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Review

Neuroendocrine regulation of cholangiocarcinoma: A status quo review

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ABSTRACT

Increasing studies have demonstrated that neuroendocrine system is involved in the development and progression of cholangiocarcinoma. The neuroendocrine hormones, neurotransmitters and neuropeptides regulate cholangiocarcinoma via affecting pathophysiology of tumor cells. The developing interaction and interplay between neuroendocrine-associated factors and tumor cells provide novel insights into neural control of tumorigenesis and reveal potential therapeutic effect on patients with cholangiocarcinoma. Herein we reviewed the latest findings and achievements which demonstrate the close interactions between neuroendocrine regulation and progression of cholangiocarcinoma. Also, future therapeutic approaches targeting neuroendocrine-associated factors are discussed which may help improve management and treatment of cholangiocarcinoma.

1. Introduction

Cholangiocarcinoma (CCA) is a highly malignant tumor characterized by poor prognosis and high mortality, which accounts for approximately 15% of primary liver cancers [1,2]. Surgical resection of CCA provides the curative treatment that prolongs survival outcomes [3–5]. However, due to its difficulty of early diagnosis and lack of clinical manifestation, most patients present with unresectable tumors at an advanced stage. Patients who received hepatic resection presented 5-year survival rate of only 20–40% [6–8]. In addition, efficacy of chemotherapy and radiotherapy remains to be confirmed in prolonging long-term survival [3,4,9,10]. Therefore, there is compelling need to discover novel targets regulating CCA cells.

Though most cancer-associated researches mainly focused on pro-oncogenic signal pathways and immuno-microenvironment [11], up-to-date studies have demonstrated that various types of neurotransmitters, neuroendocrine hormones and neuropeptides also modulate the progression of tumors such as gastric, colon and liver cancers [12–14]. In this review, we summarize the evidences from several studies that focus on the neuroendocrine regulation of CCA and call for more researches and therapeutic approaches targeting the interactions between CCA and neuroendocrine regulation.

2. Neuroendocrine regulation and progression of CCA

Recent studies have revealed that neuroendocrine system could modulate development of CCA via release of several neuroendocrine factors. The crosstalk between these neural-related factors and tumor cells leads to sustained proliferation, decreased apoptosis, induced epithelial-mesenchymal transition (EMT), angiogenesis and lymphangiogenesis, which finally facilitates CCA progression.

2.1. Sustained cell proliferation

Sustained cell proliferation is one of the hallmarks of tumors. Genetically unstable cholangiocytes initiated the sustained proliferation of abnormal cells under pathological state, which developed into CCA eventually [15]. Neuroendocrine factors have been shown to provide neurotrophic microenvironment under the pro-oncogenic state and activate downstream pathways to facilitate sustained proliferation of tumors. For instance, in cholestasis, cholangiocytes secrete serotonin which aims to counterbalance the excessive proliferation of cholangiocytes [16], while sustained elevated serotonin is discovered to induce neoplasia of cholangiocytes and promote CCA cell proliferation both in vitro and in vivo. Neurotransmitters like acetylcholine [17] and epinephrine [18] in adrenergic system, on the other hand, could bind to specific receptors in CCA cells and activate proliferating pathways, which triggers abnormal proliferation of tumor cells.

Abbreviations: CCA, Cholangiocarcinoma; EMT, Epithelial-mesenchymal transition; PNI, Perineural invasion; E, Epinephrine; NE, Norepinephrine; Ach, Acetylcholine; GABA, Gamma-aminobutyric acid; NGF, Nerve growth factor; NPY, Neuropeptide Y

