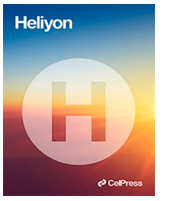
Heliyon 10 (2024) e30703

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

The janus face of serotonin: Regenerative promoter and chronic liver disease aggravator

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ARTICLE INFO

Keywords:
Serotonin
Chronic liver disease
Hepatic regeneration
SSRIs
Gut-liver axis

ABSTRACT

The progression of liver diseases, from viral hepatitis and fatty liver disease to cirrhosis and hepatocellular carcinoma (HCC), is the most representative series of pathological events in liver diseases. While serotonin (5-HT) primarily regulates brain functions such as psychology, mood, and appetite in the central nervous system (CNS), peripheral 5-HT plays a crucial role in regulating tumor development, glucose and lipid metabolism, immune function and inflammatory response related to liver diseases. These peripheral physiological processes involving 5-HT are the key mechanisms driving the development of these liver diseases. This study presents an overview of the existing literature, focusing on the role of 5-HT in HCC, cirrhosis, fatty liver disease, viral hepatitis, and liver injury. In summary, while 5-HT promotes liver regeneration, it can also contribute to the progression of chronic liver disease. These findings indicate the potential for the development and use of 5-HT-related drugs for the treatment of liver diseases, including HCC and cirrhosis.

Facts

- 5-HT tends to aggravate the progression of liver disease but facilitates liver regeneration.
- The distribution of receptors for 5-HT varies among different cellular components in the liver.
- Treatment with SSRIs often impedes the progression of HCC but exacerbates MASLD.

Open questions

It is feasible and desirable to formulate targeted drugs to precisely control 5-HT regulation of different liver diseases based on the differential distribution of 5-HT receptors among liver cell components.

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https://doi.org/10.1016/j.heliyon.2024.e30703
Received 19 December 2023; Received in revised form 1 May 2024; Accepted 2 May 2024
Available online 3 May 2024

Abbreviations

HCC	hepatocellular carcinoma
5-HT	5-Hydroxytryptamine/serotonin
CNS	central nervous system
ECs	enterochromaffin cells
Tph	tryptophan hydroxylases
5-HTP	5-hydroxytryptophan
ENS	enteric nervous system
SERT	serotonin selective reuptake transporter
MAO	monoamine oxidase
IDO	indoleamine 2,3-dioxygenase
5-HTRs	5-HT receptors
AC	adenylate cyclase
AFP	alpha-fetoprotein
SSRIs	Serotonin reuptake inhibitors
IFN	interferon
MMP	mitochondrial membrane potential
ROS	reactive oxygen species
mTOR	mammalian target of rapamycin
HSCs	hepatic stellate cells
KCs	Kupffer cells
MASLD	metabolic dysfunction-associated steatotic liver disease
MASH	metabolic dysfunction-associated steatohepatitis
NDEA	N-nitrosodiethylamine/diethylnitrosamine

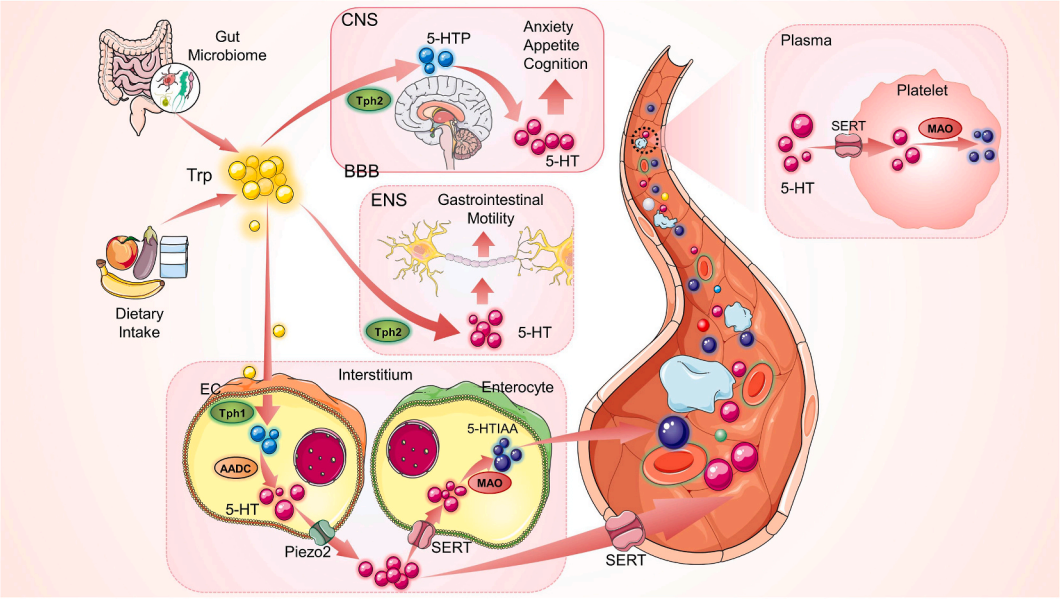

Fig. 1. The metabolism of 5-HT | Tryptophan (Trp) from dietary intake or gut microbial production is synthesized into serotonin (5-HT) through three pathways. Trp is generated in enterochromaffin cells (ECs) by tryptophan hydroxylase 1 (Tph1) to produce 5-hydroxytryptophan (5-HTP), which is subsequently decarboxylated by amino acid decarboxylase (AADC) to synthesize 5-HT. Assisted by Piezo-type Mechanosensitive Ion Channel Component 2 (Piezo2), 5-HT is released from ECs into the interstitium of intestinal cells, and is subsequently transported into enterocytes by serotonin selective reuptake transporter (SERT) and metabolized by monoamine oxidase (MAO) into 5-hydroxyindoleacetic acid (5-HIAA). 5-HT is absorbed by SERT into the blood circulation and eventually stored in platelets through SERT, and platelets can also degrade 5-HT to 5-HIAA through MAO. Tph synthesizes 5-HT with the assistance of Tph2 in the central nervous system (CNS) and enteric nervous system (ENS). Central and peripheral 5-HT do not interfere with each other functionally due to the presence of the blood-brain barrier (BBB).

1. Introduction

The liver possesses unique characteristics, including its dual blood supply and impressive regenerative capacity, which make hepatectomy a viable treatment option for liver lesions such as cancer and trauma [1]. However, the liver's rich blood supply presents a double-edged sword: while it provides abundant nourishment for liver cancer cells, it also renders the organ susceptible to metastases from gastrointestinal lesions, including liver metastases from gastrointestinal tumors and bacteria. The progression of emblematic liver diseases, such as hepatitis, fatty liver disease or alcoholic (non-alcoholic) liver disease to cirrhosis and, ultimately, hepatocellular carcinoma (HCC), continues to present significant challenges for Hepatobiliary Surgery [2]. Advancements in the understanding of the liver's local anatomy have led to improved proficiency in performing hepatectomy. Researchers in the field of Hepatobiliary Surgery are now placing greater emphasis on the early detection and diagnosis of HCC, preventing precancerous lesions, and promoting the rapid regeneration of the remaining liver tissue following hepatectomy.

