The Role of Hypothalamic Neuropeptides in Regulation of Liver Functions in Health and Disease

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Abstract: The communication between brain and peripheral tissues is mediated by neuropeptides that coordinate the functions of each organ with the activities of the entire body in specific environmental conditions. Hypothalamic neuropeptides act as neurotransmitters and hormones to regulate the physiology of food intake, digestion, and metabolism, having a direct or indirect impact on the liver. Investigations on liver pathologies found that dysfunctions of neuropeptides and their receptors are associated with liver disorders such as non-alcoholic fatty liver disease, steatohepatitis, cholestasis, cirrhosis, and liver cancer. In this article, we reviewed neuropeptides that regulate energy homeostasis and lipid and glucose metabolism in the liver and are associated with liver injuries. Firstly, peptides involved in regulatory processes in the brain and liver, such as neuropeptide Y, agouti-related protein, and the galanin family, are related to obesity and its comorbidities, including type 2 diabetes and metabolic syndrome, are presented. Secondly, a comprehensive review of neuropeptides such as secretin, vasoactive intestinal peptide, substance P, and somatostatin, which are involved in liver injuries unrelated to obesity; i.e., cholestasis-induced biliary hyperplasia, cirrhosis, hepatocellular carcinoma, and cholangiocarcinoma, is also presented. The cellular and molecular mechanisms underlining liver injuries related to the dysfunction of these neuropeptides and receptors are also described.

Keywords: neuropeptide; galanin; corticotropin releasing hormone; cholestasis; steatosis; obesity

1. Introduction

Neuropeptides are produced in the central and peripheral nervous system and are released into the systemic circulation or locally into specific organs from nerve terminals to regulate physiological functions at the cellular and tissue level [1]. Neuropeptides can act as neurotransmitters, neuromodulators, or hormones via specific receptors which are expressed in all tissues [1]. The hypothalamus regulates adaptive changes of metabolic and physiological functions such as feeding behavior, digestion, energy balance, thermoregulation, immunity, circadian rhythms, and many others according to ever-changing environmental conditions [1,2]. A major signaling pathway mediated by hypothalamic neuropeptides is the hypothalamus–pituitary–adrenal (HPA) axis, functioning as the main controller of the body's response to stress [3–5]. Neuropeptides that are produced mainly in the brain circulate through the blood to modulate hepatic function via specific receptors in hepatic cells [6–8]. However, the role of hypothalamic neuropeptides in regulating liver functions is still poorly understood, even though numerous publications have reported significant changes in certain neuropeptides during various liver diseases [9–12].

In recent years it has been established that several neuropeptides are produced in non-neuronal cells in the liver [13,14], adipose [15], and immune system [16,17]. A di-

versity of neuropeptides have been detected in the liver, acting on specific receptors in parenchymal cells [14,18], hepatic stellate cells (HSC) [14,19], cholangiocytes [13,14,20], and immune cells [16,17].

Neuropeptides are ligands of G-protein coupled receptors (GPCR) and can modulate a multitude of cellular functions in health and disease [21]. Here, we review recent studies focusing on hypothalamic neuropeptides and their receptors that regulate the physiological processes of the liver. We categorized a multitude of hypothalamic neuropeptides associated with liver diseases into two groups: (i) neuropeptides with roles in feeding behavior, metabolism, and energy homeostasis that are related to liver injuries as comorbidities of obesity, type 2 diabetes (T2D), or metabolic syndrome (MS); these are summarized in Table 1; (ii) neuropeptides associated with liver injuries unrelated to the regulation of food intake or obesity, such as cholestasis, hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and hepatitis due to autoimmune disease. These latter neuropeptides are secreted by sensory nerves or organ-specific cells, acting locally within the liver to control cell proliferation, immune response to injuries, and fibrogenesis.

This review is aimed to cover the most recent reports on hypothalamic neuropeptides that have an impact on the hepatic system. While most of the neuropeptides discussed here have been known and studied for a long time, there are a few, such as spexin and nesfatin-1, which were identified more recently, and have attracted a lot of attention for future research to develop newer, better therapies for liver diseases.

A schematic representation of the hypothalamic regions related to the neuropeptides that influence liver physiological functions, which are discussed in this review, is shown in Figure 1.
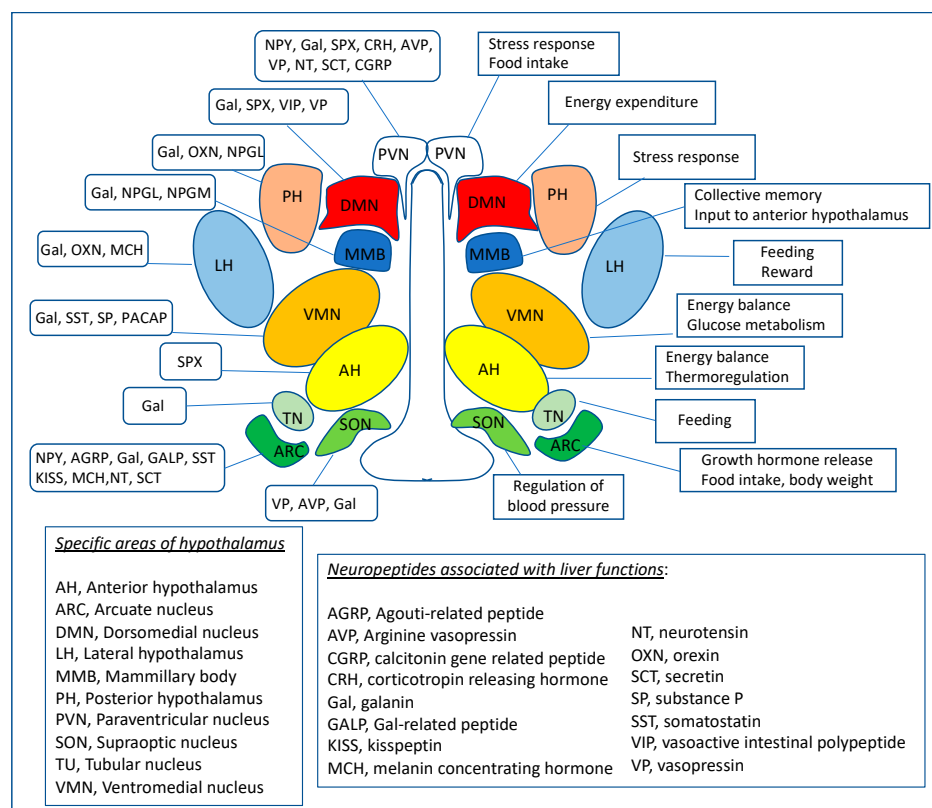
Figure 1. Map of hypothalamic neural centers which produce or are activated by neuropeptides discussed in this review. The diagram presents the hypothalamic nuclei and their functions (on the right side), including regulation of energy balance, food intake, body weight, glucose, and lipid metabolism that influence the liver. In parallel, on the left side of the map, the neuropeptides involved in numerous aspects of hypothalamus-regulated physiological functions related to the liver are presented.

Table 1. Summary of hypothalamic neuropeptides associated with liver diseases as comorbidities of obesity, imbalanced food intake, and energy homeostasis.

Neuropeptide	Disease	Dysregulation/ Symptoms	Signaling Pathways/Therapies	References
Neuropeptide Y (NPY)	Obesity and NAFLD	NPY genetic variant rs16147 correlated with obesity metabolic syndrome, insulin resistance	NPY increases proinflammatory response	[22]
	Liver steatosis	Increased intrahepatic NPY-immuno-reactive fibers.	NPY stimulated fat storage in liver and adipose via macrophage activation	[23]
Agouti-related protein (AGRP)	Obesity and NAFLD	Upregulation of *AGRP* gene in obese mice	AGRP overexpression increased food intake	[24]
Galanin (Gal)	Obesity and hepatic steatosis	Higher than normal levels of serum and liver Gal.	Gal increased feeding rate and body weight.	[25]
			Gal stimulated fat storage in adipose and liver	[26,27]
Orexins	NAFLD	Increased orexin in the liver	Orexin stimulated lipogenesis via ERK1/2 (Thr202/Tyr185)	[28]
Melanin-concentrating hormone (MCH)	NAFLD, obesity	Overeating and imbalanced energy homeostasis.	Antagonists of MCH receptors in obese mice reduced lipogenesis, inflammation, and fibrosis in liver	[29,30]
Neurotensin (NT)	NAFLD, metabolic syndrome	Higher than normal levels of plasma pro-NT in obesity	Increased NT enhanced fat absorption in the gut	[31]
Corticotropin releasing factor (CRF)	Hepatic steatosis, inflammation and fibrosis	CRF enhances steatosis and liver inflammation	CRF upregulated SREBP1, TNFα, and IL-1β by stimulation of sympathetic nervous system.	[32]
Somatostatin (SST)	Hepatic steatosis and NASH	Decreased SST in obesity-induced fatty liver disease	A synthetic analog of SST, octreotide, was tested as therapeutic strategy for high-fat diet-induced NASH	[33]
Neurosecretory peptide GL (NPGL)	Steatosis, NASH, metabolic syndrome	Precursor of NPGL is increased in hypothalamus of sugar-induced obesity	Unknown, still to be investigated	[34,35]
Secretin	NAFLD	Secretin (Sct)$^{-/-}$ and Sct-receptor$^{-/-}$ mice had less liver steatosis compared to wild-type mice when fed high-fat diet	Sct/SctReceptor/miR-125b axis promotes hepatic steatosis via Elov1 lipogenic gene upregulation	[36,37]

2. Neuropeptide Y (NPY)

NPY is a 36 amino acid peptide produced in the brain and autonomic nervous system, being well conserved among different species, with a role in food intake stimulation upon negative energy balance [38]. NPY acts as a neurotransmitter being the most potent appetite stimulant among several neuropeptides secreted by the hypothalamus [39,40]. NPY receptors have been identified in many organs, including neural [41] and gastrointestinal (GI) [42] systems. In healthy individuals, NPY regulates food intake, digestion, and metabolism and has a neuroprotective role during brain activity, sustaining resilience to stress [43]. In patients with metabolic syndrome, obesity, and other diseases related to

chronic energy imbalance, enhanced serum NPY levels have been associated with abnormal hormonal and metabolic changes leading to decreased physical activity, increased food intake, and lipid accumulation in the adipose [44].

