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Review

Role of serotonin in the hepato-gastroIntestinal tract: an old molecule for new perspectives

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Abstract. Beside its role as a neurotransmitter in the central nervous system, serotonin appears to be a central physiologic mediator of many gastrointestinal (GI) functions and a mediator of the brain-gut connection. By acting directly and via modulation of the enteric nervous system, serotonin has numerous effects on the GI tract. The main gut disturbances in which serotonin is involved are acute chemotherapy-induced nausea and vomiting, carcinoid syndrome and irritable bowel syndrome. Serotonin also has mitogenic properties. Platelet-derived serotonin is involved in liver regeneration after partial hepatectomy. In diseased liver, serotonin may play a crucial role in the progression of hepatic fibrosis and the pathogenesis of steatohepatitis. Better understanding of the role of the serotonin receptor subtypes and serotonin mechanisms of action in the liver and gut may open new therapeutic strategies in hepato-gastrointestinal diseases.

Keywords. Serotonin, platelet, gut, liver regeneration, gastrointestinal dysfunction.

Serotonin (5-hydroxytryptamine, 5HT) has been the subject of intense biological research since its synthesis in 1951 [1]. Erspamer and Asero [2] originally isolated a potent vasoconstrictor substance from the intestine, which they called 'enteramine.' In 1948, Rapport and colleagues determined that this new substance was chemically 5-hydroxytryptamine, and named it serotonin [3]. Serotonin was subsequently found in the gastrointestinal (GI) tract and central nervous system (CNS) and shown to function both as a neurotransmitter and as a local hormone in the peripheral vascular system and in the gut [4–6]. With increasing knowledge, serotonin was shown to be a mediator with a subsidiary role in many functions. In words of one pundit, serotonin seemed to be 'involved in everything, but responsible for nothing,' a kind of mediator-without-portfolio.

Novel agonists and antagonists of serotonin led to the identification of several types and subtypes of receptors, which are currently at the forefront of pharmacologic research in neuroscience and gastroenterology [7]. GI research on serotonin was initially stimulated by the observation of high amounts of serotonin in the intestinal mucosa [8]. The role of serotonin was further elaborated by the study of carcinoid tumors [9] and that mucosal application of serotonin activates afferent nerve endings causing intestinal peristalsis [10]. Over the past 20 years, serotonin has gained recognition well beyond its role as a neurotransmitter in the CNS. It appears as a physiologic mediator of GI function and motility and a component of pathological conditions. It even

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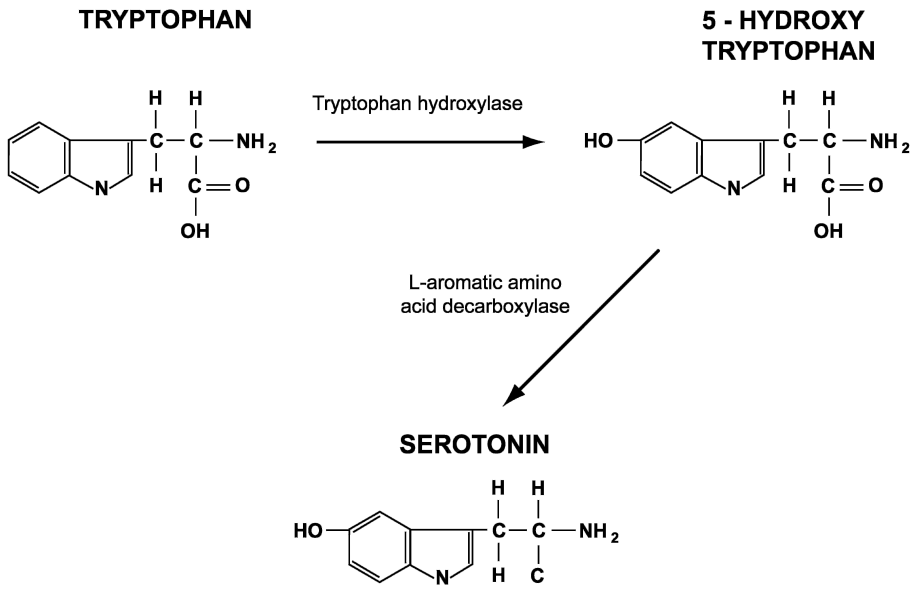

Figure 1. Biosynthesis of serotonin.

appears as a mediator of the brain-gut connection [11].

Serotonin also has mitogenic properties [12, 13], for example in modulating growth of a variety of tissues like smooth muscle cells and fibroblasts in pulmonary hypertension, the nervous system [14] and the mammary gland [15]. The development of knock-out mice lacking peripheral serotonin opened new avenues for specific research approaches looking at the effects of serotonin outside the nervous system [16]. The liver was one of the organs that benefited much from these genetic tools, since serotonin has been shown to play a pivotal role in liver regeneration after major tissue loss following hepatectomy [17] and tissue repair after an ischemic insult [18]. Serotonin was also found to mediate injury in the highly prevalent liver disease, steatohepatitis [19].

The goal of this review is to provide an overview of the implications of serotonin in the hepato-GI tract. We will focus on GI mobility, liver regeneration, ischemia/reperfusion (I/R) injury and chronic liver disease, as well as pancreas regeneration. Clinical implications and perspectives of strategies modulating the activity of serotonin, 60 years after its characterization, will be discussed.

What is serotonin?

The phylogenetically old molecule serotonin [3-(2-aminoethyl)-5-hydroxyindole] is widely distributed in animals, fungi and plants, including fruits and vegetables.

Serotonin synthesis and metabolism

About 95% of serotonin in the body is found in the GI tract, of which 90% is in enterochromaffin cells (ECs) and 10% in enteric neurons. The remaining of serotonin (5%) is found in the brain. As serotonin cannot cross the blood-brain barrier, the brain must synthesize its own serotonin. Virtually all of the serotonin in the blood is derived from the GI tract [20, 21]. Serotonin is present and synthesized in enteric nerves [22–25]. Serotonin is present at high concentration in platelets, where it accumulates from the plasma by an active transport system and participates in aggregation of platelets and coagulation of blood [20, 21]. Though serotonin is present in the diet, most of it is metabolized before entering the bloodstream. In ECs and neurons, but not in platelets, serotonin is synthesized from the essential amino acid tryptophan by two enzymatic steps. First, hydroxylation of tryptophan by the enzyme tryptophan hydroxylase (TPH) (the rate-limiting step) produces 5 hydroxytryptophan (5-HTP). The second enzymatic step is decarboxylation of 5-HTP by the enzyme L-aromatic amino acid decarboxylase producing serotonin [26] (Fig. 1). Platelets (and neurons) possess a high-affinity serotonin uptake mechanism, and platelets become loaded with serotonin as they pass through the intestinal circulation, where the local concentration is relatively high. Therefore, about 95% of serotonin found in blood is stored in platelets [27]. Serotonin in tissues can be very rapidly metabolized, mainly as a result of the activity of monoamine oxidase. In the kidney and the liver, the enzymes monoamine oxidase and aldehyde dehydrogenase convert serotonin to 5-hydroxyindole acetic acid (5-HIAA), which is excreted in the urine.

Table 1. Classification of serotoninergic receptor subtypes with a focus on GI effects [adapted from refs 11 and 33].

	Location		GI effect
	GI tract	brain	
5-HT1A	enteric nerves	hippocampus	neuronal inhibition
5-HT1B	sympathetic nerves	substantia nigra, basal ganglia	neuronal inhibition
5-HT1D		substantia nigra, basal ganglia	neuronal inhibition
5-HT1E		substantia nigra, basal ganglia	?
5-HT1F		dorsal raphe, hippocampus, cortex	?
5-HT1P	enteric nerves		neuronal depolarization
5-HT2A	ileum	cortex, caudate nucleus	contract muscle, neuronal depolarization
5-HT2B	stomach	cerebellum	?
5-HT2C		choroid plexus	?
5-HT3	vagus, sympathetic, enteric nerves	area postrema	neuronal depolarization
5-HT4	myenteric plexus	hippocampus	contract muscle, facilitate cholinergic transmission
5-HT5		cerebellum or whole brain	
5-HT6		caudate nucleus	
5-HT7		thalamus, hypothalamus, hippocampus	

The gut, as well as the CNS, has an inactivating mechanism, a transporter-mediated uptake (serotonin reuptake transporter, SERT), which is present both in the mucosa and in nerves of the enteric nervous system [28, 29]. This system plays an important role in terminating transmitter action and in maintaining transmitter homeostasis because there is no extracellular enzyme, analogous to acetylcholinesterase, that rapidly catabolizes serotonin. Mice that lack SERT exhibit increased colonic motility and increased water in stools and display an alternating pattern of diarrhea and constipation.