Serotonin (5-Hydroxytryptamine, 5-HT) is a crucial messenger in both the central nervous system (CNS) and peripheral tissues that mediates various neurological and non-neurological physiological processes. Recent studies have shown that 5-HT could be used to potentially identify early-stage liver cancer [3], regulate precancerous lesions [4], assess patients' prognosis [5], and stimulate liver regeneration [6]. In addition to its hepatic functions, 5-HT also plays a crucial role in regulating psychological and behavioral processes, vascular tension, energy metabolism, gastrointestinal motility and secretion, and insulin secretion. Initially, the understanding of the link between 5-HT and the liver was limited to liver lesions associated with carcinoid syndromes [7,8]. However, since the 21st century, there has been an increasing exploration of the role of 5-HT in liver diseases. From hepatitis [9], fatty liver [10] and acute liver injury [11] to cirrhosis [12] and liver cancer [13], the involvement of 5-HT has been identified as a significant and noteworthy contribution. However, the role of 5-HT in the liver is complex and seems contradictory, as it has the potential to both promote hepatic regeneration and accelerate tumor growth [14]. Therefore, this review aims to provide a comprehensive understanding of the regulatory role of 5-HT in liver metabolism, explore the various receptor subtypes of 5-HT and the downstream pathways activated upon its stimulation, and discuss the specific mechanisms through which 5-HT influences liver disease.

2. The metabolism of 5-HT

2.1. Synthesis

5-HT is an intermediate product in the metabolism of tryptophan. In healthy human body, most 5-HT (around 90–95 %) is synthesized by enterochromaffin cells (ECs) in the gastrointestinal mucosa, and a smaller amount is produced by 5-HTergic neurons in the central nervous system (CNS) (Fig. 1). The synthesis of 5-HT begins with tryptophan hydroxylases (Tph), which convert tryptophan, an essential amino acid, into 5-hydroxytryptophan (5-HTP) and subsequently yield 5-HT following the decarboxylating of 5-HTP by 5-HTP decarboxylase [15]. Peripheral tissues contain both neurogenic and mucosal sources of 5-HT, accounting for approximately 5 % and 95 % of peripheral 5-HT, respectively. The neurogenic source is primarily synthesized by the enteric nervous system (ENS) in the gastrointestinal tract, predominantly through the action of Tph2. This neurogenic source of 5-HT is crucial for regulating gastrointestinal motility by controlling the ENS. On the other hand, the mucosal source of 5-HT is mainly synthesized and secreted by ECs, primarily through the action of Tph1. Once synthesized, most 5-HT is released into the bloodstream to regulate various physiological functions throughout the body, while only a small fraction is stored within ECs. The free 5-HT in the circulatory system is taken up by platelets and stored in their dense granules [16,17].

2.2. Transportation

Once synthesized by ECs, 5-HT is released into the interstitium of the intestinal epithelial cells. This release is mediated by Piezo-type Mechanosensitive Ion Channel Component 2 (Piezo2). The presence of 5-HT in the interstitium promotes intestinal motility in response to various stimuli, including changes in pH, food, or toxins within the intestinal lumen [18]. When its role is fulfilled, 5-HT in the interstitium is transported back into the intestinal cells or the circulatory system through the serotonin selective reuptake transporter (SERT) [19]. Then, most 5-HT that enter the circulatory system are transported by SERT and stored in the dense granules of platelets.

2.3. Degradation

There are three main metabolic pathways identified for 5-HT in enterocytes and platelets, namely the 5-hydroxyindoleacetic acid (5-HIAA) pathway, the melatonin pathway, and the kynurenine pathway. In the 5-HIAA pathway, enterocytes and platelets utilize the enzyme monoamine oxidase (MAO) to convert 5-HT into 5-hydroxyindole aldehyde (5-HIA). Subsequently, aldehyde dehydrogenase (ALDH) metabolizes 5-HIA into 5-HIAA [20]. The melatonin pathway involves the sequential enzymatic action of aralkylamine N-acetyltransferase (AANAT) and hydroxyindole O-methyltransferase (HIOMT). These enzymes convert 5-HT into N-acetyl serotonin (NAS), which is further metabolized to form melatonin [21]. In addition, the presence of the indole moiety in 5-HT allows it to undergo metabolism by the enzyme indoleamine 2,3-dioxygenase (IDO), enabling its entry into the kynurenine pathway [21,22].

2.4. Receptors and downstream signaling pathways of 5-HT

5-HT is one of the neurotransmitters with the largest number of selectable receptors (seven families, 17 subtypes), making it versatile in performing various metabolic functions. It is important to note that the transportation of 5-HT through the SERT primarily serves degradation or recycling purposes. The classical signaling pathways mediated by 5-HT receptors (5-HTRs) have been extensively reviewed in other studies [23–25], and we only provide a brief overview of them in this section. Briefly, all 5-HTRs are G-protein-coupled receptors, except for 5-HTR_3, which acts as a ligand-gated ion channel dependent on the Na^+/K^+ ATPase. The downstream activation cascades of each receptor can vary due to the diversity of trimeric G proteins (16 α, 5 β, and 12 γ subunits). The 5-HTR_1 (including 5-$HTR_{1A, 1B, 1D, 1E, 1F}$) and 5-HTR_5 (including 5-HTR_{5A} and 5-HTR_{5B}) families are coupled to intracellular G-protein $G\alpha_{i/o}$, which inhibits adenylate cyclase (AC), resulting in a downregulation of protein kinase A (PKA)/cyclic adenosine monophosphate (cAMP) activity. Due to its functional coupling with the Gq protein, the 5-HTR_{1C} receptor has been reclassified as the 5-HTR_{2C}. Thus, the 5-HTR_2 family (including 5-$HTR_{2A, 2B, 2C}$) is typically coupled to the G-protein $G_{q/11}$, activating phospholipase C and leading to the production of inositol triphosphate (IP3) and diacylglycerol (DAG), ultimately causing an increase in intracellular calcium levels. Lastly, the 5-$HTR_{4/6/7}$ families couple to G-protein $G\alpha_s$ and trigger the PKA/cAMP signaling axis [23,26,27]. Detailed information on the individual receptor subtypes of 5-HTRs is provided in Table 1.

2.5. Serotonylation

Although most 5-HT's functions are mediated through receptors, it is important to note that 5-HT has been discovered and has exerted its effects billions of years prior to the identification of specific 5-HT receptors, indicating that 5-HT may also be capable of influencing cellular processes through non-receptor mechanisms [23]. One such mechanism is serotonylation, which refers to the covalent binding of serotonin to the primary amine of glutamine. Serotonylation operates independently of 5-HT receptors and has been found to have various implications. Recent research has revealed that serotonylation serves as a newly discovered epigenetic marker for histone H3[28,29], contributing to the regulation of cellular processes and has also been implicated in the regulation of small cell lung cancer [30], pulmonary hypertension [31,32], as well as in improving glucose metabolism [33,34]. However, considering that studies specifically investigating serotonylation in liver diseases are limited, this topic is not extensively discussed in this article.

3. 5-HT in liver injury

The hepatic damage associated with 5-HT can be observed in two main aspects: first, the potential liver toxicity mediated by serotonin reuptake inhibitors (SSRIs), and second, acute liver injury caused by dysregulation of the 5-HT degradation system (5DS).

Table 1
Summary of the functions of activated 5-HTRs.