In addition to being produced in the hypothalamus, NPY was identified in nerve fibers along peripheral organs, especially in the liver and gall bladder [45]. In the gallbladder, NPY-fibers are close to cholangiocytes, smooth muscle cells, and endothelial cells, having roles in the regulation of blood supply and bile flow within the gallbladder [45].

NPY dysfunction in the liver has been related to several injuries, including hepatic cholestasis, nonalcoholic fatty liver disease (NAFLD), and cancer. Thus, in patients suffering from intrahepatic cholestasis of pregnancy (ICP), a marked upregulation of NPY protein and mRNA expression was observed in maternal plasma and placenta, respectively [46]. Furthermore, in a rodent model, ICP offspring exhibited persistent appetite stimulation with upregulated NPY expression from the day of birth to 6 months [47]. These results suggested that the upregulation of NPY could influence fetal health and pregnancy outcomes in ICP patients. In a rodent model of cholestasis-induced liver injury, the expression of NPY and its receptors was increased in the liver after bile duct ligation (BDL) [12]. Furthermore, chronic NPY treatment decreased proliferating cellular nuclear antigen (PCNA) expression in cholangiocytes of intrahepatic bile ductal mass (IBDM) in BDL rats, suggesting that targeting NPY-signaling may be beneficial for the treatment of biliary hyperplasia [12].

A possible role of NPY in obesity-related NAFLD was studied using *NPY*-knockout ($NPY^{-/-}$) versus wild-type (WT) mice that were fed a high-fat diet (HFD) [23]. These data demonstrated that $NPY^{-/-}$ mice did not Gαin as much weight as the WT-mice even though both groups of mice consumed the same amount of food. This was consistent with the upregulation of several thermogenic genes in brown adipose tissue of $NPY^{-/-}$ mice. Furthermore, *NPY* deletion attenuated liver steatosis induced by HFD and reduced adipose inflammation, suggesting that a strategy of NPY antagonism could be an efficient therapy to treat NAFLD and obesity [23].

Research on the possible role of NPY in the impaired metabolism of lipids in NAFLD and steatohepatitis indicated that NPY could be indirectly involved, acting via its receptors in the hypothalamus and adipose. Thus, hormones such as ghrelin, leptin, and insulin can modulate *NPY* transcription in the hypothalamus via specific signaling pathways, as described [48]. Insulin downregulates *NPY* transcription in neurons under normal conditions; however, NAFLD is usually associated with insulin resistance [49]. This implies that in NAFLD, the insulin-mediated inhibition of *NPY* transcription via the InsR/IRS/PI3K/AKT/FOXO1 pathway is weakened, increasing NPY-mediated appetite and food consumption [48]. Overproduction of hypothalamic NPY results in increased fat tissue since NPY stimulates adipocyte proliferation and differentiation, acting via Y2R receptors in adipocytes [50]. It was demonstrated that adipocytes express NPY as well as its receptors YR1 and YR2 which are highly produced in obesity [51]. Normally, NPY inhibits lipolysis in adipocytes via YR1 [51]. However, insulin resistance counteracts the inhibitory effect of NPY and causes persistent lipolysis, resulting in an increased concentration of free fatty acids in the systemic circulation and, subsequently, lipid accumulation in hepatocytes [49]. These combined effects of insulin-resistance on NPY neurons and adipocytes increased circulating fatty acids and lipid accumulation in the liver. An additional factor that contributes to the indirect influence of NPY on NAFLD is the adipocyte-macrophage crosstalk which is stimulated by NPY [23]. Thus, WT mice, when fed HFD, had increased expression of NPY mRNA in adipose macrophages, which was positively correlated with liver mass/body weight ratio [23]. In contrast, *NPY*-null mice with HFD had lower free fatty acids in macrophages from adipose and less liver steatosis, suggesting that NPY is critical for NAFLD pathogenesis [23]. These studies that were focused on fatty acid metabolism and circulation identified the significant impact of insulin resistance on NPY expression in the hypothalamus and on NPY functions in the adipose, leading to liver steatosis.

Chen et al. tested the hypothesis that NAFLD may be partially attributed to increased cholesterol in the liver due to enhanced sympathetic NPY [52]. It was determined that

genes of cholesterol biosynthesis encoding for 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) and sterol regulatory element binding protein 2 (*SREBP2*) were upregulated upon intraportal vein injection with NPY [52]. It was also demonstrated that NPY activated cholesterol biosynthesis via Y1 and Y5 receptors in a rat fibroblast cell line (BRL-3A) [52]. These data suggest that NPY contributes to hepatic steatosis by enhancing cholesterol biosynthesis in the liver.

In regard to the influence of NPY on liver fibrosis, a recent report by Ortiz et al. described an intricate process in which NPY is involved and contributes to HSC activation, hepatic fibrosis, and portal hypertension [53]. Two factors, in addition to NPY, are important in the signaling of progressive liver fibrosis, i.e., (i) neprisyl (NEP), which is an endopeptidase that acts on NPY in HSC, producing fragments that are the actual activators of genes directing HSC to change the phenotype toward fibroblast-like cells; (ii) angiotensin-converting enzyme (ACE) that cleaves angiotensin II (AngII); both ACE and AngII are upregulated in activated HSC and in fibrosis [53]. Using *NEP*-null mice in vivo and NEP inhibitors in HSC in vitro, this study demonstrated that NPY acted via the Y1R receptor to induce HSC activation only when NEP was present to produce cleavage-fragments of NPY. However, NEP downregulation did not reduce portal hypertension in spite of alleviating liver fibrosis. The study proposes two signaling pathways initiated by full-length NPY (fl-NPY) and cleaved NPY (c-NPY), which have opposite effects via two G-proteins coupled to Y1R, i.e., $G_{\alpha i}$ and G_q. Thus, fl-NPY action results in weak signaling via $G_{\alpha i}$ (to adenylate cyclase/cAMP/ERK→p-ERK) to stimulate fibrosis and strong activity via G_q (ROCK→contraction) to increase contraction. In contrast, cNPY has the opposite effect, acting strongly via $G_{\alpha i}$ and weakly via G_q protein, causing increased fibrosis but less contraction. Finally, administration of Entresto (sacubril/valsartan) medical drug, which is a combination of NEP inhibitor with angiotensin I receptor (ATIR1) antagonist, achieved a significant reduction of both fibrosis and portal hypertension when applied to models of liver fibrosis [53]. This study emphasizes the ability of Y1R to modulate different signaling pathways at the same time via $G_{\alpha i}$ or G_q, depending on small structural differences of its ligands, such as the differences between full-length vs. cleaved NPY peptides. Thus, it can be concluded that NPY and its various receptors in the hypothalamus, adipose, and liver play crucial roles in obesity, insulin resistance, NAFLD, and NASH.

In regard to the effects of NPY on various forms of liver cancers, the data are somewhat different depending on the cell type involved. Thus, a study on the influence of NPY on the proliferation rate of several cell lines of CCA indicated that NPY inhibited CCA cell proliferation via elevation of inositol triphosphate (IP_3) secretion and protein kinase C-alpha (PKC-α) activation [11]. This was consistent with elevated NPY levels in tumor samples from CCA patients [11] and with decreased tumor volume in Mz-ChA-1 xenograft mice induced by NPY treatments, indicating promising anti-cancer effects aGαinst CCA. In contrast, a study on NPY and its receptors in HCC showed that the NPY5 receptor (Y5R) was increased in HCC and correlated with tumor growth and survival [54]. Moreover, NPY was secreted by peritumorous hepatocytes promoting HCC progression via a transforming growth factor-beta (TGF-β/NPY/Y5R pathway) and NPY cleavage by dipeptidylpeptidase 4 enhanced Y5R activation and tumor growth [54]. The differential effects of NPY in CCA and HCC indicate that NPY signaling pathways are very different and have opposite outcomes in tumoral cholangiocytes of CCA compared to tumoral hepatocytes of HCC. These findings emphasize the fact that each type of cancer has cell-specific anomalies even when occurring in the same organ, in this case, the liver.

While it is clear that NPY signaling plays an important role in liver pathology, more investigations are needed to understand the role of NPY in regulating liver functions, as well as the influence of NPY on various types of liver injuries. So far, clinical studies on strategies to antagonize NPY receptors in order to reduce metabolic syndrome were focused on lipid metabolism in the adipose tissue but not in the liver [48]. However, given the increasing frequency of non-obese NAFLD, it is expected that future research to test the

possibility of using Y1-Y5 antagonists as drugs to reduce hepatic steatosis in fatty liver disease in non-obese patients.