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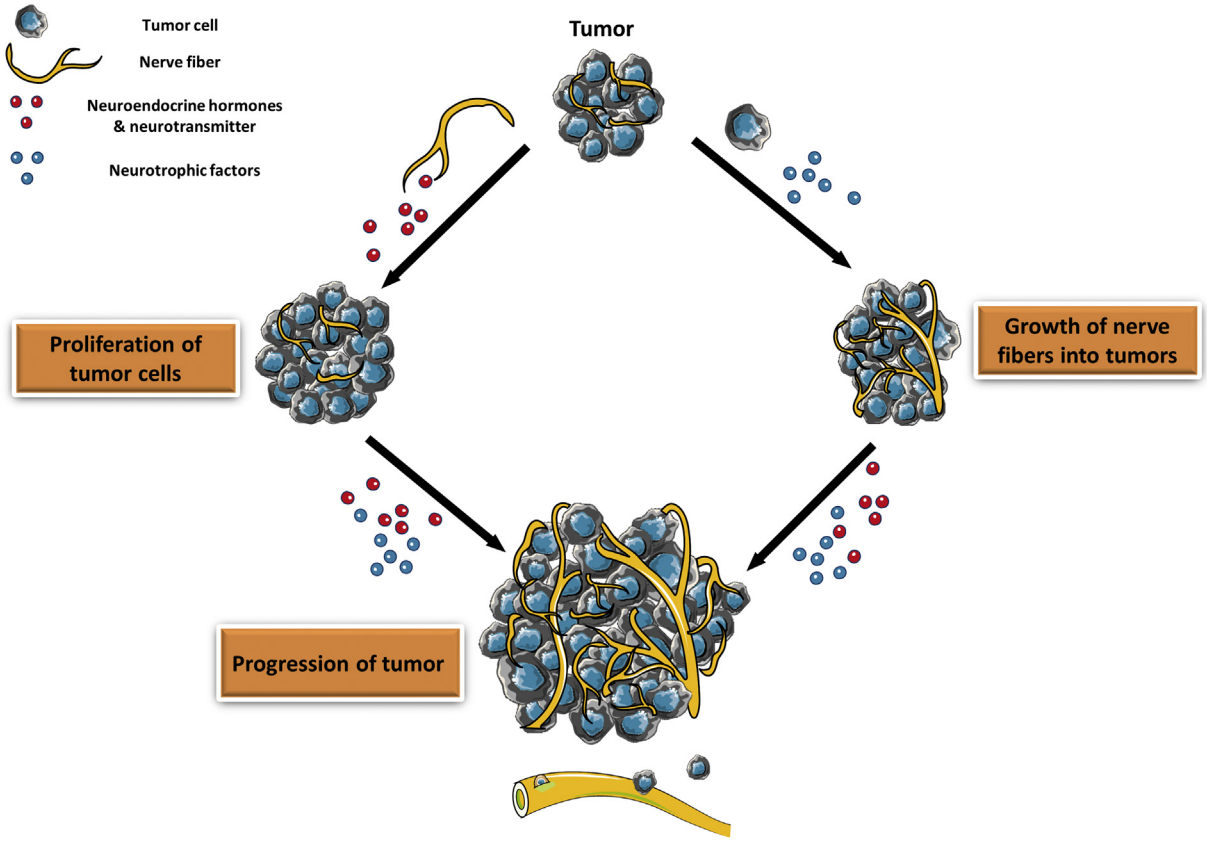

Fig. 1. Schematic illustration of perineural invasion in CCA.
Peripheral nerves surrounded by tumors secrete neurotrophic factors promoting the proliferation of tumor cells. Also, neurotrophic factors or neuropeptides released by tumor cells stimulate proximal nerve cells to develop nerve fibers into tumors, which regulate the growth of tumor cells as well.

2.2. Dysregulated cell apoptosis

Apoptosis is a form of programmed cell death that regulates to remove dead cells in a controlled process, aiming to self–renewal and maintaining tissue homeostasis [15]. It is believed that insufficient apoptosis results in uncontrolled cell proliferation, such as cancer. In biliary system, inhibition of apoptotic process may result in hyperplasia of cholangiocytes and transformation of CCA. Melatonin, a neuropeptide synthesized in the pineal gland, induces apoptosis of CCA cells by activating the reactive oxygen species (ROS)-mediated DNA damage in a concentration-dependent manner [19]. Once the axis between melatonin and its receptor are dysregulated in CCA, decreased apoptosis of cancer cells and subsequently enhanced CCA growth will be initiated. In addition, overexpression of anti-apoptotic factor Bcl-2 and mutations of K-ras were also observed in the abnormal neuroendocrine regulation, which inhibits apoptosis mechanism after a non-repairable event [20].