Receptor	Subtype	Location	Type	Functions
5-HTR_1	1A	CNS	$G\alpha_{i/o}$	negatively coupled to AC/PKA/cAMP signaling; stimulate K^+ channel, inhibit Ca^{2+}channel; regulate ERK phosphorylation
	1B	CNS	$G\alpha_{i/o}$	negatively coupled to AC/PKA/cAMP signaling; stimulate K^+ channel, inhibit Ca^{2+}channel; stimulate nuclear ERK translocation; stimulate Akt
	1D	CNS		negatively coupled to AC and inhibit cAMP; positively coupled to Ca^{2+}-dependent K^+ channels
	1E	CNS		negatively coupled to the AC pathway
	1F	CNS; pancreas		negatively coupled to the AC pathway
5-HTR_2	2A	CNS; liver; skeletal muscle; vascular; kidney; adipose tissue	$G\alpha_{q/11}$	Neurons: coupled to PLC/DAG/AC/PKC-activated pathways, inhibit Ca^{2+} channel and Na^+ channel; Muscle: induce PLC/DAG/PKC/Ca^{2+} signaling and ERK phosphorylation leading to muscular contraction; Kidney: control cell proliferation and fibrosis
	2B	CNS; liver; pancreas; adipose tissue; cardiovascular tissues	$G\alpha_q$	activate PLC and yield an increase of IP3 and DAG; stimulate Ca^{2+} channel; induce MAPK/ERK pathway; activates NF-κB
	2C	CNS	$G\alpha_{q/11}$	activate PLC, PLD and PLA2; inhibit K^+ channel, stimulate Cl^- channel; stimulate ERK1/2 phosphorylation
5-HTR_3		CNS; gut; liver; pancreas	ligand-gated cation channel	control Na^+, K^+, and Ca^{2+} movements
5-HTR_4		CNS; gut	$G\alpha_s$	positively coupled to AC and raise cAMP levels; inhibit K^+ channel conductance in neurons, but stimulate Ca^{2+} channels in cardiomyocytes resulting in an increased Ca^{2+} transient in heart
5-HTR_5		CNS	$G\alpha_{i/o}$	negatively coupled to AC/PKA/cAMP signaling; inhibit ADP-ribosyl cyclase and regulate Ca^{2+} levels
5-HTR_6		CNS	$G\alpha_s$	positively coupled to AC/cAMP pathway; inhibits K^+ channel; produce ERK phosphorylation or Jun translocation to the nucleus
5-HTR_7		CNS; kidney	$G\alpha_s$	increase AC activity and cAMP accumulation; elicit neuronal depolarization by modulating K^+ and Na^+ conductance; induce ERK phosphorylation; enhance IL-6 synthesis

Although SSRIs are generally safe in treatment, instances of hepatic toxicity are rare complications. However, recent reports of SSRI-induced liver damage have provided clinicians with valuable insights into managing such situations. For example, Colakoglu reported a case of severe cholestasis and hepatic cell damage, possibly due to an immune-mediated hypersensitivity reaction in a patient taking paroxetine [35]. Ng also reported a case of cholestatic liver injury in a 56-year-old female patient with depression treated with escitalopram, which improved after discontinuing the drug [36]. Rohit described a case involving a 41-year-old female patient who developed a rash and liver dysfunction after taking fluoxetine, but both liver function and the rash recovered after discontinuing the medication [37]. Patrick observed that the perioperative use of SSRIs in patients undergoing hepatic resection resulted in liver function impairment and poor postoperative prognosis, suggesting caution in using SSRIs during the perioperative period of hepatic resection [38]. Therefore, it is advisable for clinicians to regularly monitor liver function in patients taking SSRIs to prevent adverse outcomes.

The 5-HT degradation system (5DS) axis refers to the process in which agonists and overexpression of 5-HTR_{2A} promote the degradation of 5-HT by upregulating the expression of 5-HT synthase and monoamine oxidase-A (MAO-A), leading to the overproduction of reactive oxygen species (ROS) in mitochondria. Activation of the 5DS axis triggers the phosphorylation of c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38 MAPK), signal transducer and activator of transcription 3 (STAT3) and NF-κB, upregulates Bax, cleaved-caspase3 and cleaved-caspase9, and downregulates Bcl-2, which ultimately result in apoptosis, hypersecretion of TNF-α and IL-1β, and the development of liver diseases. In addition, inhibiting the 5DS axis by 5-HTR_{2A} antagonists can block the signaling cascade, inflammation and apoptosis, thereby preventing carbon tetrachloride (CCl4)-induced hepatotoxicity both in vitro and in vivo [11,39]. Altogether, the proposed 5DS axis provides new insights into the regulation of liver diseases by 5-HT and holds potential for the development of related therapeutic interventions.

4. 5-HT in viral hepatitis

The onset and progression of viral hepatitis depend on the interaction between the virus and the host. Factors such as the quantity, virulence, and route of virus invasion play a role in the pathogenesis of the disease. Considering that a small amount of virus usually results in latent infections and a larger amount can lead to more severe lesions, the severity and types of hepatitis lesions usually indicate a close link with the body's immune status. Studies on the involvement of 5-HT in viral hepatitis date back to the 1970s. Early research by Szpakowicz et al. found that blood levels of 5-HT were significantly higher in patients with viral hepatitis, particularly in severe cases, while serum activity of the enzyme MAO was significantly lower in all cases [40]. This suggests a potential role for blood 5-HT levels in predicting the outcome of viral hepatitis or its involvement in the development of the disease. Subsequent studies have provided further evidence supporting this effect. For instance, Lang et al. demonstrated that 5-HT release in viral hepatitis mice led to hepatic sinusoidal microcirculatory failure, resulting in delayed $CD8^+$ T cell response, continued viral replication, and the promotion of chronic viral hepatitis [41]. Arne et al. observed a significant reduction in platelet 5-HT concentration following interferon (IFN) treatment in patients with hepatitis C virus (HCV) infection [42]. Marwa Gamaleldin et al. proposed that high levels of serum 5-HT could serve as a valuable non-invasive marker for portal hypertensive gastropathy in patients with HCV-induced cirrhosis and could be used to monitor disease progression [43]. Another study focusing on drug interventions reported that the Food and Drug Administration (FDA)-approved 5-HTR_{2A} antagonist phenoxybenzamine (PBZ) inhibited major genotypes of HCV in vitro and exhibited a synergistic effect with the standard anti-HCV drug combination used in clinical practice, which indirectly suggests the involvement of 5-HT in promoting viral hepatitis [44].

Studies on 5-HT in viral hepatitis have primarily focused on the use of SSRIs to improve complications associated with IFN treatment of patients with HCV. Depression is a common complication of IFN treatment, and prophylactic treatment with SSRIs has been shown to alleviate depressive, anxious, and neurotoxic symptoms associated with IFN treatment for HCV and is well-tolerated [45–48]. SSRIs are considered safe and effective for treating IFN-induced depression [49]. Open-label studies, case reports and randomized double-blind placebo-controlled trials have confirmed that SSRIs can be considered the first treatment choice for IFN-α-induced depression [50]. Mechanistically, 5-HTR_{1A} may play an important role in the pathogenesis of IFN-induced depression. Kraus et al. found that the homozygosity for the G-allele (C1019G) of 5-HTR_{1A}, located in the transcriptional control region of the 5-HTR_{1A} gene, significantly increased the incidence and severity of IFN-induced depression in HCV patients compared to those carrying at least one C allele [51]. Amanda et al. also reported a significant correlation between genetic variations in the 5-HTR_{1A} gene and the occurrence of major depressive episodes (MDE) in HCV patients treated with IFN-α, especially in those with the CC genotype of the 5-HTR_{1A} gene [52].