3. Agouti-Related Protein (AGRP) and Melanocortin Receptors

AGRP, also known as agouti signaling protein (ASIP) or agouti-related transcript (ART)-peptide, is encoded by the *AGRP* gene. This gene was discovered as being associated with the agouti locus in mutant mice that were prone to obesity, diabetes, and tumor formation [55]. Human AGRP was isolated in two forms, full size, and a cleaved form, both acting as competitive antagonists of α-melanocyte stimulating hormone (α-MSH) at melanocortin-3 and -4 receptors (MC3R, MC4R) [55,56]. Furthermore, overexpression of human AGRP in transgenic mice caused obesity, indicating that it is an orexigenic peptide and it was expressed predominantly in the ventromedial arcuate nucleus (VAN) of the hypothalamus. Together with NPY, AGRP acts to increase food intake and decrease metabolism, being a very potent and long-lasting appetite stimulator [24,57]. However, *AGRP*-deficient mice were not only viable, but they had normal responses to starvation or HFD-induced obesity [58]. In addition, a double knockout of *AGRP* and *NPY* genes did not produce major phenotypic changes in feeding behavior or energy homeostasis compared to wild-type (WT) mice [58]. These data suggest that there are compensatory mechanisms in place to maintain feeding and survival even when one or multiple neuropeptides with roles in feeding are dysfunctional [59]. Interestingly, in contrast to AGRP, NPY, and other peptides of the proopiomelanocortin family (POMC), mutations in melanocortin receptors are associated with obesity and its comorbidities, including liver steatosis [59]. Thus, the knockout of the *MC4R* gene in mice caused severe hepatic steatosis at an early age, suggesting that the MC4R receptor could have a critical role in the regulation of fatty acid metabolism in the liver [60]. Data from experiments with both $MC3R^{-/-}$ and $MC4R^{-/-}$ mice indicated that even on a normal diet, these mice developed obesity, hepatic insulin resistance, and steatosis. POMC overexpression induced in the caudal brain stem of rats resulted in a significant reduction in food intake, body weight, serum-free fatty acids, and triglycerides (TG), as well as a 26% decrease in hepatic TG [61]. This shows that POMC overproduction could sustain an anorectic response without upregulation of orexigenic peptides since the mRNA expression of *AGRP* and *NPY* did not change. However, similar studies on POMC overexpression in the hypothalamus in lean rats via adenoviral delivery concluded that excessive hypothalamic POMC resulted in the downregulation of *MC3R* and *MC4R* and increased *AGRP* expression that exacerbated obesity in these transgenic rats [62]. Several studies showed that natural and synthetic agonists of MC4R decreased hepatic lipogenic gene expression, including sterol regulatory element-binding protein 1 (*SREBP-1*), peroxisome proliferator-activated receptor γ2 (*PPARγ2*), stearoyl-CoA desaturase 1 (*SCD1*), and acyl-CoA/diacylglycerol acyltransferase 1-2 (*DGAT1-2*), significantly reducing hepatic steatosis in overweight and diabetic mice [63,64]. Therefore, *MC4R*-deficient mice have been proposed to be used as a model for NAFLD [65]. Moreover, experiments with *MC4R*-null mice fed on a Western diet revealed strong inflammation of the liver described as "hepatic crown-like structures" whereby CD11c-positive macrophages surround hepatocytes with large lipid droplets, as found in the mouse model for human NASH [66]. Interestingly, in this particular model of NASH, depletion of CD11c macrophages abolished the "crown-like structure" together with most of the hepatic fibrosis, suggesting that CD11c+ cells have a critical role in aggravating liver injury in steatosis [67].

Overall, it can be concluded that dysregulation of POMC-derived neuropeptides, and especially dysfunctions in MC3R and MC4R, influence obesity-related pathology of the liver and could be targets for new therapies to treat obesity-related NAFLD.

4. Galanin Family (Galanin, Galanin-like Peptide, Spexin, Kisspeptin)

Several neuropeptides, including galanin (Gal), Gal-like peptide (GALP), spexin (SPX), and kisspeptin (KISS), have roles in the regulation of food intake, digestion, and metabolism and are members of the same protein family [2,68,69]. Gal, GALP, and SPX act

as neurotransmitters and hormones through specific receptors known as GalR1-3, which have very diverse pharmacological profiles [70,71]. GalR1-3 are seven-transmembrane G protein-coupled receptors (GPCR) signaling through different types of G proteins [68,69]. Even though the KISS peptide acts through a different receptor, the homology of the KISS receptor with GalRs is significant.

4.1. Galanin (Gal)

Gal is a 29/30 amino acid bioactive peptide highly expressed in the central and peripheral nervous system [72–74]. One of the main functions of Gal is to regulate neuroendocrine signaling pathways that modulate fat intake and metabolism [25,75]. The liver can be negatively affected by lipid metabolism disorders such as obesity and metabolic syndrome which are often associated with NAFLD and non-alcoholic steatohepatitis (NASH) [76,77]. Numerous clinical studies indicate that the serum level of Gal is significantly increased in patients with obesity, dyslipidemia, and metabolic syndrome [26,27,78].

Recently, increasing evidence has emerged regarding the expression of Gal by hepatocytes, HSC, and cholangiocytes in response to liver injuries [14]. Specifically, systemic and hepatic Gal was increased in BDL-induced cholestasis in rodents [79] and in patients suffering from cholestatic liver diseases [80,81]. Gal stimulated cholangiocyte proliferation in BDL rats via GalR1, which was highly expressed in cholangiocytes [13]. A study on Gal effects on the liver in the $Mdr2^{-/-}$ mouse model of cholestasis indicated that Gal contributed to hepatic fibrogenesis via coordinated activation of GalR1 in cholangiocytes and GalR2 in HSC [14]. Based on data showing that cholestasis in $Mdr2^{-/-}$ mice was correlated with increased Gal in serum and liver, it was demonstrated that Gal enhanced ductular reaction via GalR1 in cholangiocytes while stimulating activation of HSC via GalR2 (Figure 2). Experiments in vivo and in vitro using M871 antagonists specific to GalR2 and M40 pan-antagonist of GalR1 and GalR2 confirmed that Gal affected cholangiocytes and HSC, thus enhancing cell proliferation and hepatic fibrosis [14]. These data suggested that GalR1 and GalR2 could be targeted for developing pharmacological therapies for biliary hyperplasia and liver fibrosis in cholestasis-induced liver injury.

### 4.2. Galanin-like Peptide (GALP)

GALP is a peptide that shares a partial sequence with Gal, being produced mainly in the hypothalamic arcuate nucleus (ARC) to regulate feeding behavior, energy homeostasis, and reproduction [82]. GALP has an anorexigenic effect and acts through GalR2 [82] and GalR3 [83].

Following reports on the weight loss effects of GALP, studies on its influence on lipid metabolism in the liver and adipose have been carried out, demonstrating that mice administered intracranioventricular (icv) GALP exhibited lower respiratory exchange ratio and increased mitochondrial fatty acid oxidation (FAO) in the liver, as well as enhanced lipolysis in the adipose [84]. Additional studies confirmed the beneficial use of intranasal administration of GALP, reporting that GALP reduced lipid droplet levels in hepatocytes and enhanced FAO in the liver of rodents with obesity [85]. Even though GALP has been recognized as a peptide that attenuates obesity and related fatty liver diseases, the molecular mechanism underlining these effects is not completely understood and warrants further investigation.

4.3. Spexin (SPX)

A newly discovered member of the Gal family is spexin (SPX) or neuropeptide Q (NPQ), which is highly produced in the hypothalamus and has roles in energy homeostasis [86,87]. Unlike Gal, SPX binds preferentially to GalR2/GalR3 and initiates signaling pathways that counteract the orexigenic effects of Gal [88]. Extensive studies on SPX's impact on obesity [89], metabolic syndrome [90], and T2DM [91,92] have been reported, focusing on the beneficial effects of SPX on reducing body weight and improving insulin sensitivity. In regard to SPX's impact on liver function, exogenous SPX improved hepatic

transaminase levels and lowered steatosis and inflammation while inhibiting long-chain fatty acid uptake into hepatocytes isolated from diet-induced obese mice [93]. A study on the influence of SPX on the liver in patients with NAFLD compared to normal controls indicated that NAFLD patients had significantly less serum SPX [94].
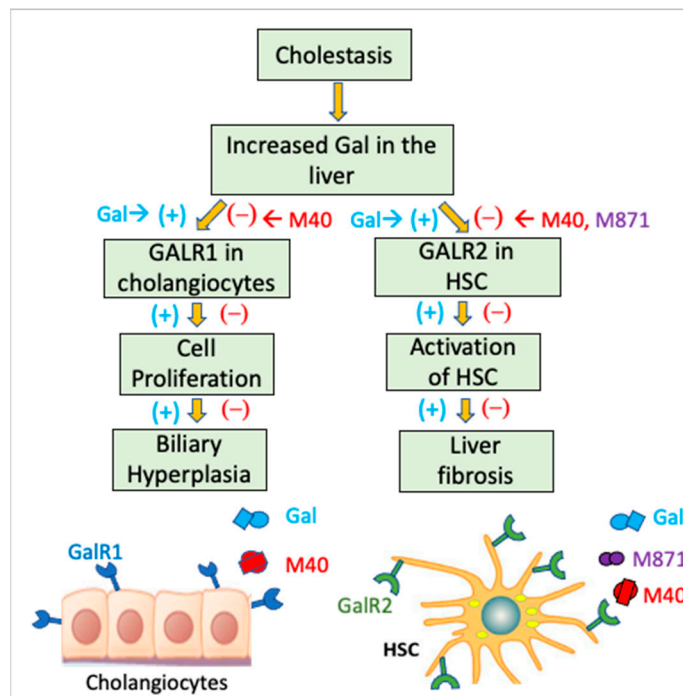
Figure 2. Role of Gal in ductular reaction-induced activation of HSC in hepatic cholestasis. It has been reported that in a rodent model of cholestasis, Gal was upregulated and induced excessive proliferation of cholangiocytes via GalR1 and activation of HSC via GalR2. Using GalR antagonists such as M871, which specifically inhibits GalR2, and M40, a pan-antagonist of both GalR1 and GalR2, this mechanism was confirmed.

Given the negative correlation of systemic SPX with obesity and dyslipidemia in children and adult patients, several in vitro studies focused on the effect of lipids on SPX expression in different types of cells, including hepatocytes. Thus, it was demonstrated that SPX inhibited gluconeogenesis in a dose- and time-dependent manner in an insulin-resistant cell model [95]. In a study using hepatocytes isolated from diet-induced obesity mice, SPX decreased long-chain fatty acid uptake by 70% [93].

Interestingly, SPX was described as a regulator of BA synthesis, reducing systemic and hepatic total bile acids (BA) in experimental animals [96]. SPX also reduced gall bladder weights and decreased hepatic cholesterol 7α-hydroxylase 1 (Cyp7A1), the rate-limiting enzyme in the BA biosynthesis pathway [97]. Future studies are warranted to investigate the cell and molecular mechanisms underlying these positive effects of SPX on the liver in the context of hepatic cholestasis.