There are two isoforms of TPH [16]. TPH1 is present in the periphery, especially in the duodenum, while TPH2 is present exclusively in the brain and is encoded by a different gene [30]. Therefore, it was possible to generate mice genetically deficient for TPH1 (TPH−/−), which lack serotonin in the periphery and exhibit no significant behavioral differences with their wild-type siblings [16]. Finally, it is possible to increase serotonin formation by administrating 5-HTP. Because decarboxylase is ubiquitous in mammalian cells, these mice are able to produce serotonin everywhere after administration of the serotonin precursor 5-HTP, bypassing the rate-limiting TPH step [17]. The development of such knock-out mice has allowed the performance of *in vivo* experiments highlighting novel effects of serotonin in the periphery.

Serotonin receptor classification

Serotonin receptors are present in enteric neurons, ECs, GI smooth muscle cells and possibly in enterocytes, immune tissues and hepatocytes [31, 32]. Seven types or families and multiple subtypes of serotonin receptors have now been identified by a combination of pharmacological techniques and molecular cloning [33]. The seven recognized types or families of serotonin receptors are termed 5-HT1 through 5-HT7. Information concerning the types and subtypes of serotonin receptors is summarized in Table 1, with a focus on GI effects. Subtypes of the 5-HT1 receptor are well characterized; these are termed 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1P [7]. Originally, there was an 5-HT1C receptor, but later it was found to be the 5-HT2C receptor and thus this subtype was moved from the 5-HT1 family to the 5-HT2 family. 5-HT1 and 5-HT2 receptors may not be critically involved in the endogenous control of gut motility [11]. Neuronal 5-HT3 receptors seem

to be the primary serotonin receptors responsible for rapid depolarization responses in myenteric neurons, leading to increased release of acetylcholine from cholinergic neurons, resulting in smooth muscle contraction [11]. In the CNS, the highest levels of 5-HT3 receptors are in the brainstem, particularly in the nucleus tractus solitaris, area postrema and dorsal motor nucleus of the vagus nerve. These structures are intimately involved in initiation and coordination of the vomiting reflex; antagonism of the 5-HT3 receptors in these nuclei is therefore likely to contribute to the antiemetic action of 5-HT3 receptor antagonists such as ondansetron, granisetron and tropisetron. Peripherally, 5-HT3 receptors are also located on vagal afferents and are important (and, in some cases, additive to 5-HT4 effects) in the peristaltic reflex [34–36]. Intestinal primary afferent neurons have 5-HT4 receptors [37, 38]. 5-HT4 receptors are involved in the peristaltic reflex [34, 36]. The last three receptors (5-HT5, 5-HT6 and 5-HT7) have been recently cloned and are distributed predominantly in the brain [33].

Role of serotonin in the GI tract

Motor and sensory effects of serotonin in the gut

The bowel has the unique ability to mediate reflexes independently from the brain and spinal cord [39]. The 'local nervous mechanism' of the bowel, in which serotonin is involved, is now known as the enteric nervous system. The name was given by Langley in his classic definition of the autonomic nervous system [40]. Langley included the enteric nervous system as one of three basic subdivisions of the autonomic nervous system beside the sympathetic and parasympathetic nervous systems. There are strong interactions between the enteric and central nervous system.

In the enteric nervous system, serotonin acts as an enteric neurotransmitter and a paracrine signaling molecule [4–6]. In the gut, serotonin is released from ECs acting locally in a paracrine fashion [41]. It has diverse motor and sensory functions in the GI tract through submucosal and myenteric neurons that respond to serotonin through a variety of receptors. Serotonin is involved in so many functions in the bowel that it is difficult to determine which of these actions are physiologically relevant. The multiplicity of responses to serotonin can be attributed to the expression within the gut wall of a wide variety of serotonin receptor subtypes [5]. Serotonin initiates diverse responses such as nausea, vomiting, intestinal secretion and peristalsis, and plays a role in bowel physiology as an enteric neurotransmitter. In physiological studies of gut smooth muscle, serotonin induces contraction or relaxation of the bowel, depending on the experimental conditions [5, 11]. For example, serotonin activates both intrinsic excitatory and inhibitory enteric motor neurons. It can stimulate cholinergic neurons to release acetylcholine, which results in smooth muscle contraction, or it can stimulate inhibitory nitrergic neurons to release nitric oxide, which results in smooth muscle relaxation. Serotonin also participates in a vagal pathway leading to relaxation of the stomach [11].

When intraluminal pressure increases, ECs release serotonin, which stimulates vagal and intrinsic (enteric) afferent nerve fibers, initiating the peristaltic reflex [10] (Fig. 2). In addition, serotonin appears to be a signaling molecule, participating in mucosal sensory transduction [39]. Serotonin also plays a role in the descending pathways from the brainstem that modulate afferent information processed by the dorsal horn.

The main determinant of gastric mechanosensitivity is gastric tone. A subset of patients with functional dyspepsia have been shown to have insufficient accommodation (decrease in gastric tone) after a meal [42, 43]. Pretreatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine has been shown to enhance gastric accommodation to a meal in healthy volunteers in the absence of any effect on fasting gastric compliance [44]. These observations suggest that serotonin release is involved in the control of the accommodation reflex and therefore in the modulation of visceral sensation during the postprandial state. Prokinetic benzamides, such as cisapride, act as 5-HT4 receptor agonists. Their gastrokinetic properties are thought to originate from their ability to stimulate 5-HT4 receptors on cholinergic nerve terminals [45, 46]. The effect of serotonin in a subset of myenteric neurons is known to evoke a slow depolarizing response. This effect is mediated by the so-called 5-HT1P receptors which are predominantly located on inhibitory motor neurons of the gastric myenteric plexus [47, 48]. Recent studies have identified sumatriptan as a 5-HT1P receptor agonist which interacts with nitrergic myenteric neurons in the guinea pig stomach and which induces gastric relaxation in cats and humans [49]. The non-selective 5-HT1A receptor agonist buspirone is thought to decrease gastric tone and increase the distension-induced volume thresholds in healthy volunteers, thereby mimicking some of the effects of sumatriptan [50]. In a placebo-controlled, double-blind, randomized, cross-over study, buspirone was shown to be superior to placebo at improving gastric accommodation in patients with functional dyspepsia [51]. The 5-HT1P and 5-HT1A receptor agonists may have addi-

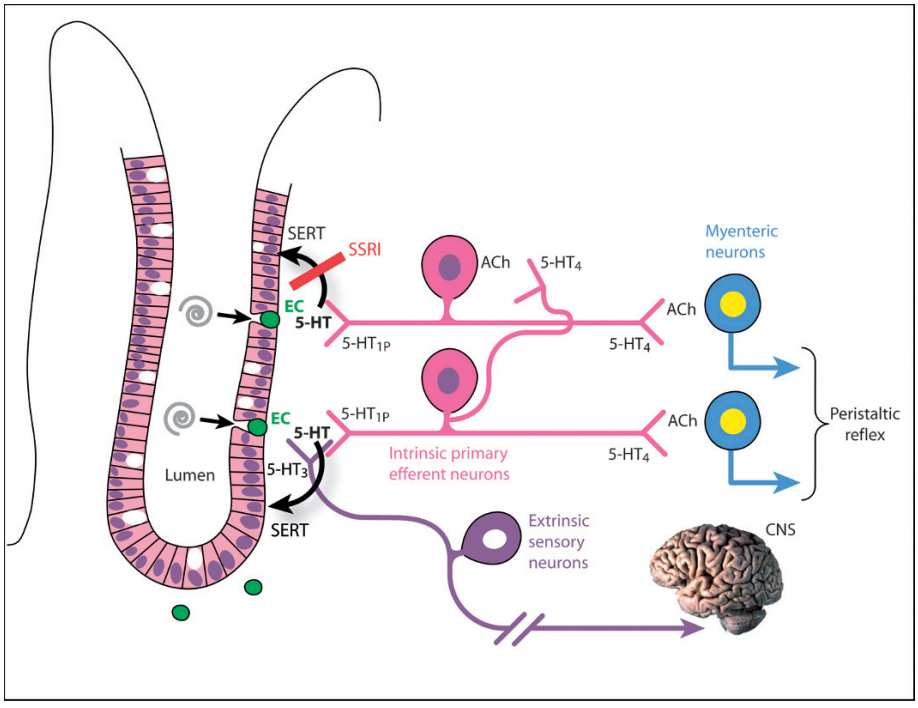

Figure 2. Action of serotonin in the bowel wall. Serotonin released from stimulated enterochromaffin cells activates submucosal intrinsic primary efferent neurons (pink) throught 5-HT1P receptors. The latter spread information to the myenteric plexus (blue) allowing peristaltic reflexes. Serotonin also activates extrinsic sensory neurons (purple) which relay information to the central nervous system. Black arrows represent reuptake of selective serotonin by its transporter (SERT) which is blocked by serotonin reuptake inhibitor (SSRI).

tional therapeutic potential for the treatment of gastric visceral hypersensitivity.

