockout mice lacking specific serotonin receptors, there is a real possibility for significant advances to be made in the field of serotonin and the liver. These studies may ultimately lead to new therapies that may enhance the regenerative capacity of the liver, helping the many people suffering from chronic liver disease.

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