2.3. EMT and invasion

Epithelial–mesenchymal transition (EMT) is a process by which epithelial cells resemble mesenchymal cells obtaining migratory and invasive properties, which plays vital roles in metastasis of cancer progression [21]. In CCA entity, EMT has been confirmed participating in elevated invasiveness and metastasis of cancer cells, the process of which is modulated by several neurotransmitters. Clobenpropit, a potent H4 histamine agonist, alters morphological development of CCA cells and disrupts EMT processes, which subsequently inhibits invasion potential and decreases tumor growth [22]. Adipocytes, the key energy components, also release multiple neuropeptides participating in tumor progression. Nie J. et al. demonstrated in vitro and vivo experiments that adipocyte–CCA cell interaction promotes the EMT of CCA cells, which is regulated by adipocyte-derived fatty acid binding protein 4 (FABP4) [23].

2.4. Angiogenesis and lymphangiogenesis

Elevated tumor-associated angiogenesis and lymphangiogenesis have been shown correlated with larger tumor size, poorer histological differentiation and unfavorable prognosis in CCA patients. In CCA cell line of HuH-28, exogenous hormone of estrogen was able to significantly enhance the protein level of vascular endothelial growth factors (VEGFs) and induced angiogenesis in vitro, which was inhibited by antagonists of estrogen receptors [24]. In clinical studies of CCA patients, estrogen is also shown to be closely associated with elevated VEGFs level and increased lymphangiogenesis in tumor tissues, which may subsequently facilitate intra- and extra-hepatic metastasis.

3. Perineural invasion in CCA

Perineural invasion (PNI), defined as nerve fibers' growth into tumor cells, is an important process involving neoplastic invasion and cancer metastasis along the nerves. CCA via PNI is a common route for metastasis, which is correlated with worse survival rates and unfavorable prognosis [25,26]. A study of 133 patients with extrahepatic cholangiocarcinoma who underwent curative resection revealed 74% of neural invasion [27]. Survival rates of CCA patients with PNI were significantly worse than patients without PNI, which indicates PNI as a potent prognostic factor.

PNI, influenced by close relationship between nerve fibers and tumor microenvironment, regulates tumor progression in different aspects. On the one hand, the peripheral nerves surrounded by tumor cells are dysregulated and secrete several neuroendocrine factors, such

as nerve growth factor (NGF), providing neurotrophic stimuli and promoting the progression of tumor directly [28]. On the other hand, tumor cells are also able to release neurotransmitters or neuropeptides in return, which accelerate nerve fibers' growth and invasion in direction of tumors. The newly developed nerve fibers combined with local tumor cells secrete various neurotransmitters providing the adaptive microenvironment for tumor progression and metastasis [29,30] (Fig. 1). To better demonstrate the PNI, a computer-based CCA three-dimensional reconstruction model confirmed the anatomic microenvironment consist of vessels, nerve fibers and peripheral cancer cells, offering foundation for perineural invasion and tumor progression [31]. Collectively, PNI along with neuroendocrine-associated factors play crucial role in tumor progression. However, the crosstalk between PNI and tumor cells in CCA is still obscure and less investigated, which should be better understood to explore the potential anti-neurogenic targets.

4. Regulation of neuroendocrine factors in CCA

4.1. Central and peripheral neurotransmitters

4.1.1. Dopamine and serotonin

Dopamine, one of the central neurotransmitters, functions as a local chemical messenger, modulating various physiological activities including reward-motivated behavior, motor control, etc. In CCA, it has been demonstrated that tumor cells express D2 dopaminergic receptors and dopamine was found overproduced and secreted at increasingly high levels [32,33]. Blockage of dopamine results in a decrease of tumor growth both in vitro and in vivo. In addition, Huang L et al. found that inhibition of monoamine oxidase A (MAOA), an enzyme degrading dopamine, was closely associated with enhanced invasiveness and worse prognosis in patients with CCA [34]. Thus, dopamine serves as a prognostic factor for CCA and targeting dopamine would be a novel therapeutic approach against CCA.