Role in secretion control

Serotonin is also a potent intestinal stimulus for secretion. The mechanisms of serotonin-induced intestinal secretion are unclear. A 5-HT2 receptor, located in the mucosa, is involved in the regulation of serotonin-stimulated intestinal electrolyte transport [52]. Serotonin is involved in cholera toxin- and bile salt-induced fluid and electrolyte secretion by activating the enteric nervous system, or, at least in part, via a release of serotonin from ECs [53]. Serotonin is also important in the pathophysiology of carcinoid diarrhea. Serotonin induces intestinal secretion, and studies performed in a few patients with carcinoid diarrhea using 5-HT3 antagonists demonstrated enhanced jejunal absorption in fluid transport [54].

Serotonin in GI disease

The main gut disturbances in which serotonin is involved are acute chemotherapy-induced nausea and vomiting, carcinoid syndrome and irritable bowel syndrome (IBS).

Chemotherapy-induced nausea and vomiting. Serotonin is a key mediator of chemotherapy-induced nausea and vomiting. Several cancer chemotherapy agents, like cisplatin, oxaliplatin or streptozotocin induce the release of serotonin from ECs in the duodenum. Released serotonin induces nausea and vomiting through stimulation of 5-HT3 receptors on vagal afferent nerves that convey information to the medullary vomiting system including the area postrema [55]. Antagonists at 5-HT3 receptors have proved to be highly effective antiemetic drugs. The 5-HT3 antagonist drugs most widely used and studied to date are ondansetron, granisetron and tropisetron. Their main use in clinical therapeutics is in the control of cisplatin and other cytotoxic chemotherapy and radiotherapy-induced emesis. 5-HT3 antagonists are significantly more efficient than metoclopramide during the first day after cisplatin treatment [56].

Carcinoid syndrome. There are convincing data indicating that serotonin is responsible for the diarrhea associated with carcinoid tumors. The majority of carcinoid patients have raised levels of plasma serotonin or urinary levels of its metabolite (5-HIAA), and carcinoid tumors contain vast quantities of serotonin [54]. Carcinoid diarrhea is caused by increased jejunal secretion and alterations in small bowel and colonic motor functions. Transit times in the small bowel and colon in patients with carcinoid diarrhea were, respectively, two and six times faster than in healthy controls [54].

Drugs that block serotonin receptors, such as methysergide and ketanserin, or that inhibit serotonin synthesis, such as p-chlorophenylalanine, are effective in the short-term treatment of diarrhea in this population [11]. Ondansetron proved effective in inhibiting carcinoid diarrhea and flushing [57, 58].

Irritable bowel syndrome. IBS is associated in some patients with altered GI transit, a variety of manometric abnormalities in the small and large intestine, increased visceral sensation and psychological features including depression and anxiety. IBS can be subdivided into diarrhea-predominant, constipation-predominant or mixed IBS [59, 60]. GI symptoms may result from dysregulation of the brain-gut mediation [61]. Although changes in the metabolism and/or function of serotonin have been well documented in patients with IBS, further work is needed to clarify the role of serotonin and its transporter in the syndrome. For example, patients with diarrhea-predominant IBS have higher levels of plasma 5-HT under both fasted and fed conditions than healthy controls, whereas patients with constipation-predominant IBS show little or no changes in plasma serotonin levels after meals [59, 62]. It has been suggested that increased levels of 5-HT might exert prokinetic effects in the GI tract, leading to diarrhea, whereas the reduced levels of serotonin in constipation-predominant IBS may cause constipation.

Although the exact role of serotonin in IBS is not clear, selective 5-HT3 antagonists, such as ondansetron, granisetron or alosetron, appear to be promising therapeutic drugs for IBS. The potential modes of action of 5-HT3 antagonists could include decrease of visceral nociception [63], inhibition of the gastrocolonic reflex [64], inhibition of colonic mobility and compliance, inhibition of small bowel transit [65] and beneficial central effects on anxiety [66]. Several placebo-controlled studies have suggested benefits of 5-HT3 receptor antagonists in patients with IBS [6]. 5-HT4 receptor agonists, e.g. tegaserod, stimulate motility and secretion through enhanced release of acetylcholine from excitatory motor neurons and interneurons. Several studies established that treatment with tegaserod for up to 12 weeks is able to improve constipation and to provide relief of pain/discomfort and bloating in constipation-predominant IBS [67]. 5-HT4 receptor agonists exert modest but inconsistent effects on esophageal motility and on gastroesophageal reflux in patients with gastroesophageal reflux disease [68]. 5-HT4 agonists do not compare well with the gold standard of therapy for gastroesophageal reflux with a proton pump inhibitor; a place for 5-HT4 agonists in the management of gastroesophageal reflux has therefore not been established. Finally, 5-HT4 receptor agonists might be efficient in gastroparesis [69].

Colorectal cancer. Thirty years ago, a proliferative effect of serotonin in a xenograft mouse model of colorectal cancer was reported. SSRIs significantly suppressed tumor growth in this model [70–73]. The data appear quite relevant as SSRIs are frequently used as antidepressants.

Newer studies using electron microscopy immunochemistry proposed serotonin as a carcinogenic substance in colon cancer differentiation [74]. Furthermore, a decreased metabolic activity and growth of cultured human colorectal carcinoma after treatment with SSRIs was reported [75]. Recently, a large epidemiological study described a reduced risk of colorectal cancer after daily intake of SSRIs compared with non-users of such antidepressants [76]. The biological mechanisms of these findings remain unknown and need further investigation [76].

Role of serotonin in the liver

Role of platelets

Platelets play a key role in haemostasis and thrombosis [77]. Platelets are also involved in the inflammatory reaction after many types of tissue injury, independent of coagulation [78]. In the liver, platelets interact with leukocytes in response to cold ischemia, enhancing leukocyte adhesion to the endothelium, thereby causing tissue injury [79, 80]. Concurrent activation of liver macrophages, called Kupffer cells, leads to further endothelial cell damage and hepatocyte apoptosis and necrosis [81].

Our group investigated the role of platelets in liver regeneration using a model of 70% hepatectomy in mice rendered thrombocytopenic, or those with pharmacologically impaired platelet activity [17]. In both models, the regenerative capacity of the liver was impaired, suggesting that platelets play an important role in liver regeneration. In a previous study on hepatic regeneration in rats, it was noted that splenectomized rats with increased platelet counts had improved liver regeneration via an unclear mechanism involving a growth factor [82]. Murata et al. [83] recently examined the effect of platelet increment on liver regeneration. Hepatectomies were carried out in untreated mice, thrombocytotic mice induced with thrombopoietin, and thrombocytopenic mice induced by antiplatelet antibody. The researchers showed that in thrombocytotic and thrombocytopenic mice, markers of liver regeneration were, respectively, increased and decreased, when compared with untreated mice. They also demonstrated that platelets accumulated in the residual liver in the early period after hepatectomy.

Role of serotonin in liver regeneration

Platelets contain many growth factors, such as platelet-derived growth factor (PDGF), hepatocyte growth factor, epidermal growth factor (EGF) and vascular

endothelial growth factor in the α granules [77]. In their dense bodies, they also store and release serotonin, which acts as a growth factor [12, 13]. In vitro, serotonin is a potent mitogen and stimulates mitosis of smooth muscle cells [13]. The role of serotonin in liver regeneration in hepatocyte cell cultures has been reported, with serotonin causing a dose-dependent increase in (^{3}H)-thymidine incorporation into hepatic DNA in the presence of insulin and EGF [84]. The 5-HT2A and 2C receptors appear to mediate mitogenic effects in fibroblasts [85, 86], and the 5-HT2B receptor is involved in the development of the heart [87] and the enteric nervous system [88]. Furthermore, in transfected fibroblasts and renal mesangial cells, a mitogenic cross-talk of serotonin receptors 5-HT2A and 5-HT2B has been shown with EGF receptor and PDGF receptor, respectively [89, 90]. Very recently an additional cross-talk of SERT and PDGFβ receptor in smooth muscle cells has been described, which leads to proliferation and migration [91].