However, not all 5-HT-activated 5-HTRs can lead to the exacerbation of viral hepatitis. DDX3, a viral host factor, was shown to upregulate IFN-β and initiate antiviral intrinsic immune responses upon exposure to hepatitis B virus (HBV) infection [53]. Moreover, it acted as a transcriptional inhibitor of HBV by binding to virus polymerase [54,55]. Kang et al. confirmed that the activation of 5-HTR_7 by 5-HT stimulated the expression of DDX3 through adenylate cyclase (AC)/protein kinase A (PKA)/extracellular regulated protein kinases (ERK)-mediated phosphorylation of p53, thereby inhibiting HBV replication. These findings highlight the potential of targeting 5-HTR_7 as a strategy to suppress HBV infection [9].

5. 5-HT in metabolic dysfunction-associated steatotic liver disease

The liver serves as a central hub for modulating the metabolic pathways of carbohydrates, lipids and amino acids. Disruptions in these metabolic pathways can lead to structural and functional abnormalities in the liver, for which metabolic dysfunction-associated steatotic liver disease (MASLD) represents a prime example of this phenomenon. The development and progression of MASLD are associated with various pathogenic mechanisms, such as the accumulation of fatty acids induced by high-fat intake, the up-regulation

of fat generation related to insulin resistance, liver injury mediated by lipid peroxidation, increased oxidative or endoplasmic reticulum stress, and disturbances in lipid and glucose homeostatic metabolism [56,57]. Within this context, 5-HT, a molecule involved in metabolic processes, was found to exhibit intricate associations with MASLD.

Activation of 5-HT has been implicated in the promotion of liver steatosis. Studies using metabolic dysfunction-associated steatohepatitis (MASH) mouse models have shown that wild-type mice exhibited increased oxidative stress and mitochondrial toxicity compared to$Tph1^{-/-}$ mice, indicating that peripheral 5-HT may contribute to the progression of MASH [58]. Eugenosedin-A, a 5-$HTR_{2A/2B}$ blocker with antioxidant, anti-inflammatory and free radical scavenging effects, has been shown to attenuate high-fat diet-induced hyperglycemia, hyperlipidemia and lipid peroxidation in C57BL/6J mice [59]. Ongoing research continues to enhance our comprehension of the distinct processes through which 5-HT instigates hepatic steatosis. These processes essentially fall within two primary categories: the first pertains to the deficiency in SERT function, and the second involves the role of the gut-liver axis; for which there could be a potential intrinsic link between them.

5.1. *SERT function deficiency*

Experiments conducted by Chen et al. demonstrated that mice lacking the SERT had reduced food intake but developed glucose intolerance, insulin resistance, obesity and hepatic steatosis, which were partially attributed to impaired phosphatidylinositide 3-kinase (PI3K) and JNK signaling in peripheral tissues [60]. Similar findings were reported by Rosa et al., who observed that SERT knockout mice had increased body weight and more severe hepatic steatosis when fed a Western-style diet [61]. Conversely, upregulation of SERT expression and downregulation of Tph1 expression were found to have beneficial effects in alleviating the symptoms of MASLD [62]. From another perspective, the use of SSRIs such as fluoxetine has been associated with hepatic fat accumulation, further supporting the role of SERT deficiency in MASLD. Lu et al. discovered that fluoxetine downregulated the expression of hepatic glucose-6-phosphatase (G6Pase), leading to increased conversion of glucose into lipids and subsequent hepatic steatosis while having no effect on fatty acid uptake [63]. Ayyash et al. suggested that fluoxetine-induced hepatic lipid accumulation may be due to the upregulation of Tph1 expression and increased intracellular synthesis of 5-HT [64]. Furthermore, their subsequent research proposed that prostaglandin-endoperoxide synthase 1 (PTGS1) and its downstream product 15d-PGJ2 might be involved in mediating the hepatic lipid abnormalities induced by fluoxetine [65].

5.2. *Gut TPH1-liver HTR_{2A} axis*

The liver receives nearly 70 % of its blood supply through the portal vein from the intestine, allowing it to not only enjoy the nutritional benefits of intestinal nutrients but also bear the burden of harmful metabolites or bacterial invasion from the intestines. Enterochromaffin cells (ECs) in the intestine are primarily responsible for producing more than 90 % of peripheral 5-HT through the action of Tph1, an enzyme that is notably absent in the liver. Being the first organ to receive blood from the portal vein, the liver is likely to accumulate significant amounts of 5-HT released into the circulation by ECs in the intestine. Choi et al. confirmed this by showing that the concentration of 5-HT in the portal vein is higher than in the peripheral vein and that the ratio of portal vein 5-HT to

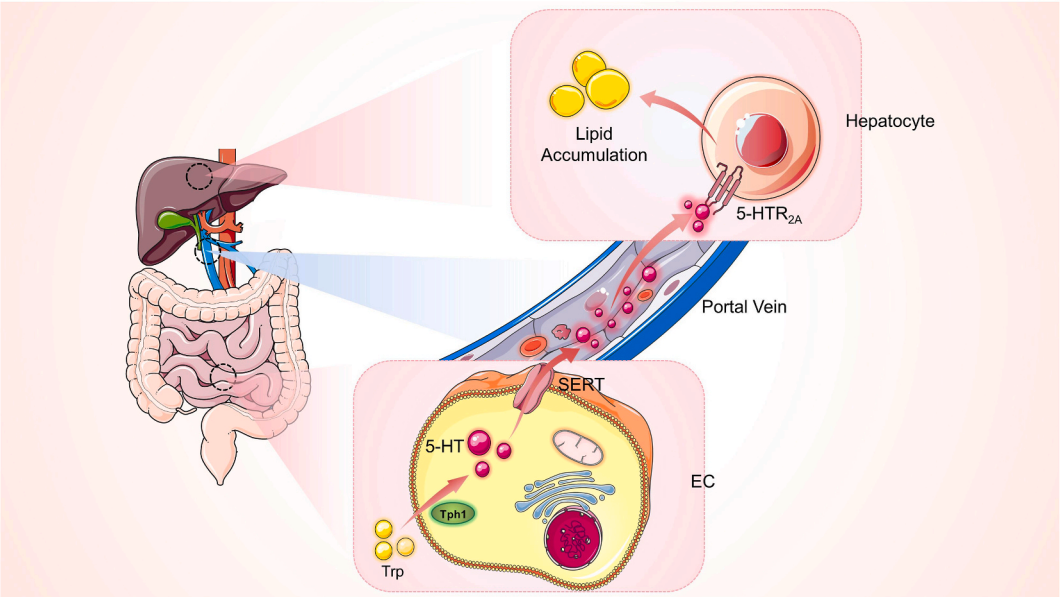

Fig. 2. The gut TPH1-liver HTR_{2A} axis in MASLD | Tph1 of intestinal ECs synthesizes the substrate Trp into 5-HT. SERT transports 5-HT into the portal vein to reach the liver. 5-HT activates 5-HTR_{2A}, promoting hepatic steatosis.

peripheral blood 5-HT correlates with the severity of MASLD [66]. A high-fat diet enhances the expression of Tph1 and increases the levels of 5-HT in the intestine and the concentration of 5-HT in the portal vein. Specifically, it promotes the expression of 5-HTR_{2A} in the liver while not affecting the expression of other 5-HT receptors [66]. These findings indicate that 5-HT, synthesized by intestinal Tph1, enters the liver through the portal vein and promotes the progression of hepatic steatosis by interacting with 5-HTR_{2A} expressed in the liver (Fig. 2). Additionally, blocking 5-HTR_{2A} in the liver or Tph1 in the intestine can attenuate the pro-steatotic effect of 5-HT. The involvement of the gut TPH1-liver HTR_{2A} axis in 5-HT and MASLD was further supported by subsequent studies by Takashi et al. [67,68]; thus, suggesting potential new therapeutic strategies for high-fat diet-induced MASLD.