4.4. Kisspeptin (KISS)

KISS is another hypothalamic neuropeptide from the Gal family and acts via the GPR54 receptor, which has significant homology to GalR1-R3 and is expressed in the central and peripheral nervous system as well as in nonneuronal cells in the liver [98]. However, GPR54 has no affinity for Gal; instead, it binds three peptides formed by enzymatic cleavage of the KISS-1 precursor protein [99]. An alternative receptor of KISS is human AXOR12, a GPCR with 81% homology to rat GPR54, expressed predominately in the brain, pituitary, and placenta [100]. Another KISS-1 receptor, GPR49, has been associated

with many forms of cancer, especially HCC, even though the molecular mechanisms are still being investigated [101,102].

The effects of KISS peptides and GPR54 receptor, also known as KISS1R, on lipid metabolism in the liver and adipose were also investigated, showing that their expression positively correlates to enhanced lipid biogenesis and accumulation in these organs [103]. A study on KISS-10 from the same family showed that it stimulated lipid synthesis in primary hepatocytes in culture [104]. Recently it has been reported that plasma KISS levels were significantly reduced as a result of gastric bypass surgery in obese patients with T2DM [105]. In contrast, experiments using HFD-fed mice with liver-specific deletion of the *KISS1R* gene indicated that KISS1R has a role in preventing NAFLD and NASH [106]. The functions of KISS and its receptors in lipid metabolism and energy homeostasis are increasingly recognized [107].

In conclusion, the neuropeptides of the Gal family play different roles in various regulatory pathways of liver physiology, acting either on the same types of receptors or on different ones. Thus, ongoing and future studies are warranted to test multiple strategies to target Gal and KISS receptors for developing drugs aGαinst liver injuries from cirrhosis to NASH and liver cancer.

5. Orexins

Orexins A and B, also known as hypocretins, have substantial amino acid homology with the gut hormone secretin. However, they are highly expressed in neurons within and around the posterior and lateral hypothalamus, having a role in the regulation of appetite [108,109]. The orexin receptors OX_1R and OX_2R were also identified [108] and characterized as a GPCR coupled to G_q and G_i, respectively [108]. Structurally, the orexin receptors are somewhat similar to the Y2 NPY receptor and localized mostly within neurons of the lateral hypothalamus, which receive terminal appositions from NPY-, AGRP-, and α-MSH-peptidergic fibers [110].

It has been demonstrated that the orexin receptors are expressed in the liver, mainly in hepatocytes, modulating metabolic pathways of energy homeostasis. Thus, OX_1R is expressed in rat hepatocytes, and it is activated and upregulated by orexin A in a dose-dependent manner, inducing cell proliferation and reducing apoptosis via OX_1R/PI3K/AKT signaling to transactivate Foxo1 and mTORC1 [111]. Recently, the orexin system was identified in the liver of birds as having a role in the regulation of lipogenesis without changing the rate of food intake [28]. Thus, orexin upregulated fatty acid synthase, acetyl-CoA carboxylase, and other lipogenic enzymes via phosphorylation of $ERK1/2^{Thr202/Tyr204}$, but not $p38^{Thr180/Tyr182}$, nor $JNK^{Thr183/Tyr185}$, in chicken hepatocytes [28].

The effects of orexin A on liver cancer cells were also investigated. It was demonstrated that OX_1R was predominantly located within HepG2 cell nuclei, suggesting a possible influence on transcription factors [112]. Indeed, orexin treatment of HepG2 resulted in oxygen-independent upregulation of HIF-1α via activation of PI3K/AKT/mTOR pathway and also increased GLUT1, glucose uptake, and ATP synthesis, suggesting a significant role of orexin in sustaining glucose-based energy production in HCC cells [112].

Interestingly, orexin A had beneficial effects on the liver in the context of the hepatitis B virus (HBV), which is one of the main causes of HCC [113]. HBx is a protein with a role in HBV pathogenicity, and it downregulates OX_1R [113]. Orexin A treatment of hepatocytes can attenuate the negative effects of HBV, reversing the oxidative stress caused by HBx that is due to the abnormal polarization of mitochondrial membranes and the excessive production of proinflammatory cytokines [113].

In summary, the dysfunction of orexin or its receptors is very different from one form of liver disease to another, and therefore, specific strategies for developing pharmacological therapies have to be applied for each type of injury. Thus, based on reported data, antagonists of OX_1R should be tested as drugs for steatosis, NAFLD, and also for certain forms of liver cancer. In contrast, orexin or synthetic agonists of OX_1R could have antiviral benefits in the case of HBV.

6. Melanin Concentrating Hormone (MCH)

MCH is an orexigenic neuropeptide produced in the hypothalamus, acting through two receptors, MCHR1 and MCHR2, to regulate energy balance by influencing hepatic and adipose lipid metabolism. While MCHR1 is associated with diet-induced obesity and NAFLD in WT mice that express only MCHR1, transgenic mice that express both MCHR2 and MCHR1 consumed less food, resisted diet-induced obesity, and had reduced steatosis, counteracting the effect of MCH via MCHR1 [114,115]. MCH promotes lipid accumulation in the liver via the MCHR1 from the lateral hypothalamic area (LH) and the parasympathetic nervous system, while it increases fat storage in the adipose through activation of MCHR1 in the arcuate nucleus (ARC) and by suppressing the sympathetic traffic [29]. Efforts were made to develop drugs based on MCHR1 antagonists. However, these therapeutics have reported hepatobiliary toxicity limiting their use [116].

Interestingly, the MCH function in LH is modulated by elements of the opioid system, such as kappa opioid receptors (kOR) from the same area of the brain [117]. Thus, kOR colocalized with MCHR1 in LH, and *kOR* gene knockout caused a significant reduction in MCH-induced liver steatosis. Moreover, silencing *kOR* in LH resulted in the decreased endoplasmic reticulum (ER) stress, inflammation, and fibrosis of the liver in both obesity-related NAFLD and in the methionine and choline-depleted (MCD) diet model of lean body steatohepatitis in mice [117].

Taking into account the interesting reports on the role of MCH and its receptors in hepatic steatosis, it can be concluded that future investigations are going to find new, safer strategies to use MCH, MCHR1, and MCHR2 as targets for treating NAFLD.

7. Corticotropin Releasing Hormone (CRH)

CRH, also known as corticotropin-releasing factor (CRF), is a hypothalamic neuropeptide produced predominantly within PVN and also in the amygdala, having roles in stress responses and circadian cycle function via behavioral, autonomic, and hormonal pathways [118]. Stress-induced CRH stimulates the anterior pituitary gland to produce POMC, the precursor of ACTH, α-MSH, and other neuropeptides with a role in the regulation of feeding behavior and energy balance [119,120]. The CRH/ACTH mediated neuroendocrine signaling to the adrenal glands, also known as the hypothalamic-pituitary-adrenal (HPA) axis, is a stress response pathway, resulting in increased systemic levels of glucocorticoids that act on vital organs, including the liver, to maintain continuous energy balance as well as metabolic and immunological homeostasis [4].

A recent study on the effect of CRH on hepatic lipid metabolism and inflammation was performed by injecting CRH into the central brain of rats, followed by the analysis of changes in the expression of liver genes induced by CRH [32]. The results indicated that central CRF modulated lipogenesis and proinflammatory genes through the sympathetic and noradrenergic nervous systems [32].

An alternative signaling pathway of CRH-induced regulation of liver functions was found to be mediated by fibroblast growth factor 21 (FGF21) [121]. It was demonstrated that hepatocyte-secreted FGF21 induced gluconeogenesis during fasting via the brain-liver axis. Fasting caused PPARα activation in the liver and subsequent upregulation of FGF21, which was released into the systemic circulation, reached the brain, and activated the HPA axis. As a result, FGF21 acted on hypothalamic neurons to activate ERK1/2 and cAMP-signaling pathways, upregulating CRH secretion and stimulating corticosterone-mediated glucogenesis in the liver [121].

There is two-way communication via the HPA axis, so liver injuries can cause dysregulation of the HPA axis. For example, during hepatic cholestasis, the systemic levels of BA become abnormally high, penetrate the blood–brain barrier and activate glucocorticoid receptors in hypothalamic neurons, causing a significant reduction in CRH secretion and suppression of HPA activity [122–124].

Three other neuropeptides, i.e., urocortin 1,2 and 3 (UCN1-3), have significant sequence homology to CRH [125] and act through specific receptor proteins, which are GPCR,

i.e., CRHR1 and CRHR2 [126,127]. An important role of UCN2 acting via CRHR2, was found in relation to pathways that are dysregulated in metabolic syndrome. Thus, in a metabolomics study, delivery of UCN2 into HFD-fed mice restored liver metabolites to normal levels, increased glucose disposal, and reduced insulin resistance [128]. Similarly, strategies to increase UCN2 in WT and *CRHR2*$^{-/-}$ mice, when fed an HFD diet, indicated that UCN2 reduced lipid accumulation in the liver while increasing insulin sensitivity via CRHR2 [129]. An investigation on the metabolic response to nutritional stress, such as HFD in *CRFR2*$^{-/-}$ mice, found that systemic cholesterol and hepatic steatosis were increased in male but not female *CRFR2*$^{-/-}$, pointing to a sexually dimorphic risk factor and a possible differential response to UCN2-based therapy of patients with fatty liver disease [130]. Further studies on the possible beneficial effects of UCN2 on the liver in humans are still warranted.

In summary, CRH is critical for a complex regulatory process that involves the liver, among other organs, to ensure the coordination of hepatic metabolism rate with the energy level required by the entire body according to many factors, including nutrition, digestion, and environmental stressors.

8. Somatostatin

Somatostatin (SST) is a 14/28 amino acid neuropeptide highly expressed in the hypothalamus as well as in the peripheral nervous system and in nonneuronal cells in the liver [131]. An important role of SST was revealed in relation to an autofeedback loop in the process of growth hormone (GH) regulation at the level of the hypothalamus [132]. Thus, GH secretion by the pituitary gland is controlled by SST and GH-releasing factor (GHRF) in the hypothalamic PVN and ARC areas. Systemic GH acts on NPY neurons in ARC and also on SST neurons in PVN via GH receptors, increasing SST secretion and inhibiting GH production [132].