With the exception of a mention in the Russian radiobiology literature about 20 years ago [92, 93], the effect of serotonin on hepatic regeneration was unknown. We recently showed that platelet-derived serotonin is involved in liver regeneration [17]. In thrombocytopenic mice, a serotonin agonist restored the deficient hepatic proliferation. The mRNA expression of serotonin receptor subtypes 5-HT2A and 2B increased after partial hepatectomy, and antagonists of these receptors inhibited liver regeneration. Furthermore, knock out mice TPH−/−, lacking peripheral serotonin due to an absence of the rate-limiting synthetic enzyme TPH1, exhibited an impaired liver regeneration after partial hepatectomy. This failure of regeneration was rescued by reloading serotonin-free platelets with the injection of the serotonin precursor 5-HTP. Papadimas et al. [94] investigated the effect of 5-HT2 blockage by ketanserin on liver regeneration after partial hepatectomy in rats. Administration of ketanserin can arrest liver regeneration only when administrated close to the G1/S transition point, which suggests that serotonin may be a cofactor for DNA synthesis.

Serotonin could also play a role in liver regeneration at the cerebral level. The relationship between the functional status of the liver and the brain has been known for centuries. In hepatic encephalopathy and other liver diseases, neurotransmission in the brain is reported to be altered [95, 96]. The serotonin brain circuits are known to be involved in hepatic encephalopathy [97]. Lateral lesions of the hypothalamus cause an increase in DNA synthesis during liver regeneration, while sympathectomy and vagotomy block this effect [98]. More recently, Pyroja et al. [99] showed that the brain 5-HT2C receptor was up-regulated during liver regeneration after partial hepatectomy and in hepatic neoplasia. The increased serotonin content and 5-HT2C receptor in the brainstem and cerebral cortex is suggested to facilitate the active hepatocyte proliferation, possibly through the sympathetic stimulation [99].

Role of serotonin in hepatic I/R injury

While inhibition of platelet activity reduces ischemic tissue injury in the heart [100], lung [101] and pancreas [102], little is known about the impact of platelets and serotonin on normothermic I/R injury of the liver. Mice deficient for P-selectin, an adhesion molecule critical to the postischemic platelet-endothelial cell interaction [103], display reduced platelet and neutrophil sequestration and a better survival following warm ischemia [104]. In addition, the inhibition of platelet adhesion by the administration of antifibrinogen antibody decreases short-term liver injury after ischemia [105]. However, these experimental approaches also inhibit leukocyte-mediated effects; thus, the specific contribution of platelets to warm I/R injury of the liver remained unknown.

Murata et al. [106] investigated the role of serotonin and platelet function in the pathogenesis of hepatic I/R injury in a model of 60 and 90 min hepatic warm ischemia in dogs using a portocaval shunt. Hepatic I/R resulted in increased platelet aggregation and increased serotonin levels in the hepatic veins, but not in the portal vein. We recently assessed the role of platelets in normothermic I/R injury in liver using models of impaired platelet function, immune thrombocytopenia, and mice lacking TPH1 (TPH−/−) [18]. Neither inhibition of platelet function nor platelet depletion led to a reduction of postischemic tissue injury. Interestingly, postischemic inflammation, as well as liver regeneration and consequently tissue repair, were strikingly impaired. In particular, platelet-derived serotonin was found to mediate hepatocyte proliferation, which is an integral component of postischemic tissue repair. Liver regeneration and repair were significantly impaired in platelet-depleted animals. Mice lacking peripheral serotonin were deficient in hepatocyte proliferation, but otherwise displayed normal tissue remodeling. The results acquit platelets of causing postischemic liver injury, but highlight their importance in different steps of postischemic tissue repair through the modulation of inflammation and the release of serotonin.

Role of serotonin in non-alcoholic steatohepatitis

Very recently, our group suggested that serotonin degradation plays a major role in the pathogenesis of non-alcoholic steatohepatitis (NASH) [19]. NASH is

thought to result from a two-hit process [107]. The first hit is the hepatocellular accumulation of fatty acids, which sensitizes the liver to further injury. Oxidative stress acts as a second hit, leading to lipid peroxidation, mitochondrial damage (megamitochondria), hepatocellular injury (ballooning, Mallory bodies), and finally to chronic inflammation and fibrosis. Degradation of serotonin is catalyzed by the mitochondrial enzyme monoamine oxidase A, generating 5-HIAA as well as reactive oxygen species (ROS) such as hydrogen peroxide. ROS generated by monoamine oxidase-mediated catabolism of serotonin were recently reported to play a pivotal role in cardiomyocyte death [108]. In a murine model of diet-induced steatohepatitis, TPH−/− mice displayed an equal degree of steatosis, yet reduced hepatocellular injury and less severe inflammation compared to wild-type mice. The difference in these two NASH-defining features was attributed to an increased uptake and catabolism of serotonin, yielding enhanced levels of ROS and lipid peroxides, which mediated hepatocellular injury by mitochondrial damage and inflammation. This was the first study disclosing SERT expression in the mouse liver, as well as in patients with NASH and provides evidence that serotonin plays a crucial role in the pathogenesis of steatohepatitis. SERT might offer a novel target for the prevention and treatment of NASH.

Serotonin in liver cirrhosis

Different studies have shown decreased concentrations of intra-platelet serotonin in cirrhotic patients [109–111]. Beaudry et al. [112] found higher plasma levels of serotonin in patients with cirrhosis, whereas levels of the serotonin metabolite 5-HIAA were significantly decreased. They concluded that serotonin metabolism was impaired in cirrhotic patients.

The hepatic stellate cell (HSC) is recognized as one of the key mediators in the progression of hepatic fibrosis [113, 114]. In normal healthy liver, HSC function is to regulate sinusoidal blood and the traffic of macromolecules across the space of Disse, and HSCs also act as a store for vitamin A. Following chronic injury, HSCs are involved in hepatic wound healing and fibrosis. Serotonin was found to attenuate apoptosis and to costimulate proliferation of HSCs in the presence of PDGF in cultured rat HSCs [115]. Proliferation was inhibited and the apoptosis rate was increased with 5-HT2B receptor antagonists. The transcription of connective tissue growth factor was increased in rat HSCs after incubation with serotonin. 5-HT2B receptor expression was associated with fibrotic tissue in immunohistological stainings of rat livers from a CCL_4-cirrhosis model. Finally, HSCs were shown to express a functional SERT and to participate in both active uptake and release of serotonin. The authors suggested that HSCs respond to serotonin in a profibrogenic manner and that 5-HT2 receptor antagonists may also be used for the treatment of liver disease.

Recent reports have demonstrated the presence of serotonin receptors in glomerular mesangial cells [116, 117]. Furthermore serotonin has been reported to stimulates the production of transforming growth factor β (TGF-β) and type IV collagen in human mesangial cells through the 5-HT2A receptor [117]. Since glomerular mesangial cells and HSCs are of similar histological origin, the roles of glomerular mesangial cells in glomerular disease resemble those of HSCs in liver cirrhosis. Li et al. [118] demonstrated that serotonin enhanced production of TGF-β by HSCs through the 5-HT2A receptor and may play a role in the pathogenesis of liver cirrhosis and portal hypertension.

Serotonin in chronic cholestasis

Serotonin is involved in clinical symptoms of cholangiopathies like pruritus and fatigue [119]. In a rat model of cholestasis, a selective 5-HT1A agonist improved overall activity [120]. The authors speculated that an enhancement of serotonergic neurotransmission mediated through 5-HT1A receptors alleviates fatigue in cholestatic liver disease. A recent study has shown the expression of the serotonin receptors 1A and 1B in rat cholangiocytes [121]. Their activation markedly inhibits the growth and choleretic activity of the biliary tree. Cholangiocytes from cholestatic rats overexpressed and oversecreted serotonin, and treatment with a neutralizing antibody of serotonin enhanced cholangiocyte proliferation. The authors stressed the existence of an autocrine loop based on serotonin that limits the growth and the functional activity of the biliary tree in the course of chronic cholestasis. These findings suggested the involvement of serotonin-mediated pathways in cholestatic disease. However, a recent randomized controlled trial did not suggest any benefit of ondansetron in the treatment of pruritus and scratching activity in chronic cholestasis [122].