Previous evidence suggested that the transport of 5-HT synthesized by ECs into the bloodstream is facilitated by SERT. Thus, a dysfunction in SERT was expected to suppress the physiological effects of 5-HT. Surprisingly, studies have shown that SERT knockout or treatment with SSRIs actually increases 5-HT synthesis and leads to hepatic steatosis. Moreover, intestinal-derived 5-HT has been found to stimulate hepatic lipid accumulation, contributing to the development of MASLD. These findings indicate that the transport of 5-HT into the portal vein may not solely depend on SERT function. It is speculated that there might be a negative feedback regulation between 5-HT and SERT in the intestine. For instance, when SERT function is inhibited, 5-HT transport is disrupted, resulting in increased expression of Tph1 and a subsequent feedback loop promoting 5-HT synthesis. Additionally, the physiological effects of 5-HT may occur independently of SERT in this context. However, further investigations are necessary to validate this hypothesis.

6. 5-HT in cirrhosis

Liver tissue homeostasis relies on an effective yet controlled self-repair mechanism to counteract injuries. Fibrosis is a natural part of the liver's healing response to injury. However, when the injury stimulus persists, an uncontrolled fibrotic response can be triggered, leading to the progression from fibrosis to cirrhosis. Cirrhosis occurs due to ongoing hepatocyte damage caused by various factors, including viral hepatitis, alcohol consumption, cholestasis, and autoimmune disorders. This damage leads to the infiltration of inflammatory cells and the release of inflammatory mediators and humoral factors such as hepatocyte growth factor (HGF), transforming growth factor β1 (TGF-β1), and interleukin-6 (IL-6). These factors activate hepatic stellate cells (HSCs), which undergo excessive activation and transdifferentiation into myofibroblasts. The myofibroblasts produce an abundance of extracellular matrix (ECM), resulting in the accumulation of fibrous connective tissue within the liver parenchyma. This process leads to the structural remodeling of liver lobules, the formation of pseudo-nodules, and the disruption of intraparenchymal blood flow. HSC hyperactivity and excessive ECM production are the primary contributors to the development of cirrhosis, while disturbances in intrahepatic hemodynamics play a crucial role in driving the progression and irreversibility of this pathological condition.

The relationship between 5-HT and cirrhosis has been extensively studied since Fiore-Donati et al. first proposed in 1958 that intervention with 5-HT can impact the outcome of CCl_4-induced cirrhosis in the liver [69], with numerous research conducted on this topic in the following decades [70–72]. Most of the current studies suggest that: ①Plasma 5-HT levels are higher in patients with cirrhosis than in those without cirrhosis; ②Overexpression of 5-HT activates 5-HTRs, which promotes fibrosis; ③Treatment with 5-HT receptor antagonists can often lead to the alleviation of cirrhosis.

The mechanisms through which 5-HT regulates the progression of cirrhosis have been extensively investigated (Fig. 3). Among all the 5-HT receptors, 5-HTR_2 (5-$HTR_{2A,\ 2B,\ 2C}$) and 5-HTR_7 are undoubtedly the most closely linked to cirrhosis. Ruddell et al. reported the expression of 5-$HTR_{1B,\ 1F,\ 2A,\ 2B,\ and\ 7}$ in both rats and humans. However, only 5-$HTR_{1B,\ 2A,\ and\ 2B}$ were induced in activated HSCs, with expression levels of 5-$HTR_{2A\ and\ 2B}$ in these activated being significantly higher (106-fold and 52-fold, respectively) in activated HSCs compared to quiescent cells [73]. HSCs actively uptake or release 5-HT via SERT, which subsequently activates 5-HTR_{2B}, promoting HSC proliferation by inhibiting apoptosis. This effect was reversed when a 5-HTR_{2B} antagonist was used, suggesting a close association between 5-HTR_{2B} and liver fibrosis in rats [73]. Similar findings were reported by Li et al., who observed high expression levels of 5-$HTR_{1A,\ 2A,\ and\ 2B}$ in HSCs, reported that 5-HT significantly increased the expression of TGF-β1 and Smad4, promoting HSC proliferation and that this effect could be antagonized by ketanserin, a 5-HTR_{2A} antagonist [74]. Zhang et al. conducted a study showing that Selenium-Enriched Green Tea effectively suppressed the expression of hepatic 5-$HTR_{2A/2B}$, leading to improved ECM deposition and scar formation, thereby ameliorating liver fibrosis [75]. Ebrahimkhani et al. made an interesting observation that 5-HTR_{2B} is highly expressed in activated HSCs but has low expression in normal liver cells [76]. The activation of 5-HTR_{2B} in HSCs by 5-HT stimulates the expression of TGF-β1 through ERK signaling and the transcription factor JunD, which inhibits hepatic cell proliferation [76]. In normal liver injury repair, activating TGF-β1 expression mediated by 5-HTR_{2B} in activated HSCs was shown to contribute to the termination of parenchymal cell proliferation, limiting the regenerative response to prevent excessive growth. However, in the pathophysiological context of ongoing liver fibrogenesis, persistent injury stimuli activate 5-HTR_{2B} by 5-HT, promoting the uncontrolled proliferation of HSCs and negatively regulating liver regeneration [76]. Moreover, this deleterious effect of 5-HTR_{2B} activation seems to surpass the beneficial effect of 5-HTR_{2A} activation, which is expressed in hepatocytes and promotes hepatocyte regeneration [6]. Thus, timely termination of injury signaling or the use of 5-HTR_{2B} antagonists (i.e., SB-204741) could promote HSCs apoptosis, thereby allowing the pro-hepatocyte regenerative effect of activated 5-HTR_{2A} on hepatocytes to prevail. It seems that 5-HTR_{2B} is more specifically targeted towards HSCs in the liver, while 5-$HTR_{2A,\ 2C,\ and\ 7}$ seem more closely associated with inflammation and oxidative stress damage in liver fibrosis. Saeid et al. treated thermal-injured mice with a $5HTR_{2A/2C}$ antagonist (Ketanserin) and found that it could promote anti-fibrotic effects by regulating the phenotype of macrophages [77]. A study by Atallah et al. showed that blocking 5-HTR_{2A} with Ketanserin or 5-HTR_7 with SB-269970 reduced oxidative stress/TGF-β1-induced liver fibrosis in CCl4-challenged rats [78], which were consistent with those reported by Dalia et al. [79]. Liang and Shan conducted in vivo and in vitro experiments showing that hyperglycemia or type 2 diabetes can upregulate the expression of 5-HTR_{2A}, the synthetic enzyme for 5-HT, and MAO-A, leading to increased intracellular 5-HT levels, mitochondrial reactive oxygen species (ROS) generation, and

myofibroblastization of HSCs. Consequently, this cascade results in the synthesis of TGF-β1, inflammation, and an increase in fibrotic factors. Further, the administration of a 5-HTR_{2A} antagonist, Sarpogrelate hydrochloride (SH), was shown to ameliorate this process [80].