The effects of SST are mediated through five specific GPCRs (SSTR1-5), which have nanomolar affinities for SST and are widely expressed in various normal and neoplastic tissues [131]. SSTR1-5 share common signaling pathways, including adenylate cyclase inhibition, modulation of mitogen-activated protein kinases (MAPK's), and activation of phosphotyrosine phosphatases (PTP's) having an overall inhibitory effect of cell proliferation via cell cycle arrest while stimulating pro-apoptotic mechanisms [131].

In the liver, GH acts through insulin-like growth factor (IGF1,2) and its receptors IGFR1,2 [133]. IGFs are produced mostly by hepatocytes and are controlled by insulin signaling. A pathophysiological association between IGF2 and cancer cell proliferation was demonstrated using human hepatoma cell lines [133]. Since it was established that the obvious function of SST is counteracting GH activity, SST and synthetic SST analogs were tested for the ability to stop excess cell growth in hepatic diseases such as HCC, CCA, cirrhosis, and polycystic liver disease (PLD). Experiments with rodent models indicated that SST and its analogs protected the liver from injuries caused by several types of stress, such as restraint stress [134], TAA-induced cirrhosis [135], and hepatic–ischemia/reperfusion injury [136]. It was reported that a combination of octreotide (SST analog) and celecoxib (COX-2 inhibitor) attenuated TAA-induced liver damage by reducing HSC activation, hepatic inflammation, and fibrosis [137].

Clinical studies followed, indicating positive results in using SST and its analogs to treat PLD [138,139] and hepatic steatosis associated with acromegaly [140]. Numerous studies were also conducted on the effects of SST-like compounds in the treatment of liver cancer [141], and significant improvement was reported for the use of SST and its analogs in HCC therapies [142–144]. Fewer studies were published on the effects of SST on CCA [145], and the findings were not consistent in different reports [140].

Interestingly, based on observations of SST treatments of patients with liver steatosis and inflammation in the context of PLD and acromegaly, where GH excess and insulin resistance have a significant impact on the liver [146], recent reports were published on studies of SST's effect on obesity-induced fatty liver disease. Thus, octreotide was recommended

as a novel therapeutic strategy for HFD-induced NASH and obesity-related metabolic syndrome based on data indicating that octreotide reversed HFD-induced steatosis and normalized the rate of glycogen biosynthesis via activation of Akt/GSK3β (glycogen synthase kinase 3β) and upregulation of glycogen synthase mRNA in the liver [33].

A few reports evaluated the possible side effects of using SST and its analogs in different therapies and cautioned about cases of hyperbilirubinemia and gallstones associated with octreotide treatments [147]. Interestingly, it was determined that octreotide is an inhibitor substrate of OATP1B1,2 and MRP-2, which are bile acid and bilirubin transporters from the liver into the bile ducts [148].

Overall, it can be concluded that SST contributes to the regulation of a multitude of systemic and local processes in the brain, liver, and other organs, having the potential to be used in future therapies for fatty liver disease and hepatobiliary dysfunctions.

9. Neurosecretory Protein GL (NPGL) and GM (NPGM)

In 2014, Ukena et al. reported the identification of a novel neuropeptide in the avian brain with regulatory roles in feeding behavior [149]. Based on its amino acid signature, the peptide was named neuropeptide GL, or NPGL, and was characterized as being produced in the medial mammillary (MM) and infundibular nucleus (IN) of the hypothalamus of chicks during certain periods of development [149]. Subcutaneous infusion of NPGL caused chicks to Gαin weight without changes in food intake. It was then revealed that the *NPGL* gene is conserved in mice and rats, having roles in the regulation of growth and energy homeostasis [150]. More recently, the same research group investigated the effects of NPLG on obesity using mice that overexpressed the *NPGL* gene in the hypothalamus and concluded that NPGL peptide in excess could act as an obesogenic factor within a short period (e.g., 8 weeks in mice) causing accumulation of lipids in both adipose and liver [34]. Moreover, a study on sugar consumption in relation to obesity and liver steatosis concluded that mice overexpressing hypothalamic NPGL, and fed a medium fat diet supplemented with either glucose or fructose, resulted in increased body weight and fatty liver with the fructose-rich diet but not with a diet rich in glucose [35]. These data emphasize the specific and very different effects of fructose versus glucose on NPGL-induced signaling in the liver and warrant further research on the effects of specific nutrients on neuropeptides and their signaling in relation to metabolism.

Interestingly, another neuropeptide named NPGM was found to be the product of a paralogous gene of *NPGL*, i.e., *NPGM*, also in the hypothalamus of chicken [151]. NPGM is produced in histaminergic neurons in the MM area, and it has a localization similar to histidine decarboxylase, which catalyzes histamine formation [151]. When NPGM is administered via acute icv injection, it reduces food intake, similarly to histamine [151]. However, a following study using a two-week osmotic pump icv infusion of NPGM in six-day-old chicks showed that NPGM increased body mass and water intake but not food appetite while causing liver steatosis via downregulation of PPARα [151]. The regulatory mechanisms of NPGM versus NPGL are still to be investigated and understood.

In summary, NPGL and NPGM are newly discovered hypothalamic neuropeptides that are associated with an increase in body weight and liver steatosis without changes in food appetite. Future work could reveal the receptor molecules through which these peptides act and if they could be targets for treatments of non-obese NAFLD.

10. Nesfatin-1

Nesfatin-1 was first identified in rat hypothalamus as a polypeptide with anorexic effects, formed by enzymatic cleavage of nucleobindin-2 (NUCB2), a protein highly conserved from fish to mammals [152]. Like other neuropeptides with a role in the regulation of feeding behavior, nesfatin-1 is preponderant in ARC and PVN centers of the hypothalamus and also outside CNS, especially in the GI tract having functions related to lipid metabolism, energy homeostasis, and tissue regeneration after injuries [153]. Investigations on the pos-

sible role of nesfatin-1 in the liver started when a few clinical studies reported a significant reduction in serum nesfatin-1 levels in patients with NAFLD [154] and obesity [155].

Investigations on molecular mechanisms of action of nesfatin-1 have not found specific receptors so far but have revealed the involvement of G-proteins and protein kinases C and A [152]. Evidence for a GPCR type of nesfatin-1 binding protein in the liver was obtained from experiments with hepatocytes in vitro, whereby nesfatin-1 induced phosphorylation of AMPK, downregulation of lipogenic transcription factors PPARγ and SREBP1 and a significant reduction in lipid synthesis [156]. Moreover, it has been suggested that nesfatin-1 could act as an endogenous inverse agonist of ghrelin receptor GHSR (growth hormone secretagogue receptor) since in HFD-fed mice, nesfatin-1 enhanced AKT level in the liver, which is a GHSR-dependent mechanism [157].

Based on reports about the remarkable antioxidant, anti-inflammatory, and antiapoptotic effects of treatment with nesfatin-1 in models of intestinal ulceration, studies on the influence of nesfatin-1 on the cholestatic injury of the liver followed [158]. Thus, in a rat model of OJ (obstructive jaundice), it was demonstrated that nesfatin-1 treatment alleviated the OJ-caused liver damage, decreasing neutrophile infiltration, bile duct proliferation, edema, and hepatocyte necrosis [158].

In conclusion, nesfatin-1 is a relatively novel neuropeptide, and its characterization and study in relation to a multitude of physiological processes, including liver diseases, has just begun. The data reported so far from investigations of its role in the brain, liver, GI tract, cardiovascular system, and others suggest the following: (i) nesfatin-1 is downregulated in diseases that incur cell apoptosis and necrosis, and its administration as replacement therapy could help cell and organ regeneration; (ii) nesfatin-1 is upregulated above the normal level in diseases such as cancer for which strategies of blocking its effects could result in significant improvement of the present therapies.

Hypothalamic neuropeptides that affect the liver in diseases unrelated to food intake behavior are listed in Table 2. The liver diseases in which these neuropeptides exhibit dysfunctions include cholestasis, cirrhosis, HCC, CCA, and PLD (Table 2). Some of these peptides may have tangency with obesity and fatty liver diseases; however, their main functions are other than regulation of food intake at the central nervous system level.

11. Substance P (SP)

SP is a proteolytic product of tachykinin, a precursor peptide encoded by the *Tac1* gene [159].

Even though SP is from the same peptide family as NPY, its functions are very different, being associated with the regulation of cell and molecular mechanisms in liver diseases that are unrelated to obesity, such as cholestasis, hepatitis, HCC or CCA [159]. In the liver, SP is secreted by peripheral terminals of vagal and spinal afferent nerves [160]. SP acts through the neurokinin-1 receptor (NK1R), and it has been shown that $NK1R^{-/-}$ mice that underwent BDL exhibited a reduced ductular reaction [161]. Mechanistic studies on cholestasis-induced fibrosis of the liver indicated that SP/NK1R signaling decreased senescence gene expression in HSC and increased HSC activation via TGF-β1/Smad3 [162]. Antagonists of NK1R were also able to protect hepatocytes from apoptosis in a model of tumor necrosis-alpha (TNF-α)-induced liver damage [163].

A possible role of SP in carcinogenesis was also investigated. Thus, a study of SP influence on human CCA cells and tumor growth in a xenograft model in nu/nu nude mice concluded that inhibition of NK1R signaling and suppression of SP secretion in the liver could help in CCA management [164].

Recent reports indicated functions of SP related to the modulation of the immune response to liver injuries [165]. Thus, using a mouse model of liver damage induced by concanavalin A (ConA), it was demonstrated that the levels of SP and transaminases were increased in ConA-treated mice, and treatment with an NK1R antagonist reversed this trend. It was found that Kupffer cells (KC) express NK1R, and treatment of KC in vitro with SP resulted in increased secretion of proinflammatory cytokines [165].