Serotonin in pancreatic regeneration

Pancreatic regeneration has been studied in small animals and knowledge in this field is now expanding, especially in the areas dealing with molecular biology and genetic science [123]. However, knowledge of pancreas regeneration in humans is limited to date. Many transcription factors, such as PDX-1 and growth factors, such as EGF or vascular endothelial growth factor, have been suggested to be involved in the proliferation, differentiation and maintenance of

endocrine and exocrine pancreas. Unlike liver regeneration, there are no data showing a direct role of serotonin in pancreas regeneration. However, recent studies have suggested that hypothalamic serotonin, through 5-HT1A and 5-HT2C receptors, has a functional role in pancreatic regeneration via sympathetic regulation [124–126]. These very early results would suggest that the regeneration of the remnant pancreas after subtotal pancreatectomy would be a good target of certain therapies modulating serotonin action to enhance pancreatic regeneration.

Conclusion and perspectives

Recent research advances have shown that many effects of the well-known molecule serotonin remain largely unknown

Serotonergic modulation of upper gut sensitivity appears promising for the development of novel approaches for the treatment of functional disorders of the upper GI tract. However, it is apparent that the mechanisms underlying the many effects on the GI tract have yet to be fully elucidated. 5-HT3 antagonists are established treatment in patients with diarrhea-predominant IBS and those with nausea-associated chemotherapy. 5-HT4 agonists have beneficial effects in patients with constipation-predominant IBS and chronic constipation. The role of 5-HT4 receptor agonists in functional dyspepsia, gastroparesis, gastroesophagial reflux and functional dyspepsia is still under investigation.

Serotonin has been shown to be involved in several liver diseases like I/R injury, steatohepatitis, chronic cholestasis and liver cirrhosis. It may play an important role in the progression of hepatic fibrosis through HSCs [115]. However, it is unclear whether altered serotonin homeostasis is a driving force in the progression of hepatic fibrosis or is instead a consequence of fibrosis. Nevertheless, these findings raise the possibility that serotonin receptor antagonists may have potential as future therapeutic agents in the treatment of chronic liver disease like cirrhosis, which remains a major public health problem worldwide.

There are now increasing arguments that serotonin can act as a potent growth factor, for example in liver regeneration. Since platelets carry the majority of serotonin in the bloodstream, the relationship between platelets, serotonin and liver regeneration could have direct ramifications for clinical care. Platelet dysfunction and thrombocytopenia are common in cirrhotic patients undergoing liver transplantation due to portal hypertension and subsequent hypersplenism. Furthermore, during living-donor liver transplantation, liver regeneration is crucial for both the donor and the recipient patients [127, 128]. This is particularly critical in those recipients that experience small-for-size liver graft dysfunction [129]. Another population in which thrombocytopenia could potentially impair liver regeneration are those patients receiving neoadjuvant chemotherapy prior to undergoing elective liver resection for malignancy. Preoperative chemotherapeutic agents often cause significant bone marrow suppression including relative thrombocytopenia. Modulating serotonin content locally or increasing platelet counts systemically may be an effective strategy to improve liver regeneration and function in the transplant setting or following major hepatic resection.

Further exploration of downstream effects of serotonin in the hepatocyte cell cycle and its interaction with other cytokines and growth factors will provide a better understanding of the complex pathways involved in liver regeneration [130]. Platelet-derived serotonin may directly influence the proliferation of hepatocytes [84] or may be involved in the release of growth factors, such as interleukin-6 at the site of liver injury [131, 132]. Greater knowledge of the role of the serotonin receptor subtypes and the genes regulating these mechanisms will be important in understanding the biological basis and response to therapy (pharmacogenomics) in functional liver and GI disorders.

1 Hamlin, K. E. and Fischer, F. E. (1951) The synthesis of 5-hydroxytryptamine. J. Am. Chem. Soc. 73, 5007.
2 Erspamer, V. and Asero, B. (1952) Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. Nature 169, 800–801.
3 Rapport, M., Green, A. and Page, I. (1948) Serum vasoconstrictor: isolation and characterization. J. Biol. Chem. 176, 1243–1251.
4 Gershon, M. D., Drakontides, A. B. and Ross, L. L. (1965) Serotonin: synthesis and release from the myenteric plexus of the mouse intestine. Science 149, 197–199.
5 Gershon, M. D. (2004) Serotonin receptors and transporters – roles in normal and abnormal gastrointestinal motility. Aliment. Pharmacol. Ther. 20 (Suppl. 7), 3–14.
6 Gershon, M. D. and Tack, J. (2007) The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 132, 397–414.
7 Hoyer, D., Hannon, J. P. and Martin, G. R. (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol. Biochem. Behav. 71, 533–554.
8 Thompson, J. H. (1971) Serotonin and the alimentary tract. Res. Commun. Chem. Pathol. Pharmacol. 2, 687–781.
9 Lembeck, F. (1953) 5-Hydroxytryptamine in a carcinoid tumor. Nature 172, 910.
10 Bulbring, E. and Crema, A. (1959) The release of 5-hydroxytryptamine in relation to pressure exerted on the intestinal mucosa. J. Physiol. 146, 18–28.
11 Kim, D. Y. and Camilleri, M. (2000) Serotonin: a mediator of the brain-gut connection. Am. J. Gastroenterol. 95, 2698–2709.
12 Seuwen, K. and Pouyssegur, J. (1990) Serotonin as a growth factor. Biochem. Pharmacol. 39, 985–990.
13 Fanburg, B. L. and Lee, S. L. (1997) A new role for an old molecule: serotonin as a mitogen. Am. J. Physiol. 272, L795–L806.