However, some researchers have reported findings inconsistent with the analyses above. Oyvind found that Terguride, an effective antagonist of 5-HTR_2, did not prevent the development of liver fibrosis induced by CCl4 in rats [81]. Beyzagul suggested that a 5-HTR_7 agonist, rather than an antagonist, could reduce oxidative stress and inflammatory response in CCl4-induced liver fibrosis [82].

7. 5-HT in HCC

7.1. Balance between liver regeneration and tumor progression

Hepatocellular carcinoma (HCC) accounts for approximately 90 % of liver cancer cases and is the third leading cause of cancer-related deaths globally. It is projected that there will be over 1 million new cases of HCC by 2025 [83,84]. Despite the availability of immunotherapeutic and targeted drugs, the five-year survival rate for HCC remains low [85]. In the United States, the two-year survival rate is less than 50 %, and the five-year survival rate is only about 10 % [86]. Initially, researchers discovered that thrombocytosis was associated with the development, invasion, or metastasis of HCC [87,88]. However, subsequent studies have shown that the substances present within platelets, rather than the platelets themselves, play a role in the development and progression of HCC. Studies conducted in N-nitrosodiethylamine (NDEA)-induced rat models of HCC demonstrated that 5-HT is a more sensitive serum marker than alpha-fetoprotein (AFP) for predicting early-stage HCC [3]. Mamdouh et al. also confirmed the potential of 5-HT as an early diagnostic marker for HCC in clinical practice [89]. Padickakudy et al. discovered that the levels of intra-platelet 5-HT (IP5-HT) before surgery were found to have a significant impact on the prognosis of HCC patients who underwent partial hepatectomy. Specifically, maintaining IP5-HT levels within the range of 73 ng/ml to 134 ng/ml resulted in a balance between the pro-hepatic regenerative and pro-tumor effects of 5-HT. However, excessively high IP5-HT levels were associated with a greater risk of early tumor recurrence, while overly low IP5-HT levels were associated with a greater risk of postoperative complications such as chemotherapy-associated steatohepatitis (CASH), liver fibrosis and cirrhosis [14]. This presents a conflicting situation where the desired outcome is for 5-HT to promote hepatic regeneration after hepatectomy, while the excessive activity of 5-HT may stimulate tumor progression. Therefore, there is a need to regulate and strike a balance in the activity of 5-HT to achieve optimal outcomes in HCC treatment.

7.2. SSRIs and HCC

The activity of 5-HT relies on its transport into cells or platelets through the SERT. SSRIs effectively block SERT activity, thereby inhibiting the transport, storage, and release of 5-HT. Although SSRIs have been commonly used as antidepressants for psychiatric disorders, they have also shown therapeutic potential in regulating immunity in cancer patients, inhibiting cell proliferation, and exhibiting antitumor effects against various types of cancer cells. Interestingly, evidence suggests an association between the use of SSRIs and a reduced risk of HCC. In a population-based study involving 59,859 HCC cases and 285,124 matched controls, it was found that different types of SSRIs, including fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine, were associated with a lower risk of HCC, demonstrating a dose-dependent relationship [90]. Another study focusing on HCV-infected patients treated with interferon (IFN) found that higher cumulative doses of SSRIs were associated with a reduced risk of HCC [91]. Furthermore, it has been reported that the association between SSRIs and reduced HCC risk extends to individuals with alcohol use disorder [92]. A recent systematic review, including 1,051,096 participants and 22,316 HCC patients, revealed that the use of SSRIs decreased the risk of HCC by 34 % in a dose-dependent manner. Subgroup analyses showed that the magnitude of the benefit associated with SSRIs was significantly higher among individuals with hepatitis infection compared to the general population [93]. Consistent use of SSRIs for several years has been shown to be particularly beneficial in preventing the occurrence of HCC, especially in individuals with hepatitis infection.

Based on clinical findings regarding the relationship between SSRIs and HCC, researchers have explored the underlying mechanisms, among which the MAPK pathway, Wnt/β-catenin pathway and autophagy-related mechanisms have garnered significant attention. Mun et al. proposed that fluoxetine, an SSRI, could reduce the viability of Hep3B HCC cells, induce the loss of mitochondrial membrane potential (MMP) and the formation of ROS, and decrease the expression of ERK1/2 while increasing the expression of JNK and p38 MAPK, which collectively exert a pro-apoptotic effect on HCC cells [94]. Chen et al. investigated the molecular mechanism of the toxicity of sertraline in human liver cancer HepG2 cells and identified its features. The results showed that sertraline decreased the viability of HepG2 cells in a dose- and time-dependent manner, inducing apoptosis through the activation of the intrinsic checkpoint protein caspase-9 by sertraline, which resulted in the release of cytochrome *c* from the mitochondria to the cell membrane. Notably, the induction of apoptosis and cell death in sertraline-treated cells was found to be mediated by the activation of the JNK pathway rather than the ERK1/2 or p38 pathways in the MAPK pathway. Silencing the upstream kinase MAP4K4 of JNK weakened the sertraline-induced apoptosis and cell death [95]. Another important pathway implicated in liver tumorigenesis is the Wnt signaling pathway, which involves β-catenin. Abnormal activation of β-catenin leads to its accumulation in the cytoplasm and initiates the Wnt signaling pathway, resulting in abnormal cell proliferation and differentiation and ultimately leading to tumorigenesis. Studies have demonstrated that SSRIs can inhibit liver tumor formation induced by β-catenin mutation in zebrafish [96]. Autophagy is an intracellular mechanism that allows cells to self-digest damaged organelles and proteins, thereby maintaining cell survival, differentiation, and overall homeostasis [97]. While autophagy generally plays a protective role in cells, excessive autophagy can result in cellular

damage. This dual nature of autophagy highlights its potential to clear tumor cells. The mammalian target of rapamycin (mTOR) is a central regulator of autophagy, and its suppression is crucial for initiating autophagy [98]. Zhang et al. demonstrated that sertraline and fluoxetine, both SSRIs, can block the protein kinase B (AKT)/mTOR pathway. This inhibition of the AKT/mTOR pathway led to the inhibition of growth in mouse HCC cells in in vitro experiments, xenograft models, and in vivo models induced by NDEA/CCL4. Moreover, sertraline and fluoxetine have been shown to work synergistically with sorafenib to block the AKT/mTOR pathway, resulting in inhibitory effects on HCC cells in both in vitro and in vivo settings [99]. Similarly, escitalopram, another SSRI, has demonstrated the ability to induce autophagy in HCC cells (HepG2 and Huh-7). This induction is evident by the increased light chain 3 (LC3)-II/LC3-I ratio and upregulation of autophagy-related proteins, including autophagy-related protein (ATG)-3, ATG-5, ATG-7, and Beclin-1 [100].

Overall, these findings suggest a potential link between the 5-HT signaling pathway and the development of depression and HCC, based on which SSRIs could be considered a viable addition to the systemic treatment regimen for HCC and provide research ideas and references for their future use in cancer therapy.