Thus, it can be concluded that SP is increased in liver injuries and affects cholangiocytes, HSC, hepatocytes, and KC via NK1R, aggravating hepatic inflammation and fibrosis.

12. Calcitonin Gene-Related Peptide (CGRP)

Soon after identification of calcitonin (CT), a hormone with role in autocrine/paracrine regulation of liver metabolism, Bracq et al. found out that calcitonin genes *CALCI* and *CALCII* express cell-specific alternative splicing forms in the liver, i.e., CGRPI in hepatocytes and CGRPII in hepatic sensory nerves which are nerve fibers of vagal or dorsal root/spinal origin that do not innervate directly hepatocytes, but the stroma surrounding the hepatic triades consisting of portal vein, hepatic artery and bile duct [166,167]. CGRPI receptors were also identified in the liver, suggesting a paracrine regulation of nonparenchymal cells by hepatocytes via CGRPI signaling [166]. Moreover, clinical observations indicated that CGRPI was elevated in patients suffering from cirrhosis compared to patients with minor hepatic dysregulation [168]. Investigations on the possible role of CGRPI in hepatobiliary diseases showed that $CGRPI^{-/-}$ mice exhibited reduced biliary hyperplasia [169] and also reduced hepatic fibrosis after BDL [170]. Thus, it was concluded that in cholestasis, CGRPI contributes to liver injury promoting fibrosis through changes in the senescence of cholangiocytes and HSCs via p38 and JNK signaling [170].

These data suggest that new therapies for hepatobiliary diseases could target CGRPI.

Table 2. Summary of neuropeptides with role in liver diseases which are unrelated to obesity, nor regulation of feeding behavior.

Neuropeptide	Disease	Dysregulation/Symptoms	Signaling Pathways/ Therapies	References
Vasopressin	HRS, Cirrhosis-related hemorrhage	Variceal bleeding in cirrhotic patients	Unknown	[171,172]
Arginine Vasopressin (AVP)	Cirrhosis, hepatitis, HCC	Contributes to hepatic inflammation and fibrosis	Blocking AVP receptors may be therapeutic	[173]
Substance P	Autoimmune hepatitis	Increased SP-fibers in the liver, close to lymphocytes;	SP colocalization with TNFα and NF-κB in lymphocytes amplifies inflammation.	[174]
	HCC	Chronic hepatic inflammation and fibrosis, cancer	Blocking SP–HSC–HCC axis causes reduction in HCC development.	[175]
	Cholestatic liver injury	Experimental cholestasis by BDL	Systemic application of SP reduced fibrogenic TGFβ and increased anti-inflammatory cytokines; it enhanced regulatory T cells.	[176]
Somatostatin (SST)	Resection/transplantation of liver	Increased portal flow, liver failure	Exogeneous administration regulates portal flow, protects the liver	[177]
	HCC	Chronic inflammation, fibrosis, carcinogenesis	SST and its analog reduce angiogenesis and hepatoma cell proliferation via apoptosis	[141]
	Polycystic liver disease (PLD)	Hepatic inflammation	SST decreases liver volume in PLD	[139]
Pituitary adenylate cyclase-activating peptide (PACAP)	Liver ischemia-reperfusion injury	Acute hepatocyte death in liver transplantation	Promotes hepatocellular protection via CREB and KLF4-enhanced autophagy	[178,179]
Vasoactive intestinal peptide (VIP)	Cholestasis	Bile duct injuries and hyperbilirubinemia	Exogenous VIP restores damaged tight junctions in bile ducts	[180]
Corticotropin releasing factor (CRF)	Hepatic fibrosis	CRF administration in rats aggravates acute liver injury	CRF enhances TNFα and IL-1β, the latter by stimulation of sympathetic nervous system.	[32]
Secretin	Parenteral nutrition (PN)-associated liver disease (PNALD).	Rat model of PNALD: secretin reduced total bilirubin and bile acid	Secretin induces cAMP/PKA activation and increased cholangiocyte proliferation under liver injury	[181]
	Cholangiocarcinoma	Dysregulation of cAMP/PKA pathway in cholangiocytes	Unknown	[182]

13. Neurotensin (NT)

Since its discovery as a hypothalamic neuropeptide, NT has been characterized as a brain-gut peptide secreted in the central and peripheral nervous system as well as along the GI tract [183]. Moreover, NT was reported to bind with high affinity to membranes of cells isolated from the digestive system, including the liver [184]. So far, three NT receptors have been identified and are known as NTSR1-3, which are distributed differently in various tissues [185,186]. Two of these are typical GCPR, while NTSR3 is a different type of receptor, having a single transmembrane domain [185].

Several studies investigated the possible functions of NT and its receptors in the liver in health or disease. NT was associated with liver development and regeneration, being increased in the liver during embryogenesis and fetal development and repressed in adult livers [187,188]. Studies on hepatic regeneration using hepatocytes in vitro indicated that NT stimulated DNA synthesis and cell proliferation via EGF- and TGFα-signaling [189]. It was also reported that NT stimulated drug-induced carcinogenesis in rodent models of liver cancer, inducing cell proliferation in preneoplastic lesions [190]. Receptors of NT have been associated with numerous forms of cancer, including HCC [186]. A driving force for tumor invasion is attributed to chronic inflammation caused by various conditions such as viral hepatitis, alcohol addiction, or NAFLD, and NT has been reported to promote proinflammatory cytokines in HCC, particularly via the IL-8, MAPK, and NF-kB pathways [186,191].

Recently, it was revealed that NT could regulate BA metabolism and FXR-dependent BA transporters in the ileum in the context of obesity [192]. However, the possible role of NT in the modulation of FXR activity and BA biosynthesis in the liver is still unknown. Interestingly, NT may have a role in hepatic cholestasis since studies on rats undergoing BDL showed NT-induced improvement of liver injury evidenced by less ductular reaction and reduced hepatic inflammation [193,194].

Since early studies indicated that NT had hyperglycemic and hypercholesterolemic effects, and the liver has a central role in regulating glucose and lipid metabolism, recent investigations have focused on NT's role in the liver in relation to fatty liver diseases in T2D, metabolic syndrome, and obesity. A bioinformatics analysis of gene expression in the livers of T2D patients versus healthy volunteers revealed NT as one of the eight hub genes involved in this disease [195]. Moreover, NT was proposed to be a prognostic marker for the development of obesity because an increased level of systemic pro-NT (a stable precursor of NT) was correlated to obese and insulin-resistant individuals [196]. Consistent data were obtained in studies on animal models using $NT^{-/-}$ mice, which showed that these mice were protected from HFD-induced obesity, insulin resistance, and hepatic steatosis [196].

A recent study evaluated the impact of two genetic variants, one of *NT* and the other of *NTSR1*, on liver damage in patients suffering from metabolic-associated fatty liver disease (MAFLD), showing that both variants were associated with advanced fibrosis and HCC in MAFLD [197]. In spite of some conflicting data [198,199], newer reports confirmed that circulating pro-NT was correlated to NAFLD and should be used as a noninvasive tool for screening for this disease [200].

Given the interesting reports on the involvement of NT in the regulation of energy homeostasis in the liver, new research could be carried out on this topic in the foreseeable future.

14. Secretin, Vasoactive Intestinal Peptide (VIP), and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)

Secretin, VIP, and PACAP belong to a superfamily of peptides that have significant amino acid sequence homology to GHRF, binding with high affinity to specific receptors while being able to act on common receptors for which they exhibit lower affinities [201]. Chronologically, secretin, VIP, and their receptors were discovered and studied since the 1980s, while PACAP was identified a decade later. These peptides are expressed in the central and peripheral nervous system that controls GI physiological functions [201]. The

receptors for these neuropeptides are widely distributed in all the vital organs, but they have been studied extensively in the liver and pancreas, being frequently related to the pathologies of these particular organs.

14.1. Secretin (SCT)

SCT was first identified as a hormone peptide released postprandially from duodenal S-cells to stimulate secretions from the pancreas and liver for food digestion in the upper part of the GI system [202]. Later on, it was demonstrated that SCT and its receptor SCTR are expressed in PVN and ARC centers of the hypothalamus that are engaged in controlling body energy homeostasis via appetite regulation [202]. It was reported that SCT could be an anorectic neuropeptide, suppressing food intake via its receptor and melanocortin pathway [202].

SCT was reported to enhance hydrocholeresis [203] and biliary bicarbonate secretion [204] and to have a high affinity for binding sites of membranes isolated from intrahepatic bile duct epithelium, being coupled to G-protein signaling pathways [205]. Moreover, SCT increased cholangiocyte proliferation after liver injuries such as BDL or partial hepatectomy, while it was downregulated when large damage to bile ducts was caused by treatment with hepatotoxic substances such as CCl_4 [206]. In $Mdr2^{-/-}$ mice used as a model of hepatic cholestasis, the abnormally high proliferation of cholangiocytes was reversed by the knockout of *SCTR* [207]. It was demonstrated that SCT was elevated in serum from patients with primary biliary cholangitis (PBC). Studies on models of this dysfunction proposed that the downregulation of TGF-β receptor II (TGFβRII), which occurs in PBC, induces microRNA-125b/TGF-β1/TGF-βR1/VEGF-A signaling contributing to exacerbation of SCT/SCTR, ductular reaction and increased hepatic fibrosis [208]. A multitude of functions of the SCT/SCTR axis in relation to hepatobiliary diseases and detailed mechanisms underlying them have been recently described [36].

In summary, SCT plays an important role in hepatobiliary physiology, and its dysregulation in cholestasis-induced liver injury continues to be studied with great interest.

14.2. VIP

Early studies on the effect of VIP on the liver demonstrated that VIP enhanced glucose output from hepatocytes by increasing the basal cAMP level while stimulating glycogenolysis and gluconeogenesis and counteracting insulin's effects [209]. Later on, several reports described high affinity binding sites on plasma membranes from hepatocytes [210], followed by the isolation and structural characterization of VIP receptors [211,212].