Serotonin (5-HT), another central neurotransmitter known for regulating different feelings, also serves important roles in cholestasis and CCA via interacting with serotonin 1A and 1B receptors. In cholestasis, serotonin secretion plays roles in inhibiting excessive proliferation of cholangiocytes. However, in CCA, Alpini et al. revealed the sustained elevated level of both serotonin synthesis enzyme (TH1) and local serotonin in tumor tissue. It implies that serotonin may promote proliferation of malignant tumor cells in CCA which is opposite to that in cholestasis. Further experiments confirmed the stimulating effect on CCA cell proliferation and tumor growth modulated by increased serotonin, which can be blocked through inhibiting synthesis and secretion of serotonin [35]. Due to different feedback response in aspects of cholangiopathies, the investigation of serotonin still needs to be further studied.

4.1.2. Epinephrine and norepinephrine

Epinephrine (E) and norepinephrine (NE) are indispensable neurotransmitters in adrenergic system which regulates cardiovascular function, smooth muscle tone, etc. [36]. Previous studies demonstrated that E and NE also contribute to modulation of various tumors [37,38]. The first discovery to regulating CCA by adrenergic system was the findings that CCA cell lines Mz-ChA-1 and TFK-1 expressed the α-2A, α-2B and α-2C adrenergic receptor subtypes [39]. In the further vitro study, stimulation of tumor cells by α-2 adrenoreceptor agonist reduced the growth of CCA, which is mediated by up regulation of cAMP and a subsequent inhibition of EGF-induced MAPK activity. On the contrary, another study presented that expression of α-1 adrenergic and β-2 receptors in CCA cells were significantly higher than less invasive tumor cells [17], which facilitated nervous and lymphatic metastasis. Due to controversial function of different adrenergic neurotransmitters in CCA, the investigation of it still needs to be further studied.

4.1.3. Acetylcholine

Based on acetylcholine muscarinic (M receptors) and nicotinic receptors (N receptors) expressed in CCA cells, acetylcholine (Ach) known as the main neurotransmitter involved in cholinergic system, plays an enhancing role in tumorigenesis of CCA [18,40]. One recent study showed that poorly differentiated CCA with distant metastasis had a significantly higher expression rate of M3 receptor than CCA without metastasis [40]. On the basis of the M1 receptors expressed in CCA cells, stimulation with specific M receptor agonist, could promote CCA growth through the intracellular cascade of IP3 formation and increase of Ca2+ levels [41]. In addition, a specific kind of bile acid, taurolithocholic acid (TLCA) could also induce CCA cell growth by activating M receptors and subsequent $EGFR/EKR_{1/2}$ signaling pathway. This enhancing effect could be inhibited by non-selective M receptor antagonist such as atropine [42]. Apart from M receptors, α7 N receptor (α7-nAChR) was also found highly expressed in human CCA cell lines. Stimulation with nicotine and α7-nAChR agonist could accelerate the proliferation of tumor cells and tumor growth both in vivo and in vitro experiments [43]. Collectively, cholinergic system plays a promoting role in CCA development and progression, which reveals potential targets in regulating CCA (Table 1).

4.2. Neuroendocrine hormones

4.2.1. Estrogen

Estrogen, the primary sex hormone, is involved in various physiological functions including reproductive system, cholesterol mobilization, bone density, etc. However, abnormal level of estrogen is a well-established risk factor for various cancers. It has been revealed that estrogen level is increased in male CCA patients and shows an association with shorter survivals [44]. Further vitro studies demonstrated the promoting effect of estrogen on CCA cells proliferation and invasion in dose-dependent manners. On the basis of estrogen receptors (ER-α and ER-β) expressed in CCA tissues, tamoxifen, an estrogen antagonist, exerts inhibitory effects on proliferation of CCA cell lines and reduces tumor size in mouse models [45]. The inhibitory effect by tamoxifen was likely mediated by increased apoptotic cell death and Fas/APO-1 signaling pathway [46]. In addition, Alvaro D et al. demonstrated that

Table 1
Summary of central and peripheral neurotransmitters regulating cholangiocarcinoma cell biology.