14 Eddahibi, S., Raffestin, B., Pham, I., Launay, J. M., Aegerter, P., Sitbon, M. and Adnot, S. (1997) Treatment with 5-HT potentiates development of pulmonary hypertension in chronically hypoxic rats. Am. J. Physiol. 272, H1173–H1181.
15 Matsuda, M., Imaoka, T., Vomachka, A. J., Gudelsky, G. A., Hou, Z., Mistry, M., Bailey, J. P., Nieport, K. M., Walther, D. J., Bader, M. and Horseman, N. D. (2004) Serotonin regulates mammary gland development via an autocrine-paracrine loop. Dev. Cell. 6, 193–203.
16 Walther, D. J., Peter, J. U., Bashammakh, S., Hortnagl, H., Voits, M., Fink, H. and Bader, M. (2003) Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science 299, 76.
17 Lesurtel, M., Graf, R., Aleil, B., Walther, D. J., Tian, Y., Jochum, W., Gachet, C., Bader, M. and Clavien, P. A. (2006) Platelet-derived serotonin mediates liver regeneration. Science 312, 104–107.
18 Nocito, A., Georgiev, P., Dahm, F., Jochum, W., Bader, M., Graf, R. and Clavien, P. A. (2007) Platelets and platelet-derived serotonin promote tissue repair after normothermic hepatic ischemia in mice. Hepatology 45, 369–376.
19 Nocito, A., Dahm, F., Jochum, W., Jang, J. H., Georgiev, P., Bader, M., Renner, E. L. and Clavien, P. A. (2007) Serotonin mediates oxidative stress and mitochondrial toxicity in a murine model of nonalcoholic steatohepatitis. Gastroenterology 133, 608–618.
20 Erspamer, V. and Testini, A. (1959) Observations on the release and turnover rate of 5-hydroxytryptamine in the gastrointestinal tract. J. Pharm. Pharmacol. 11, 618–623.
21 Bertaccini, G. (1960) Tissue 5-hydroxytryptamine and urinary 5-hydroxyindoleacetic acid after partial or total removal of the gastro-intestinal tract in the rat. J. Physiol. 153, 239–249.
22 Dreyfus, C. F. and Bornstein, M. B. (1977) Synthesis of serotonin by neurons of the myenteric plexus in situ and in organotypic tissue culture. Brain Res. 128, 125–139.
23 Costa, M., Furness, J. B., Cuello, A. C., Verhofstad, A. A., Steinbusch, H. W. and Elde, R. P. (1982) Neurons with 5-hydroxytryptamine-like immunoreactivity in the enteric nervous system: their visualization and reactions to drug treatment. Neuroscience 7, 351–363.
24 Gershon, M. D. and Tamir, H. (1981) Release of endogenous 5-hydroxytryptamine from resting and stimulated enteric neurons. Neuroscience 6, 2277–2286.
25 Yu, P. L., Fujimura, M., Okumiya, K., Kinoshita, M., Hasegawa, H. and Fujimiya, M. (1999) Immunohistochemical localization of tryptophan hydroxylase in the human and rat gastrointestinal tracts. J. Comp. Neurol. 411, 654–665.
26 Tyce, G. M. (1990) Origin and metabolism of serotonin. J. Cardiovasc. Pharmacol. 16 Suppl 3, S1–S7.
27 Da Prada, M., Pletscher, A., Tranzer, J. P. and Knuchel, H. (1967) Subcellular localization of 5-hydroxytryptamine and histamine in blood platelets. Nature 216, 1315–1317.
28 Chen, J. X., Pan, H., Rothman, T. P., Wade, P. R. and Gershon, M. D. (1998) Guinea pig 5-HT transporter: cloning, expression, distribution, and function in intestinal sensory reception. Am. J. Physiol. 275, G433–G448.
29 Wade, P. R., Chen, J., Jaffe, B., Kassem, I. S., Blakely, R. D. and Gershon, M. D. (1996) Localization and function of a 5-HT transporter in crypt epithelia of the gastrointestinal tract. J. Neurosci. 16, 2352–2364.
30 Walther, D. J. and Bader, M. (2003) A unique central tryptophan hydroxylase isoform. Biochem. Pharmacol. 66, 1673–1680.
31 Gebauer, A., Merger, M. and Kilbinger, H. (1993) Modulation by 5-HT3 and 5-HT4 receptors of the release of 5-hydroxytryptamine from the guinea-pig small intestine. Naunyn Schmiedebergs Arch. Pharmacol. 347, 137–140.
32 Bonhaus, D. W., Bach, C., DeSouza, A., Salazar, F. H., Matsuoka, B. D., Zuppan, P., Chan, H. W. and Eglen, R. M. (1995) The pharmacology and distribution of human 5-hydroxytryptamine2B (5-HT2B) receptor gene products: comparison with 5-HT2A and 5-HT2C receptors. Br. J. Pharmacol. 115, 622–628.
33 Barnes, N. M. and Sharp, T. (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152.
34 Foxx-Orenstein, A. E., Kuemmerle, J. F. and Grider, J. R. (1996) Distinct 5-HT receptors mediate the peristaltic reflex induced by mucosal stimuli in human and guinea pig intestine. Gastroenterology 111, 1281–1290.
35 Kadowaki, M., Wade, P. R. and Gershon, M. D. (1996) Participation of 5-HT3, 5-HT4, and nicotinic receptors in the peristaltic reflex of guinea pig distal colon. Am. J. Physiol. 271, G849–G857.
36 Tuladhar, B. R., Kaisar, M. and Naylor, R. J. (1997) Evidence for a 5-HT3 receptor involvement in the facilitation of peristalsis on mucosal application of 5-HT in the guinea pig isolated ileum. Br. J. Pharmacol. 122, 1174–1178.
37 Grider, J. R., Kuemmerle, J. F. and Jin, J. G. (1996) 5-HT released by mucosal stimuli initiates peristalsis by activating 5-HT4/5-HT1p receptors on sensory CGRP neurons. Am. J. Physiol. 270, G778–G782.
38 Furness, J. B., Kunze, W. A. and Clerc, N. (1999) Nutrient tasting and signaling mechanisms in the gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses. Am. J. Physiol. 277, G922–G928.
39 Gershon, M. D. (2000) 5-HT (serotonin) physiology and related drugs. Curr. Opin. Gastroenterol. 16, 113–120.
40 Langley, J. N. (1921) The Autonomic Nervous System, Part I Heffer, Cambridge, UK
41 Pan, H. and Gershon, M. D. (2000) Activation of intrinsic afferent pathways in submucosal ganglia of the guinea pig small intestine. J. Neurosci. 20, 3295–3309.
42 Tack, J., Piessevaux, H., Coulie, B., Caenepeel, P. and Janssens, J. (1998) Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 115, 1346–1352.
43 Notivol, R., Coffin, B., Azpiroz, F., Mearin, F., Serra, J. and Malagelada, J. R. (1995) Gastric tone determines the sensitivity of the stomach to distention. Gastroenterology 108, 330–336.
44 Tack, J., Broekaert, D., Coulie, B., Fischler, B. and Janssens, J. (2003) Influence of the selective serotonin re-uptake inhibitor, paroxetine, on gastric sensorimotor function in humans. Aliment. Pharmacol. Ther. 17, 603–608.
45 Tonini, M., Galligan, J. J. and North, R. A. (1989) Effects of cisapride on cholinergic neurotransmission and propulsive motility in the guinea pig ileum. Gastroenterology 96, 1257–1264.
46 Buchheit, K. H. and Buhl, T. (1991) Prokinetic benzamides stimulate peristaltic activity in the isolated guinea pig ileum by activation of 5-HT4 receptors. Eur. J. Pharmacol. 205, 203–208.
47 Tack, J. F., Janssens, J., Vantrappen, G. and Wood, J. D. (1992) Actions of 5-hydroxytryptamine on myenteric neurons in guinea pig gastric antrum. Am. J. Physiol. 263, G838–G846.
48 Michel, K., Sann, H., Schaaf, C. and Schemann, M. (1997) Subpopulations of gastric myenteric neurons are differentially activated via distinct serotonin receptors: projection, neurochemical coding, and functional implications. J. Neurosci. 17, 8009–8017.
49 Tack, J., Coulie, B., Wilmer, A., Andrioli, A. and Janssens, J. (2000) Influence of sumatriptan on gastric fundus tone and on the perception of gastric distension in man. Gut 46, 468–473.
50 Coulie, B., Tack, J., Maes, B., Geypens, B., De Roo, M. and Janssens, J. (1997) Sumatriptan, a selective 5-HT1 receptor agonist, induces a lag phase for gastric emptying of liquids in humans. Am. J. Physiol. 272, G902–G908.
51 Dinan, T. G., Mahmud, N., Rathore, O., Thakore, J., Scott, L. V., Carr, E., Naesdal, J., O'Morain, C. A. and Keeling, P. W. (2001) A double-blind placebo-controlled study of buspirone-stimulated prolactin release in non-ulcer dyspep-