7.3. Signaling pathways of 5-HT/5-HTRs axis in HCC progression

The 5-HT/5-HTRs axis plays a vital role in the regulatory proliferative effects of 5-HT on liver cells, including hepatocytes and hepatoma cells. Multiple 5-HTRs have been investigated and identified as being involved in the progression of HCC. Notably, 5-$HTR_{1A, 1B, 1D}$, 5-HTR_{2B} and 5-HTR_{7} have been implicated in HCC development. We have summarized the pathways linking 5-HTRs and HCC in Fig. 4.

Sulaiman et al. conducted a study on liver regeneration after partial hepatectomy and hepatocarcinogenesis induced by NDEA. They observed a significant increase in 5-HT levels and a concurrent decrease in 5-HTR_{1A} expression. Based on their findings, the authors suggest that the activation of 5-HTR_{1A} hinders hepatocyte DNA synthesis and exerts a negative regulatory effect on the growth of HCC cells [101]. However, a different perspective was presented in the study by Soll et al. They found that 5-HTR_{1A} was expressed similarly in both tumor and non-tumor tissues of HCC patients. On the other hand, they observed significant overexpression of 5-HTR_{1B} and 5-HTR_{2B} in HCC [102]. The cell growth mediated by 5-HT can be partially explained by the activation of classical MAP kinases, such as ERK1/2, a pathway commonly activated in various cancers, including HCC [103–105]. The activation of both 5-HTR_{1B} and 5-HTR_{2B} can initiate the MAPK pathway and phosphorylate $ERK1/2^{102}$. Another subtype of 5-HTR_{1}, namely 5-HTR_{1D}, has been found to be significantly upregulated in both HCC tissues and cell lines. Moreover, high expression of 5-HTR_{1D} was reported to associate with poorer overall survival and a higher recurrence probability in HCC patients. Further investigations revealed that the pro-tumorigenic

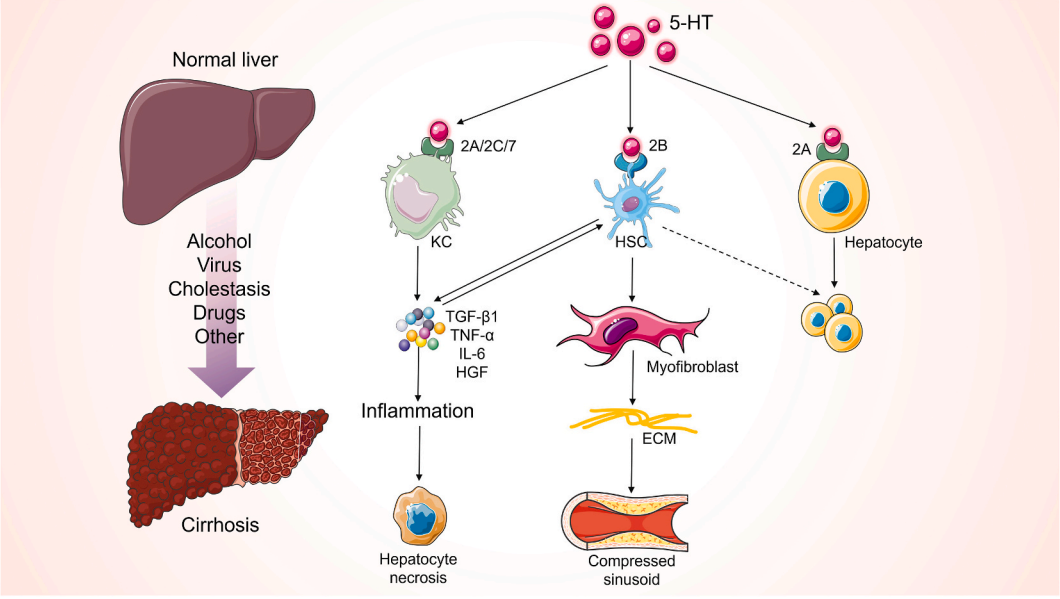

Fig. 3. Regulation of cirrhosis by 5-HT | 5-HT expression increases when the liver is exposed to alcohol, viruses, cholestasis and hepatotoxic drugs. 5-HT can: (i)activate 5-HTR_{2A} on liver cells to promote their proliferation; (ii)activate 5-HTR_{2B} on hepatic stellate cells (HSCs) to induce their transformation into myofibroblasts, and 5-HTR_{2B}-activated HSCs can inhibit 5-HTR_{2A}-activated hepatic cell proliferation; myofibroblasts secrete extracellular matrix (ECM) and collagen, disrupting the normal liver structure and compressing liver sinusoids leading to disordered hepatic blood circulation; (iii)activate 5-$HTR_{2A/2C/7}$ on Kupffer cells (KCs) to mediate the release of inflammatory mediators and humoral factors, such as hepatocyte growth factor (HGF), transforming growth factor β1 (TGF-β1), and interleukin-6 (IL-6), which can mediate inflammation causing hepatocyte necrosis. Moreover, activated HSCs can also mediate the release of inflammatory mediators and humoral factors, which in turn promote HSCs activation. Ultimately, through the collective action of these mechanisms, liver cirrhosis forms. The solid line indicates promotion and the dotted line indicates inhibition.