Family	Member	Signaling receptor	Effects on cholangiocarcinoma cells
Central neurotransmitter	Dopamine	Dopamine 2 receptors	Promoted growth of CCA in vitro and in vivo
	Serotonin	Serotonin 1A & 1B receptors	Facilitated CCA proliferation and growth
Peripheral neurotransmitter	Epinephrine/norepinephrine	α-2A, α-2B and α-2C adrenergic receptors	UK 14, α-2 adrenergic receptor agonist, inhibited EGF-induced MAPK activity and reduced the growth of CCA
		α-1 and β-2 adrenergic receptors	Facilitated CCA growth, nervous and lymphatic metastasis
	Acetycholine	Muscarinic receptors	Triggered IP3 formation and increase of intracellular Ca2+ levels, promoting CCA growth
			TLCA activated EGFR/ERK1/2 and induced CCA cell growth
		α7 nicotinic receptor	Nicotine and PNU282987 accelerated cell proliferation and tumor growth

estrogens also interact with insulin growth factor-1 (IGF-1), playing additive proliferation role in CCA cells. Activated downstream pathway of ERK and phosphatidylinositol-3 kinase/Akt is responsible for the enhancing role which could be blocked by both ER antagonists and IGF1-R antibodies [47]. These results suggest that estrogen is a valuable target in CCA growth and inhibition of estrogen may have an effective and sustained inhibitory effect.

4.2.2. Secretin and gastrin

Secretin is a gastrointestinal hormone that regulates physiology of both cholangiocyte and CCA cells. Its receptors are exclusively expressed in cholangiocytes instead of hepatocytes [48]. In normal cholangiocytes, secretin plays mitogenic factors by stimulating ductal secretion with increase of intracellular cAMP. On the contrary, the effect of secretin on cAMP levels is suppressed in CCA cells and secretin subsequently inhibits CCA growth both in vitro and in vivo. The decreased level of proliferating cell nuclear antigen and elevated cleaved-caspase 3 expression were supposed to mediate the inhibitory effect of secretin [49]. Another gastro-hormone, gastrin, also exerts inhibitory impact on growth and proliferation of CCA by decreasing secretin-stimulated cAMP levels and bile secretion [50]. In addition, by interacting with cholecystokinin receptors (CCK-A, CCK-B) expressed on cancer cells, gastrin induces intracellular Ca2 + −dependent activation of protein kinase C-alpha and thus inhibits the proliferation of CCA cell lines in a dose- and time- dependent behavior [51]. Due to limited studies of this field, more molecular researches on modulation of secretin and gastrin in CCA are anticipated.

4.2.3. Histamine and somatostatin

Histamine is a biogenic amine that is widely recognized for its role in immune responses. It is also largely synthesized in digestive system and modulates CCA progression through interaction with H1–H4 histamine receptors (HRs) known as G-protein coupled receptors [52]. Several studies demonstrated that inhibition of H1/H2HR reduced histamine secretion in CCA cell lines and thus decreased CCA growth [53]. However, H3/H4HR displayed the opposite effect on CCA. The H3HR agonist, RAMH has been shown to inhibit CCA growth, which was accompanied by an increase IP3 levels and PKCα phosphorylation [54]. Moreover, agonizing of H4HR disrupts invasion potential and decreases tumor growth of CCA [22]. The diverse effects by HRs may be attributed to different activating signaling pathways. These findings are important in understanding the different response induced by histamine in CCA growth. Modulation of H1–H4HRs may present great importance for the management of balance between CCA progression and inhibition.

On the basis of similar G protein-coupled receptors (SSTR) expressed in cholangiocytes, somatostatin exerts its inhibitory effects of reducing acid secretion and preventing the release of other hormones in the digestive system [55,56]. Tan CK et al. demonstrated that by interacting with SSTR, somatostatin and its analog (octreotide and lanreotide) inhibited in vivo of tumor growth in mouse models implanted with human CCA cells. The potential mechanism might be associated with a decreased number of cells in G2/M and S phases and an increased number of cells in G0/G1 phase [56]. Based on inhibitory effect of somatostatin on CCA, recent study has planned to apply it into clinical research, which aims to confirm its effect and provide therapeutic approaches for patients (Fig. 2).