Another aspect of VIP function was reported to be related to hepatic bile formation and transport. Thus, VIP increased the volume and flow of bile and its output along the biliary tree [213,214]. However, VIP-induced activation of adenylate cyclase was impaired in hepatic cholestasis, probably due to poor interaction between G-proteins and adenylate cyclase [215,216]. The following studies focused on the role of VIP in cholangiocytes and concluded that VIP stimulated the secretion of fluid and bicarbonate via cAMP-independent pathways in these cells [217]. A recent report indicated that VIP administration promoted the restoration of tight junctions between cholangiocytes in bile ducts damaged due to cholestasis [180].

VIP and its receptors were also investigated in human liver cancer HepG2 cells. VIP inhibited HepG2 cell proliferation while increasing cAMP levels and reducing STAT-3 phosphorylation, proving to have an antiproliferative effect in liver cancer [218]. Moreover, VIP counteracted the IL-6-induced proliferation rate of HepG2 cells in vitro [218]. VIP and its receptors, VPAC1/2, were present in resected HCC and in the HCC cell line Huh7, where it was shown to induce apoptosis of cancer cells via the cAMP/Bcl-xL pathway [219].

An anti-inflammatory influence of VIP was reported for immune-mediated liver injury in vivo, taking place mainly via receptor VPAC1 [220]. Moreover, in an ischemia-reperfusion model of liver injury, VIP played an anti-inflammatory and immunomodulatory

role, possibly via inhibition of toll-like receptor 4 (TLR4) [221] and activation of cAMP-mediated protein kinase A signaling [222].

In conclusion, VIP has been described as a peptide with beneficial effects on the hepatobiliary system, and it could be a good candidate for clinical trials for treatments of hepatic cholestasis and other liver diseases that involve inflammation, as well as in HCC.

14.3. PACAP

In 1990, PACAP was identified as a new hypothalamic peptide, having 68% homology with VIP and being around 1000 times more potent than VIP in stimulating cAMP in pituitary cells [223]. PACAP was shown to bind receptors in plasma membranes from many peripheral organs, including the liver [223]. Thus, it was suggested that PACAP had a low affinity for VIP binding sites and also exhibited a higher affinity for a specific group of binding sites on hepatocyte membranes [224,225]. Two types of cDNAs encoding for PACAP receptors were identified in the brain, liver, and other organs, having remarkable similarity to receptors of VIP, secretin, glucagon, and GHRH [226,227].

Studies on the function of PACAP in the liver suggested that PACAP stimulated glucose output from the liver more than VIP did, and cAMP and Ca^{2+} were important secondary messengers for this signaling mechanism [228].

In conclusion, more research is needed to explain the functions of PACAP in relation to liver physiology.

15. Vasopressin and Arginine Vasopressin

Chronic liver diseases, when left untreated, lead to cirrhosis which is conducive to portal hypertension and hepatorenal syndrome, i.e., dysfunctional blood circulation in the GI tract and kidneys [229]. Therefore, in cirrhosis and liver resection surgeries, a common complication is variceal bleeding. For more than 20 years, the recommended therapy for acute variceal bleeding has been the use of vasoactive drugs such as vasopressin (VP, also known as antidiuretic hormone or ADH) and arginine vasopressin (AVP) [229]. These neuropeptides are synthesized in the supraoptic nucleus of the anterior hypothalamus and stored in the posterior lobe of the pituitary gland, having roles in the physiological functions of the HPA axis [230]. Preclinical studies evidenced that VP, AVP, and their synthetic homolog terlipressin (TP), enhanced liver regeneration after partial hepatectomy (PT) in lean and steatotic mice [172]. TP successfully passed clinical trials and has been used as the main therapy for cirrhosis-caused ascites and variceal bleeding for two decades [231]. However, more recent clinical studies concluded that even though TP reverses hepatorenal syndrome in 40% of patients, it has some negative side effects, such as lowering cardiac output [232]. Efforts have been made to improve the established therapies for cirrhosis-related variceal bleeding. Thus, it was proposed that the cardio-suppressive effects of TP could be reversed by using β-adrenoceptors agonists such as dobutamine [232]. Also, synthetic agonists of the AVP receptor were tested versus TP, and it was found that partial agonists of the AVP receptor were more effective and had less negative side effects on the kidneys, as compared to TP [171].

Overall, VP, AVP, and synthetic analogs such as TP have been used with moderate success in the treatment of variceal bleeding associated with hepatorenal syndrome. Recent reports suggest that further investigations are warranted to improve the use of these biomolecules and also to find new synthetic drugs with fewer side effects in the near future.

16. Translational Studies on Hypothalamic Neuropeptides as Targets for Liver Disease Therapies

Generally, biomedical studies are aimed at developing novel therapies based on newly identified biomolecules or procedures with key roles in signaling and metabolic pathways involved in physiological dysfunctions and diseases. Thus, starting with observations from various sources such as in vitro and in vivo experiments or data from medical studies on patients suffering from specific conditions, certain cell and molecular mechanisms have

been characterized as targets for appropriate therapies. Thereafter, preclinical studies in vivo were run on potential drugs or procedures, followed by clinical trials on volunteers, and thus, new therapies have been developed.

As evidenced in the previous sections of this review, extensive preclinical research has produced a vast amount of knowledge on the role of hypothalamic neuropeptides in the regulation of various liver physiological functions. However, only a few of these have been considered for translational studies in clinical trials with applications for liver disease therapies. Most hypothalamic neuropeptides have been tested for the ability to improve neurological and psychological dysfunctions such as anxiety, depression, and post-traumatic stress disorder. So far, very few of these peptides have been considered for clinical trials to be used as therapies for liver diseases.

The neuropeptides, analogs, or inhibitors of their respective receptors that were used in clinical trials in relation to liver injuries are shown in Table 3. A few drugs were designed to reduce hyperphagia, acting as antagonists of MC1R or agonists of MC4R, and were tested in clinical trials with the purpose of being used for the treatment of obesity and comorbidities such as fatty liver disease. Thus, the TTP435 inhibitor of AGRP was tested for its efficacy in lowering obesity via hypothalamic suppression of hyperphagia in a study carried out in 2008. During this trial, even though the main goal was to measure the effect of TTP435 on BMI and food appetite, assays for liver function and plasma-free fatty acids were also performed. In a recent clinical trial from 2021, setmelanotide, an agonist of MC4R, was tested for its anti-obesogenic effects based on data from mechanistic studies showing the activity of this particular receptor to reduce food intake [233]. However, the results of these studies were not made public [233]. In a clinical trial using CRH in the form of corticorelin tablets, the effects of CRH on food cravings were measured, and also, liver assays were performed. Similarly, NT, either alone or in combination with GLP-1, was tested as a therapy for obesity and overeating disorders associated with liver damage.

Table 3. Neuropeptides and analogs tested in clinical trials as therapies for diseases related to liver injury.

Neuropeptide/Receptor/Drug	Disease/Therapeutical Application	Assays/Tests/Measurements	Clinical Trial Identifier/Phase/Country	Start Year/End Year
Agouti-related protein/melanocortin receptor inhibitor/TTP435	Obesity Weight loss	Change in body weight, BMI, serum baseline glucose, insulin, free fatty acids, leptin, after 8 weeks	NCT00779519/ Phase 2/ TransTech Pharma/Canada	2008/2011
Setmelanotide	Hypothalamic obesity	Change in body weight, BMI, changes in waist circumference, change in hunger after 16 weeks	NCT04725240	2021–2022
Corticotropin-releasing hormone (CRH)/CRH receptor/Corticorelin	Craving Mood Addiction Substance-related disorders	Stress hormone level (plasma ACTH, cortisol). Subjective measures of stress, craving, mood.	NCT01984177/ Phase 1/Center for Addiction and Mental Health/Canada	2013/2016
Neurotensin + Glucagon-like peptide 1 (GLP-1)	Obesity	Ad libitum food intake. VAS for hunger. Plasma glucose, NT, GLP-1, insulin, BA, ghrelin, leptin	NCT04186026/ Phase 1/University of Copenhagen/ Denmark	2019/2024
Neurotensin (NT)/	Effect on food intake, appetite	Visual analog scales (VAS) for food appetite, plasma glucose, insulin, bile acids, NT, ghrelin	NCT03522792/ Phase 1/ University of Copenhagen/ Denmark	2017/2019
Somatostatin (SST)/SST receptor/SST	Post hepatectomy liver failure	Complication rate. Time of Recovery. In-hospital mortality.	NCT02882347 Phase 3 Korea	2015/2017
Somatostatin (SST)/SST receptor/SST	Liver failure. Impaired hepatic circulation in patients with liver resection.	Complication rate. Time of Recovery. In-hospital mortality.	NCT04010669/ Phase 3/Korea University Anam Hospital, Korea	2015/2017