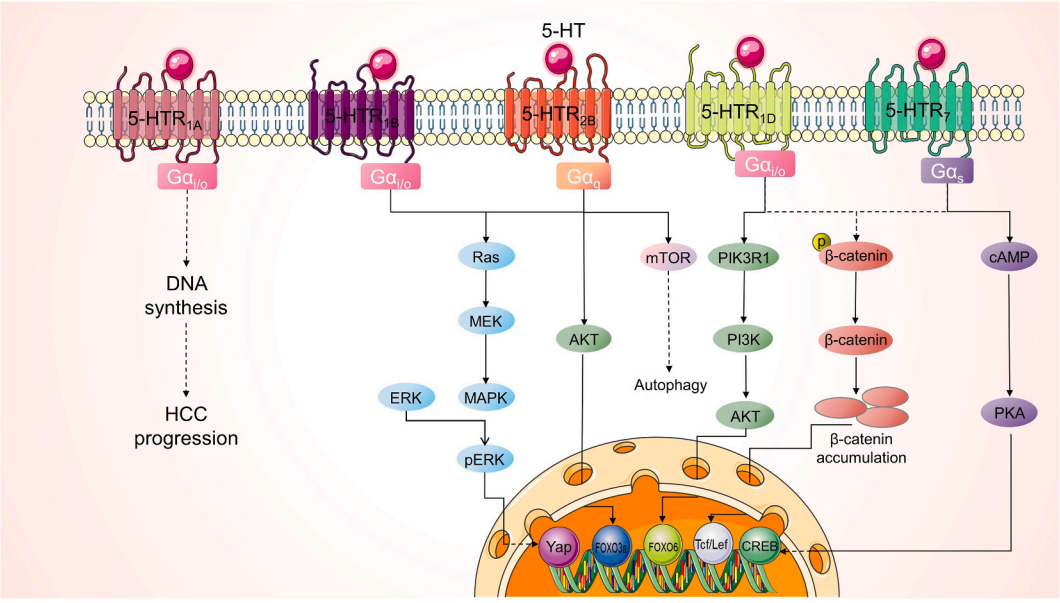

Fig. 4. Signaling pathways of 5-HT/5-HTRs axis in HCC | 5-$HTR_{1A,\ 1B,\ 1D}$, 5-HTR_{2B} and 5-HTR_{7} are involved in HCC progression. 5-HT activates 5-HTR_{1A} and inhibits DNA synthesis in HCC cells, thereby hindering HCC progression. 5-HT activates 5-$HTR_{1B/2B}$ to promote oncogene Yes-related protein (Yap) expression by upregulating pERK levels through the MAPK pathway. Activated 5-HTR_{2B} also mediates the upregulation of FOXO3α by AKT as well as activates mTOR to inhibit autophagy. The activation of 5-$HTR_{1D/7}$ triggers the inhibition of β-catenin phosphorylation. This inhibition prevents the degradation of β-catenin, leading to its accumulation. As a result, the transcription of T-cell factor/lymphoid enhancer factor (Tcf/Lef) is activated, causing abnormal proliferation and differentiation of cells. Activation of 5-HTR_{1D} can also activate FOXO6 through the PI3K/AKT pathway. And activation of 5-HTR_{7} can also activate cAMP response binding protein (CREB) through the cAMP/PKA pathway. Except for activated 5-HTR1A, which inhibits HCC, the rest of the signaling pathways are shown to promote HCC development and progression. The solid line indicates promotion and the dotted line indicates inhibition.

role of 5-HTR_{1D} could be achieved through its interaction with PIK3R1, resulting in the activation of the PI3K/AKT/FOXO6 pathway [106]. Additionally, another study confirmed that the overexpression of 5-HT_{1D} significantly promotes the proliferation, colony formation, migration and invasion of liver cancer cell lines HepG2 and SMMC-7721, as well as increases the expression of Wnt/β-catenin pathway-related proteins and tumor-associated target genes, including β-catenin, survivin, C-myc, and Cyclin D1[107]. Among the 5-HT receptors, 5-HTR_{2B} is probably the most studied in HCC. It not only promotes HCC cell growth by phosphorylating ERK1/2 but also inhibits autophagy [108] and upregulates the expression of FOXO3a [109], thereby facilitating the proliferation of serum-deprived HCC cells. Furthermore, the activation of 5-HTR_{2B} by 5-HT can promote the expression of oncogene Yes-associated protein (Yap) by upregulating the levels of pERK, demonstrating the pro-HCC effect of the 5-HT/5-HTR2B/pERK/Yap axis [110]. Usually, Yap interacts with TEADs to form the Yap-TEAD complex, which plays an important role in tumorigenesis. VGLL4, a novel tumor suppressor, competes with Yap to bind to TEADs, disrupting the formation of the Yap-TEADs complex and impeding tumor formation. Also, promoting Yap expression by 5-HT can disrupt the balance between Yap and VGLL4, thereby promoting the progression of HCC [111]. 5-HTR_{7} expression is upregulated in HCC tissues. Activation of 5-HTR_{7} leads to the upregulation of insulin-like growth factor 1 (IGF-1), a critical tumor growth factor, through the cAMP response binding protein (CREB)/AKT signaling pathway [112]. In addition, activation of the Wnt/β-catenin signaling pathway by 5-HTR_{7} also promotes HCC cell growth, and it was found that the 5-HTR_{7} antagonist SB-258719 can attenuate this effect and inhibit tumor growth [113].

There seems to be controversy among researchers regarding the distribution of 5-HTRs in HCC tissue and non-tumor tissue. In fact, this is a critically important issue as it relates to the development of targeted therapeutics. In the discussion section of this study, we explore this topic in greater detail to provide a comprehensive understanding of the expression and distribution of 5-HTRs in HCC and their implications for therapeutic interventions.

8Discussion and conclusion

5-HT, an ancient biogenic amine, has been critical in regulating metabolism and development for billions of years. In mammals, its initial discovery in the CNS revealed its role as a neurotransmitter in regulating mood, psychology and appetite, leading to the development of antidepressant drugs like SSRIs. However, further exploration of peripheral 5-HT has provided a new perspective for understanding various physiological and pathological processes. Peripheral 5-HT is now known to be involved in mediating the development of different types of tumors, regulating lipid and glucose metabolism, vascular tension, immune function and inflammatory processes. These physiological and pathological processes play a key role in the occurrence of liver diseases such as HCC, cirrhosis, fatty liver and hepatitis.

In general, peripheral 5-HT has been found to promote the development and progression of liver diseases such as HCC, cirrhosis, fatty liver, and viral hepatitis. However, it is important to note that 5-HT also plays a role in promoting hepatocyte regeneration, which creates a paradox. While inhibiting 5-HT may seem like a feasible approach to halt the progression of liver disease, it would also block the pro-proliferative effect of hepatocytes, which is crucial for liver regeneration, especially after hepatectomy. Resolving this contradiction is essential to ensure the appropriate application of 5-HT agonists, antagonists, or SSRIs in the treatment of liver disease.

5-HT has a wide range of receptors in the peripheral tissues. The distribution of 5-HTRs in different tissues or cells varies, providing a potential breakthrough for the above-mentioned paradox. Some studies have reported the existence of different 5-HTRs in liver cells, HCC cells, stellate cells and Kupffer cells. The use of specific receptor blockers or agonists on the corresponding effector cells may achieve precise intervention in targeting these cells. For example, it may be feasible to block the pro-cancer effects of 5-HT and enhance its pro-hepatic regenerative effects by blocking specific 5-HTR on hepatocellular carcinoma cells and simultaneously enhancing specific 5-HTR on normal hepatocytes. Moreover, a similar effect might be achieved by modulating 5-HTRs-mediated pathways. Of course, these assumptions presuppose the identification of the exact specific 5-HTRs on hepatocellular carcinoma cells, normal hepatocytes, hepatic stellate cells, hepatic macrophages, and endothelial cells. Although attempts have been made by researchers [102,106,113], a common understanding is still lacking. For example, Soll et al. suggested that 5-$HTR_{1B/2B}$ expression is elevated in hepatocellular carcinoma [102], whereas Zuo et al. found high expression of 5-HTR_{1D}^{106}.

In addition to agonists or inhibitors of 5-HTRs, efforts have been made to develop targeted drug delivery systems for 5-HTRs, with targeting the overexpressed 5-HTRs on tumor cells for the delivery of anti-cancer drugs offering a more effective approach compared to traditional drug delivery methods. Vijaya et al. demonstrated the use of 5-HT as a targeting ligand to deliver plasmid DNA specifically to cells expressing 5-HTR_{1A} receptors [114]. In addition to the delivery of plasmid DNA, a 5-HT-based synthesized bioconjugate, serotonin stearic acid (ST-SA), achieved precise and effective delivery of the doxorubicin hydrochloride drug system to HCC [115]. Although the role of 5-HT in liver diseases seems promising, further research is required to determine the distribution of 5-HT receptors in specific liver tissue cells under different physiological and disease conditions, including investigating differences in receptor distribution among various components at different time points and even within the tumor microenvironment.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Benliang Mao: Writing – original draft, Visualization, Resources, Data curation, Conceptualization. **Shoupei Liu:** Writing – original draft, Visualization, Resources. **Shanfei Zhu:** Visualization, Resources, Data curation. **Fan Wu:** Writing – review & editing, Funding acquisition. **Wei Yuan:** Writing – review & editing, Writing – original draft. **Yong Yan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Bailin Wang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81974442) and the Natural Science Foundation of Guangdong Province (2020A1515010799, 2021A1515011261). We thank ZYEdit for its linguistic assistance during the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30703.

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