4.3. Other neuropeptides

4.3.1. GABA

Gamma-aminobutyric acid (GABA) is one of the main inhibitory neuropeptides reducing excitability in the nervous system. Recently liver represents another important site of GABA synthesis and metabolism. It has been demonstrated to mediate inhibitory effect through ionotropic (GABA-A) and metabotropic (GABA-B) receptors in primary liver tumors. For example, CCA cells expressing GABA receptors respond to GABA stimulation with decreased proliferation and migration [57,58]. Signaling cascade of increased IP3 and cAMP levels with activation of PKA and dephosphorylation of $ERK_{1/2}$ modulate the inhibitory effect on CCA cells [59]. In addition, Huang Q et al. also revealed that the anti-cancer effects exerted by GABA may be associated with the JAK/STAT3 pathway [60]. Recently, efficacy and safety of GABA has been under further clinical investigation for malignancies.

4.3.2. NGF

Recently, nerve growth factor (NGF), known as a neurotropic peptide regulating growth of neurons, has been shown to be involved in tumor induction, proliferation, invasion and apoptosis [61–64]. Gigliozzi A et al. discovered that proliferative hyperplasia in biliary system was associated with elevated expression of NGF and its specific receptor TrkA, indicating that NGF and TrkA were vital factors involved in proliferation of bile ducts [65]. In the malignancy of CCA, several studies showed that NGF secreted by CCA cells could promote proliferation, colony formation and tumorigenicity in a positive feedback behavior [66]. Apart from function of tumorigenesis, NGF also acts as neurotropic factors facilitating nerve axons development into tumor, which facilitates perineural invasion and tumor metastasis. In clinical studies, it has been demonstrated that expression of NGF was significantly related with lymph node metastasis and intraneural invasion in CCA [67]. Furthermore, high expression of NGF and TrkA serve as an unfavorable prognostic factor that predicts poor prognosis of patients with CCA [68]. Thus, NGF combined with TrkA pathway may reveal the target for early intervention and treatment of CCA.

4.3.3. NPY and melatonin

Neuropeptide Y (NPY), mainly found in brain, is also highly expressed in the intrahepatic nerve fibers and cholangiocytes in the biliary tree. In rat models of bile duct ligation, biliary hyperplasia was suppressed through mechanism of paracrine and autocrine of NPY. This represents that synthesis and secretion of NPY functions as inhibitory factors on bile ducts. Further experimental studies on CCA confirmed the results that administration of exogenous NPY was able to decrease proliferation and cell invasion [69]. Melatonin, another neuropeptide synthesized in the pineal gland, interacts with associated type 1A/1B (MT1/MT2) receptors and acts similar inhibitory effect on CCA [70] (Table 2). Dysregulated synthesizing enzymes of AANAT and ASMT result in low melatonin secretion and enhanced CCA growth. Due to limited reports on these two brain neuropeptides, further experiments are encouraged to validate their inhibitory effect on CCA.

5. Potential therapeutic approaches for neuroendocrine-regulated CCA

5.1. Inhibitors or antagonists of neuroendocrine factors

Neuroendocrine factors including dopamine, serotonin, acetylcholine and histamine exert promoting effect on growth of CCA via interaction with specific receptors. Therefore, antagonists inhibiting these promoting factors and receptors may represent good candidates for decreasing the growth of CCA. For example, administration of the D2 and D4 dopamine receptor antagonists could block the proliferative cholangiocarcinoma cell lines induced by dopamine. Alpha-methyldopa targeting dopamine production was able to suppress CCA growth by up to 25% [33]. In addition, therapeutic inhibitors such as atropine (acetylcholine M receptors antagonist) [43], tamoxifen (estrogen antagonist) [45,46], mepyramine and ranitidine (H1, H2 histamine receptors antagonist) [53,54] have currently been employed in ongoing clinical trials for cancers. The therapeutic efficacy is expected to be enhanced if multiple antagonists were combined targeting these factors.