Table 3. *Cont.*

Neuropeptide/Receptor/Drug	Disease/Therapeutical Application	Assays/Tests/Measurements	Clinical Trial Identifier/Phase/Country	Start Year/End Year
Octreotide, an SST analog	Locally advanced, metastatic liver cancer	Median survival within 6 months. Toxicities.	NCT00257426/Phase 2/University of North Carolina, USA	2005–2007
Octreotide	Hepatectomy	Liver recovery rate. Area under the curve of bilirubin. Liver volume by CT scan.	NCT03179995/Phase 2/Fox Chase Cancer Center, PA, USA	2017–2088
Octreotide	Polycystic Liver Disease	Percent change in liver volume by MRI and CT scan. Mean score of health-related quality of life.	NCT00426153/Phase 3/ Mayo Clinic, USA	2007–2008
Substance P (SP) or Neurokin-1/NK1-R antagonist/Serlopitant	Pruritus *	Severity of pruritus on a scale of 0–100	NCT03836001/ Phase 2/ Stanford University, USA	2019/2022
Substance P (SP) or Neurokin-1/NK1-R antagonist/Aprepitant	Pruritus **	Severity of pruritus on a scale of 0–100	NCT01625455/ Phase 4/ Vanderbilt University Medical Center/USA	2012/2016
Terlipressin (glycine vasopressin)	Cirrhosis with hepatorenal syndrome type 1 (HRS1)	Double-blind study to confirm reversal of HRS1	NCT01143246/Phase 2 Mallinckrodt/ USA	2010–2013
Terlipressin	Efficacy and safety in hepatorenal syndrome type 1 HRS), and cirrhosis	HRS reversal based on serum creatin assays	NCT02770716/Phase 3/Mallinckrodt/ USA	2016–2019
Terlipressin	Hepatectomy	Blood loss. Lactate level in serum.	NCT02588716/Phase 2 Assiut University Hospital, Egypt	2015–2017
Terlipressin	Hepatobiliary surgery	Portal pressure changes	NCT02718599/Phase2 Assiut University Hospital, Egypt	2016–2017
Terlipressin versus STT and/or Octreotide (Sandostatin)	Cirrhosis with acute variceal bleeding	Acute kidney incidence. In-hospital mortality.	NCT03846180/ General Hospital of Shenyang MR, China	2019–2019
Terlipressin plus albumin therapy	Hepatorenal syndrome in acute-on-chronic liver failure	Acute kidney injury reversal. Baseline organ failure(s). Mortality versus time course.	NCT04416282/ Institute of Liver and Biliary Sciences, India	2020–2022
Terlipressin	Portal vein pressure after liver tumor resection	Change in portal vein pressure. Incidence of hepatic dysfunction and acute renal failure within 8 months. Adverse effects of terlipressin.	NCT03352349/ Shanghai Zhongshan Hospital, China	2017–2018
Terlipressin with paracentesis albumin	Cirrhosis with recidivation of ascites	Mean number of paracentesis over 6 months. Total ascites retrieval, cirrhosis complications, liver transplantations, and mortality over 6 months.	NCT00986817/Phase 3 Saint Antoine Hospital, France	2009–2015
Terlipressin plus Octreotide	Cirrhosis and portal hypertension	Change in portal vein pressure	NCT04353193/phase 4 Hospital Clinic of Barcelona, Spain	2020–2020
Terlipressin versus Octreotide, STT	Cirrhosis with variceal bleeding	Failure to contain bleeding and rebleeding within 5 days of treatment.	NCT00966355/phase 4 Korea University, Korea	2006–2010
Tesamorelin (analogue of GHRH)	NAFLD in HIV-infected patients	Change in liver mass by MRI, histological quantification of NAFLD severity, serum transaminases	NCT02196831/ Massachusetts General Hospital, USA	2015–2019

* This study was carried out on volunteers with Epidermolysis Bullosa; however, this drug could be relevant for patients suffering from cholestasis since one of clinical symptoms is pruritus. ** This study was carried out on volunteers with Sezary Syndrome; however, this drug could be relevant for patients suffering from cholestasis since one of clinical symptoms is pruritus.

SST and its synthetic analog octreotide have been tested in numerous clinical trials for efficacy and safety when used for liver recovery after hepatectomy, polycystic liver disease, and liver cancer (Table 3).

Terlipressin or glycine-vasopressin was introduced to overcome the adverse effects of VP in treatments of cirrhosis and liver failure-related hepatorenal syndrome (HRS) and acute variceal bleeding (AVB) [234]. More recent trials proposed and tested the use of terlipressin in cases of acute-on-chronic liver failure to control variceal bleeding and extend patient survival [234]. Alternative clinical studies assessed the efficacy and safety of terlipressin in combination with octreotide in patients with cirrhosis portal hypertension and variceal bleeding (Table 3). Even though several clinical trials demonstrated that Terlipressin was effective in cirrhosis reversal and had significant survival benefits in patients with HRS and AVB, it has not been approved by the Food and Drug Administration (FDA) [234]. Thus, it has been recognized that terlipressin has secondary effects, such as the risk of respiratory failure and sepsis in patients with acute-on-chronic liver disease and hepatorenal failure type 1 [235,236].

SP was tested as an anti-pruritus medication associated with diseases unrelated to the liver (Table 3). However, future studies could investigate the use of SP or its synthetic analogs to relieve pruritus that is associated with cholestasis and other forms of hepatobiliary dysfunctions.

Interestingly, another hypothalamic peptide that was assessed for a potential drug for fatty liver disease is growth hormone-releasing hormone (GHRH), which acts on the pituitary gland, enhancing GH secretion. Thus, it has been noted that tesamorelin, a commercially available drug based on GHRH, for patients with HIV to reduce visceral fat, alleviated liver steatosis in a clinical study, as shown in Table 3 [237]. Moreover, a report on the effects of tesamorelin on hepatic transcriptomic profiles in HIV patients suffering from NAFLD co-morbidity indicated that tesamorelin upregulated genes of oxidative phosphorylation and downregulated many genes involved in inflammation, cell proliferation, and fibrosis [238]. It would be of interest to assess the effects of GHRH or synthetic analogs on NAFLD in patients without HIV infection. It has been known for a long time that serum GH levels and especially pulsatile secretion of GH were reduced in obese patients and in models of obesity [239]. Preclinical studies indicated that GH increased lipid metabolism by favoring lipolysis and lipid oxidation resulting in reduced body fat and improved insulin sensitivity. However, GH had adverse effects such as hypoglycemia and high systemic levels of IGF-1. New strategies to regulate GH signaling in relation to lipid metabolism are tested using drugs that act upstream GH, such as GHRH, or downstream GH, at the GHSR level [239].

Newer therapies have been developed based on the use of stem cells, gene editing, or immune-related procedures. Even though these newer therapies have been applied for the treatment of several ailments, including osteoarthritis, for example, no such practical applications were made for liver diseases, even though preclinical studies demonstrated promising results. A good example is NPY which was found to regulate vital activities such as the proliferation, differentiation, and migration of stem cells [43]. So far, it was demonstrated that NPY had roles in the regulation of bone marrow and adipose stem cells, with effects on activation versus quiescence, proliferation, and migration. Since NPY and its receptors are expressed and have regulatory functions in the liver, it would be interesting to test the possible effects of NPY on the liver stem and progenitor cells to find new therapies for liver regeneration after hepatectomy or other injuries that require stimulation of hepatocyte proliferation for treatment. A comprehensive review article by Peng et al. describes promising data for the use of NPY in stem cell therapy to treat conditions such as neurodegenerative diseases, retinal degeneration, myocardial infarction, osteoporosis, and obesity [240]. Studies on the potential use of NPY in cell stem therapy for liver injuries that require hepatocyte regeneration are warranted even at the level of preclinical studies.

It can be concluded that translational research on hypothalamic neuropeptides as potential therapies for liver diseases is still to be developed. Based on a large amount of information from preclinical studies indicating a multitude of effects of these peptides on

liver functions, new and better therapies are warranted to be applied for the treatment of liver diseases.

17. Conclusions and Future Directions

The research on the role of neuropeptides in controlling the physiological processes of the whole body, from the cellular level to tissues, organs, and functional systems, is expanding, and it reveals intricate networks of communication among various parts of the nervous and peripheral organs through peptides that can act as neurotransmitters, hormones, cytokines or other types of signaling molecules. Based on the information reviewed in this article, we can conclude that many hypothalamic peptides and their specific receptors have important roles in regulating feeding behavior, food digestion, metabolism, and energy homeostasis not only at the level of the nervous system but also in the liver, since most types of hepatic cells express receptors for the hypothalamic peptides known so far. We also reviewed data on dysfunctions of neuropeptides and their receptors that are associated with liver diseases that are affecting millions of people around the world, such as obesity, metabolic syndrome, NAFLD, NASH, cirrhosis, and HCC. It can be concluded that strategies to modulate receptors of hypothalamic neuropeptides can influence the functions of hepatocytes, cholangiocytes, and HSC, thus ameliorating steatosis and steatohepatitis or reducing ductular reactions and hepatic fibrosis in a variety of liver diseases. However, only a few modulators of neuropeptide receptors have been developed as therapies for liver diseases. Based on research results from preclinical studies, more work should be conducted to use these data for promoting new therapies for a large range of diseases that involve liver injury.

An important goal of these studies, for practical reasons, is the development of new therapies for liver diseases based on hypothalamic peptides and their receptors. Drug-based therapies that act on endogenous receptors to change certain functions of the liver have been used for many decades and are continuously improved. However, in addition to drug/receptor types of therapies, newer methods have been recently introduced and can be categorized into cell-, gene-, and immune therapies. However, none of these novel methods of therapy have been applied to the use of hypothalamic peptides for the treatment of liver diseases as yet. During the last two decades, biomedical research made great progress in understanding the functional interaction between brain and peripheral systems as well as the networks of signaling pathways that ensure normal homeostasis of physiological processes. Therefore, the possibilities for developing a new generation of therapies for liver diseases are open. For example, in preclinical studies, much progress was made using adeno-associated virus (AAV)-mediated gene therapy in liver fibrosis, including the use of cell-specific promoters within the AAV genome to limit gene expression in specific cells of the liver [241]. While many genes encoding for transcription factors (e.g., FOXA2), RNAs (e.g., miR-19b, TGF-β1-shRNA), enzymes (ACE2) with anti-fibrotic effects were targeted into hepatocytes or HSC, genes designed to modulate hypothalamic neuropeptides peptides by this method are still warranted [241].

Another new type of therapy involves the use of immune cells that are genetically engineered to suppress and delete specific cells with a critical role in liver pathogenesis. For example, in CCl4-induced liver fibrosis in mice, infusion of T cells designed to clear senescent HSC with a major role in fibrosis resulted in a significant reduction in fibrosis [242]. Frequently, many of these new therapies that are tested in preclinical studies have negative side effects; however, they may be improved by combination therapy, whereby certain negative outcomes could be mitigated by simultaneous or coordinated use in combination with neuropeptides with roles in liver physiology.

In conclusion, hypothalamic neuropeptides and their respective receptors are important regulatory factors in the liver, and their use in newer therapeutical methods could contribute to producing more beneficial and better-performing therapies in the near future.

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