sia–are central serotoninergic responses enhanced? Aliment. Pharmacol. Ther. 15, 1613–1618.
52 Siriwardena, A. and Kellum, J. M., Jr. (1993) A 5-HT2 receptor mediates serotonin-induced electrolyte transport in rat left colon. J. Surg. Res. 55, 323–329.
53 Peregrin, A. T., Ahlman, H., Jodal, M. and Lundgren, O. (1999) Involvement of serotonin and calcium channels in the intestinal fluid secretion evoked by bile salt and cholera toxin. Br. J. Pharmacol. 127, 887–894.
54 von der Ohe, M. R., Camilleri, M., Kvols, L. K. and Thomforde, G. M. (1993) Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. N. Engl. J. Med. 329, 1073–1978.
55 Tyers, M. B. and Freeman, A. J. (1992) Mechanism of the antiemetic activity of 5-HT3 receptor antagonists. Oncology 49, 263–268.
56 Marty, M., Pouillart, P., Scholl, S., Droz, J. P., Azab, M., Brion, N., Pujade-Lauraine, E., Paule, B., Paes, D. and Bons, J. (1990) Comparison of the 5-hydroxytryptamine3 (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. N. Engl. J. Med. 322, 816–821.
57 Platt, A. J., Heddle, R. M., Rake, M. O. and Smedley, H. (1992) Ondansetron in carcinoid syndrome. Lancet 339, 1416.
58 von der Ohe, M. R., Camilleri, M. and Kvols, L. K. (1994) A 5HT3 antagonist corrects the postprandial colonic hypertonic response in carcinoid diarrhea. Gastroenterology 106, 1184–1189.
59 McLean, P. G., Borman, R. A. and Lee, K. (2007) 5-HT in the enteric nervous system: gut function and neuropharmacology. Trends Neurosci. 30, 9–13.
60 Camilleri, M. (2002) Serotonergic modulation of visceral sensation: lower gut. Gut 51 Suppl 1, i81–i86.
61 Camilleri, M. and Ford, M. J. (1994) Functional gastrointestinal disease and the autonomic nervous system: a way ahead? Gastroenterology 106, 1114–1118.
62 Atkinson, W., Lockhart, S., Whorwell, P. J., Keevil, B. and Houghton, L. A. (2006) Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. Gastroenterology 130, 34–43.
63 Prior, A. and Read, N. W. (1993) Reduction of rectal sensitivity and post-prandial motility by granisetron, a 5 HT3-receptor antagonist, in patients with irritable bowel syndrome. Aliment. Pharmacol. Ther. 7, 175–180.
64 von der Ohe, M. R., Hanson, R. B. and Camilleri, M. (1994) Serotonergic mediation of postprandial colonic tonic and phasic responses in humans. Gut 35, 536–541.
65 Maxton, D. G., Morris, J. and Whorwell, P. J. (1996) Selective 5-hydroxytryptamine antagonism: a role in irritable bowel syndrome and functional dyspepsia? Aliment. Pharmacol. Ther. 10, 595–599.
66 Costall, B. and Naylor, R. J. (1992) Anxiolytic potential of 5-HT3 receptor antagonists. Pharmacol. Toxicol. 70, 157–162.
67 Kellow, J., Lee, O. Y., Chang, F. Y., Thongsawat, S., Mazlam, M. Z., Yuen, H., Gwee, K. A., Bak, Y. T., Jones, J. and Wagner, A. (2003) An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 52, 671–676.
68 Tutuian, R., Mainie, I., Allan, R., Hargreaves, K., Agrawal, A., Freeman, J., Gale, J. and Castell, D. O. (2006) Effects of a 5-HT(4) receptor agonist on oesophageal function and gastro-oesophageal reflux: studies using combined impedance-manometry and combined impedance-pH. Aliment. Pharmacol. Ther. 24, 155–162.
69 Asakawa, H., Hayashi, I., Fukui, T. and Tokunaga, K. (2003) Effect of mosapride on glycemic control and gastric emptying in type 2 diabetes mellitus patients with gastropathy. Diabetes Res. Clin. Pract. 61, 175–182.
70 Tutton, P. J. and Barkla, D. H. (1982) Influence of inhibitors of serotonin uptake on intestinal epithelium and colorectal carcinomas. Br. J. Cancer. 46, 260–265.
71 Tutton, P. J. and Steel, G. G. (1979) Influence of biogenic amines on the growth of xenografted human colorectal carcinomas. Br. J. Cancer. 40, 743–749.
72 Tutton, P. J. and Barkla, D. H. (1978) The influence of serotonin on the mitotic rate in the colonic crypt epithelium and in colonic adenocarcinoma in rats. Clin. Exp. Pharmacol. Physiol. 5, 91–94.
73 Barkla, D. H. and Tutton, P. J. (1981) Influence of histamine and serotonin antagonists on the growth of xenografted human colorectal tumors. J. Natl. Cancer. Inst. 67, 1207–1211.
74 Seretis, E., Gavrill, A., Agnantis, N., Golematis, V. and Voloudakis-Baltatzis, I. E. (2001) Comparative study of serotonin and bombesin in adenocarcinomas and neuroendocrine tumors of the colon. Ultrastruct. Pathol. 25, 445–454.
75 Yue, C. T. and Liu, Y. L. (2005) Fluoxetine increases extracellular levels of 3-methoxy-4-hydroxyphenylglycol in cultured COLO320 DM cells. Cell Biochem. Funct. 23, 109–114.
76 Xu, W., Tamim, H., Shapiro, S., Stang, M. R. and Collet, J. P. (2006) Use of antidepressants and risk of colorectal cancer: a nested case-control study. Lancet Oncol. 7, 301–308.
77 Troxler, M., Dickinson, K. and Homer-Vanniasinkam, S. (2007) Platelet function and antiplatelet therapy. Br. J. Surg. 94, 674–682.
78 Mannaioni, P. F., Di Bello, M. G. and Masini, E. (1997) Platelets and inflammation: role of platelet-derived growth factor, adhesion molecules and histamine. Inflamm. Res. 46, 4–18.
79 Sindram, D., Porte, R. J., Hoffman, M. R., Bentley, R. C. and Clavien, P. A. (2000) Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. Gastroenterology 118, 183–191.
80 Sindram, D., Porte, R. J., Hoffman, M. R., Bentley, R. C. and Clavien, P. A. (2001) Synergism between platelets and leukocytes in inducing endothelial cell apoptosis in the cold ischemic rat liver: a Kupffer cell-mediated injury. FASEB J. 15, 1230–1232.
81 Kohli, V., Selzner, M., Madden, J. F., Bentley, R. C. and Clavien, P. A. (1999) Endothelial cell and hepatocyte deaths occur by apoptosis after ischemia-reperfusion injury in the rat liver. Transplantation 67, 1099–1105.
82 Tomikawa, M., Hashizume, M., Highashi, H., Ohta, M. and Sugimachi, K. (1996) The role of the spleen, platelets, and plasma hepatocyte growth factor activity on hepatic regeneration in rats. J. Am. Coll. Surg. 182, 12–16.
83 Murata, S., Ohkohchi, N., Matsuo, R., Ikeda, O., Myronovych, A. and Hoshi, R. (2007) Platelets promote liver regeneration in early period after hepatectomy in mice. World J Surg 31, 808–816.
84 Balasubramanian, S. and Paulose, C. S. (1998) Induction of DNA synthesis in primary cultures of rat hepatocytes by serotonin: possible involvement of serotonin S2 receptor. Hepatology 27, 62–66.
85 Julius, D., Livelli, T. J., Jessell, T. M. and Axel, R. (1989) Ectopic expression of the serotonin 1c receptor and the triggering of malignant transformation. Science 244, 1057–1062.
86 Julius, D., Huang, K. N., Livelli, T. J., Axel, R. and Jessell, T. M. (1990) The 5HT2 receptor defines a family of structurally distinct but functionally conserved serotonin receptors. Proc. Natl. Acad. Sci. USA 87, 928–932.
87 Nebigil, C. G., Hickel, P., Messaddeq, N., Vonesch, J. L., Douchet, M. P., Monassier, L., Gyorgy, K., Matz, R., Andriantsitohaina, R., Manivet, P., Launay, J. M. and Maroteaux, L. (2001) Ablation of serotonin 5-HT(2B) receptors in mice leads to abnormal cardiac structure and function. Circulation 103, 2973–2979.
88 Fiorica-Howells, E., Maroteaux, L. and Gershon, M. D. (2000) Serotonin and the 5-HT(2B) receptor in the development of enteric neurons. J. Neurosci. 20, 294–305.
89 Gooz, M., Gooz, P., Luttrell, L. M. and Raymond, J. R. (2006) 5-HT2A receptor induces ERK phosphorylation and proliferation through ADAM-17 tumor necrosis factor-alpha-