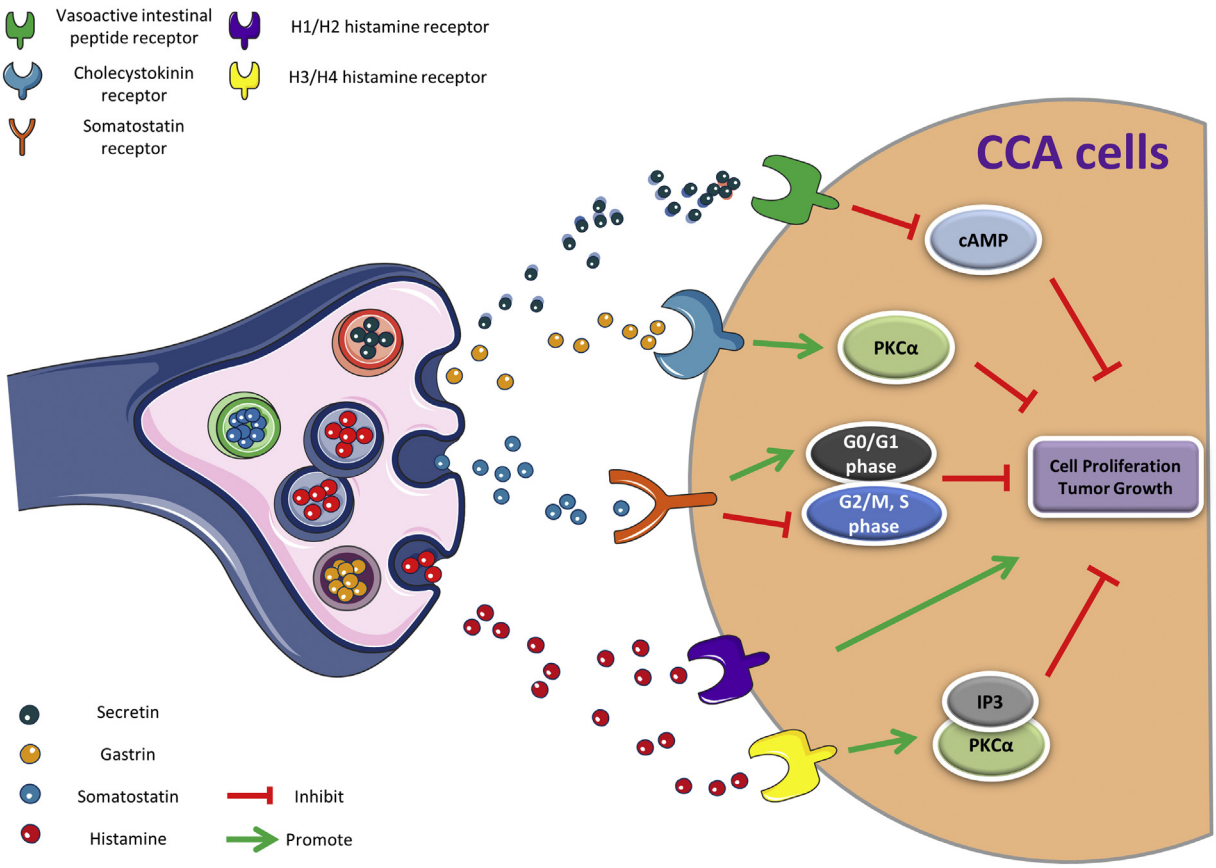

Fig. 2. Effect of neuroendocrine hormones on CCA.
Histamine interacts with H1/H2 HRs, which promotes cell proliferation and tumor growth of CCA. On the other hand, gastrin, somotostatin and histamine-H3/H4 HRs exert inhibitory effect on growth of CCA through interaction with specific receptors and activating downstream signaling pathway.