converting enzyme (TACE) activation and heparin-bound epidermal growth factor-like growth factor (HB-EGF) shedding in mesangial cells. J. Biol. Chem. 281, 21004–21012.
90 Nebigil, C. G., Launay, J. M., Hickel, P., Tournois, C. and Maroteaux, L. (2000) 5-Hydroxytryptamine 2B receptor regulates cell-cycle progression: cross-talk with tyrosine kinase pathways. Proc. Natl. Acad. Sci. USA 97, 2591–2596.
91 Liu, Y., Li, M., Warburton, R. R., Hill, N. S. and Fanburg, B. L. (2007) The 5-HT transporter transactivates the PDGF{beta} receptor in pulmonary artery smooth muscle cells. FASEB J. 21, 2725–2734
92 Kulinskii, A. S., Saratikov, A. S., Vstavskaia Iu, A. and Udovitsina, T. I. (1983) Effect of substances altering the metabolism of endogenous serotonin on mitotic activity in the regenerating liver of mice (in Russian). Farmakol. Toksikol. 46, 92–95.
93 Aslamova, L. I., Blium Ia, B., Tsudzevich, B. A. and Kucherenko, N. E. (1985) Cyclic nucleotide levels in the regenerating liver of rats following irradiation and protection by serotonin (in Russian). Radiobiologiia 25, 324–327.
94 Papadimas, G. K., Tzirogiannis, K. N., Panoutsopoulos, G. I., Demonakou, M. D., Skaltsas, S. D., Hereti, R. I., Papadopoulou-Daifoti, Z. and Mykoniatis, M. G. (2006) Effect of serotonin receptor 2 blockage on liver regeneration after partial hepatectomy in the rat liver. Liver Int. 26, 352–361.
95 Basile, A. S., Jones, E. A. and Skolnick, P. (1991) The pathogenesis and treatment of hepatic encephalopathy: evidence for the involvement of benzodiazepine receptor ligands. Pharmacol. Rev. 43, 27–71.
96 Jones, E. A. (1995) Fatigue associated with chronic liver disease: a riddle wrapped in a mystery inside an enigma. Hepatology 22, 1606–1608.
97 Lozeva-Thomas, V. (2004) Serotonin brain circuits with a focus on hepatic encephalopathy. Metab. Brain. Dis. 19, 413–420.
98 Kiba, T., Tanaka, K. and Inoue, S. (1995) Lateral hypothalamic lesions facilitate hepatic regeneration after partial hepatectomy in rats. Pflugers Arch. 430, 666–671.
99 Pyroja, S., Joseph, B. and Paulose, C. S. (2007) Increased 5-HT2C receptor binding in the brain stem and cerebral cortex during liver regeneration and hepatic neoplasia in rats. J. Neurol. Sci. 254, 3–8.
100 Xu, Y., Huo, Y., Toufektsian, M. C., Ramos, S. I., Ma, Y., Tejani, A. D., French, B. A. and Yang, Z. (2006) Activated platelets contribute importantly to myocardial reperfusion injury. Am. J. Physiol. Heart. Circ. Physiol. 290, H692–H699.
101 Okada, Y., Marchevsky, A. M., Zuo, X. J., Pass, J. A., Kass, R. M., Matloff, J. M. and Jordan, S. C. (1997) Accumulation of platelets in rat syngeneic lung transplants: a potential factor responsible for preservation-reperfusion injury. Transplantation 64, 801–806.
102 Kuroda, T., Shiohara, E., Homma, T., Furukawa, Y. and Chiba, S. (1994) Effects of leukocyte and platelet depletion on ischemia-reperfusion injury to dog pancreas. Gastroenterology 107, 1125–1134.
103 Khandoga, A., Biberthaler, P., Enders, G., Teupser, D., Axmann, S., Luchting, B., Hutter, J., Messmer, K. and Krombach, F. (2002) P-selectin mediates platelet-endothelial cell interactions and reperfusion injury in the mouse liver in vivo. Shock 18, 529–535.
104 Yadav, S. S., Howell, D. N., Steeber, D. A., Harland, R. C., Tedder, T. F. and Clavien, P. A. (1999) P-selectin mediates reperfusion injury through neutrophil and platelet sequestration in the warm ischemic mouse liver. Hepatology 29, 1494–1502.
105 Khandoga, A., Biberthaler, P., Enders, G., Axmann, S., Hutter, J., Messmer, K. and Krombach, F. (2002) Platelet adhesion mediated by fibrinogen-intercelllular adhesion molecule-1 binding induces tissue injury in the postischemic liver in vivo. Transplantation 74, 681–688.
106 Murata, R., Hamada, N., Nakamura, N., Kobayashi, A., Fukueda, M., Taira, A. and Sakata, R. (2003) Serotonin activity and liver dysfunction following hepatic ischemia and reperfusion. In Vivo 17, 567–572.
107 Day, C. P. and James, O. F. (1998) Steatohepatitis: a tale of two 'hits'? Gastroenterology 114, 842–845.
108 Bianchi, P., Kunduzova, O., Masini, E., Cambon, C., Bani, D., Raimondi, L., Seguelas, M. H., Nistri, S., Colucci, W., Leducq, N. and Parini, A. (2005) Oxidative stress by monoamine oxidase mediates receptor-independent cardiomyocyte apoptosis by serotonin and postischemic myocardial injury. Circulation 112, 3297–3305.
109 Marasini, B., Biondi, M. L. and Agostoni, A. (1989) Platelet and plasma serotonin in patients with liver cirrhosis. J. Clin. Chem. Clin. Biochem. 27, 419–421.
110 Laffi, G., Marra, F., Gresele, P., Romagnoli, P., Palermo, A., Bartolini, O., Simoni, A., Orlandi, L., Selli, M. L., Nenci, G. G. (1992) Evidence for a storage pool defect in platelets from cirrhotic patients with defective aggregation. Gastroenterology 103, 641–646.
111 Borcsiczky, D., Szalay, F., Tekes, K., Tarcali, J., Magyar, K. and de Chatel, R. (1996) Platelet serotonin (5-HT) content is decreased in patients with alcoholic liver cirrhosis, but elevated in Gilbert's syndrome. J. Hepatol. 25, 781–782.
112 Beaudry, P., Hadengue, A., Callebert, J., Gaudin, C., Soliman, H., Moreau, R., Launay, J. M. and Lebrec, D. (1994) Blood and plasma 5-hydroxytryptamine levels in patients with cirrhosis. Hepatology 20, 800–803.
113 Mann, D. A. and Smart, D. E. (2002) Transcriptional regulation of hepatic stellate cell activation. Gut 50, 891–896.
114 Bataller, R. and Brenner, D. A. (2005) Liver fibrosis. J. Clin. Invest. 115, 209–218.
115 Ruddell, R. G., Oakley, F., Hussain, Z., Yeung, I., Bryan-Lluka, L. J., Ramm, G. A. and Mann, D. A. (2006) A role for serotonin (5-HT) in hepatic stellate cell function and liver fibrosis. Am. J. Pathol. 169, 861–876.
116 Kasho, M., Sakai, M., Sasahara, T., Anami, Y., Matsumura, T., Takemura, T., Matsuda, H., Kobori, S. and Shichiri, M. (1998) Serotonin enhances the production of type IV collagen by human mesangial cells. Kidney Int. 54, 1083–1092.
117 Ishida, T., Hirata, K., Sakoda, T., Kawashima, S., Akita, H. and Yokoyama, M. (1999) Identification of mRNA for 5-HT1 and 5-HT2 receptor subtypes in human coronary arteries. Cardiovasc. Res. 41, 267–274.
118 Li, T., Weng, S. G., Leng, X. S., Peng, J. R., Wei, Y. H., Mou, D. C. and Wang, W. X. (2006) Effects of 5-hydroxytamine and its antagonists on hepatic stellate cells. Hepatobil. Pancreat. Dis. Int. 5, 96–100.
119 Bergasa, N. V. (2003) Pruritus and fatigue in primary biliary cirrhosis. Clin. Liver. Dis. 7, 879–900.
120 Swain, M. G. and Maric, M. (1997) Improvement in cholestasis-associated fatigue with a serotonin receptor agonist using a novel rat model of fatigue assessment. Hepatology 25, 291–294.
121 Marzioni, M., Glaser, S., Francis, H., Marucci, L., Benedetti, A., Alvaro, D., Taffetani, S., Ueno, Y., Roskams, T., Phinizy, J. L., Venter, J., Fava, G., Lesage, G. D. and Alpini, G. (2005) Autocrine/paracrine regulation of the growth of the biliary tree by the neuroendocrine hormone serotonin. Gastroenterology 128, 121–137.
122 Jones, E. A., Molenaar, H. A. and Oosting, J. (2007) Ondansetron and pruritus in chronic liver disease: a controlled study. Hepatogastroenterology 54, 1196–1199.
123 Sumi, S. and Tamura, K. (2000) Frontiers of pancreas regeneration. J Hepatobil. Pancreat. Surg. 7, 286–294.
124 Mohanan, V., Kaimal, S. B. and Paulose, C. S. (2005) Decreased 5-HT1A receptor gene expression and 5-HT1A receptor protein in the cerebral cortex and brain stem during pancreatic regeneration in rats. Neurochem. Res. 30, 25–32.
125 Mohanan, V. V., Chathu, F. and Paulose, C. S. (2005) Decreased 5-HT2C receptor binding in the cerebral cortex and brain stem during pancreatic regeneration in rats. Mol. Cell. Biochem. 272, 165–170.

126 Mohanan, V. V., Khan, R. and Paulose, C. S. (2006) Hypothalamic 5-HT functional regulation through 5-HT1A and 5-HT2C receptors during pancreatic regeneration. Life Sci. 78, 1603–1609.
127 Marcos, A., Fisher, R. A., Ham, J. M., Shiffman, M. L., Sanyal, A. J., Luketic, V. A., Sterling, R. K., Fulcher, A. S. and Posner, M. P. (2000) Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. Transplantation 69, 1375–1379.
128 Olthoff, K. M. (2003) Hepatic regeneration in living donor liver transplantation. Liver Transplant 9, S35–S41.
129 Dahm, F., Georgiev, P. and Clavien, P. A. (2005) Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. Am. J. Transplant. 5, 2605–2610.
130 Clavien, P. A., Petrowsky, H., DeOliveira, M. L. and Graf, R. (2007) Strategies for safer liver surgery and partial liver transplantation. N. Engl. J. Med. 356, 1545–1559.
131 Cressman, D. E., Greenbaum, L. E., DeAngelis, R. A., Ciliberto, G., Furth, E. E., Poli, V. and Taub, R. (1996) Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. Science 274, 1379–1383.
132 Durk, T., Panther, E., Muller, T., Sorichter, S., Ferrari, D., Pizzirani, C., Di Virgilio, F., Myrtek, D., Norgauer, J. and Idzko, M. (2005) 5-Hydroxytryptamine modulates cytokine and chemokine production in LPS-primed human monocytes via stimulation of different 5-HTR subtypes. Int. Immunol. 17, 599–606.