5.2. Agonists or analogs of neuroendocrine factors

Proliferation of CCA cells and growth of tumors can be directly inhibited by some neuroendocrine factors including secretin, gastrin, somatostatin and GABA. Based on the inhibiting effects of these factors, a series of agonists or analogs are under experiments in clinical studies. For instance, UK14, an α-2 adrenoreceptor agonist reduced the growth of CCA via activating α-2 adrenergic receptors subtypes expressed in CCA cells [39]. Analogs of somatostatin, octreotide and lanreotide, have been demonstrated to inhibit in vitro of CCA cell proliferation and in vivo of tumor growth in mice models [56]. Therefore, a phase II clinical study has been conducted to test the therapeutic efficacy of lanreotide in treatment of patients with CCA [71]. Also, GABA and its analogs baclofen, are under clinical investigation as potential new therapeutic approaches for CCA and other malignancies [72]. Thus, agonists or exogenous analogs of these inhibiting factors would act as important therapeutic tools, with potential to decrease tumor growth and slow down advanced tumor progression.

5.3. Inhibition of signaling pathways

Though the mechanisms into neuroendocrine regulation of CCA are yet well known, specific pathways such as EGFR/$ERK_{1/2}$ and PI3K/Akt signaling have been confirmed participating in the interactions between neuroendocrine factors and tumor progression. Pro-tumorigenic signaling pathway of PI3K/Akt/NF-kB activated by NGF and its receptor TrkA suggests that inhibitors targeting this pathway may reveal valid and sustained suppressing effect on tumor progression [73,74]. Therefore, synthetic PI3K and Akt inhibitors, inhibitors of NF-kB transactivation, etc. can be developed to downgrade tumor progression, reduce recurrence and prolong survival rates [75–77]. Moreover, a combination of inhibitors targeting different kinases or proteins on the signaling is believed to gain an enhanced effect. Due to limited studies focusing on the networks between neuroendocrine factors and tumors, more extensive researches and further trials of inhibitors targeting the pathways are encouraged and expected to confirm the therapeutic effect on CCA.

Table 2
Summary of other neuropeptides' effects on cholangiocarcinoma cell biology.

Other neuropeptides	Signaling receptor	Effects on cholangiocarcinoma cells
GABA	GABA receptors	Decreased proliferation and migration of cell lines via activation of PKA and dephosphorylation of ERK 1/2
Melatonin	MT1/MT2 receptors	Induced apoptosis of CCA cells by activating ROS-mediated DNA damage
Nerve growth factor	TrkA	Promoted proliferation, colony formation and tumorigenicity of CCA cells Facilitated nerve infiltration, nodal metastasis and tumor progression
Neuropeptide Y		Exogenous NPY decreased proliferation and invasion of CCA cells

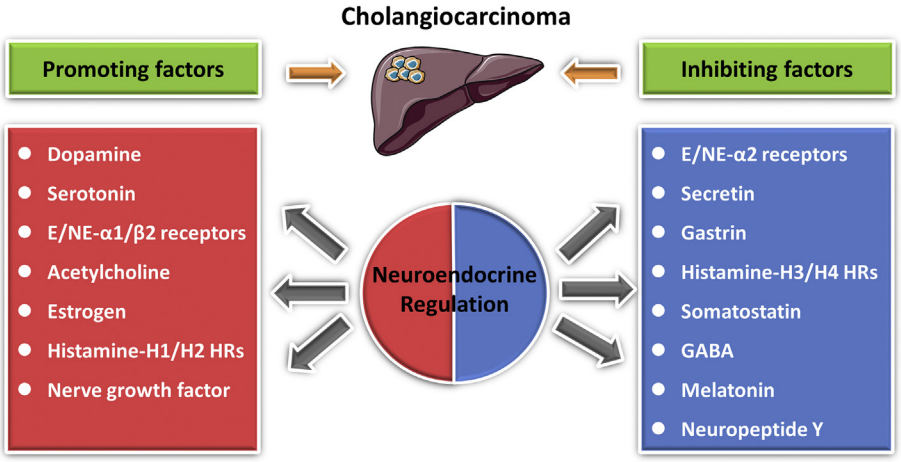

Fig. 3. Demonstration of neuroendocrine regulation of CCA.
Different neurotransmitters, neuropeptides and hormones are secreted to modulate CCA via promoting or inhibiting growth of CCA, which may represent therapeutic target of CCA treatment.

6. Conclusions and future perspectives

Increasing amount of evidences has indicated the substantial role of neuroendocrine hormones, neurotransmitters and neuropeptides in regulating the pathophysiology of CCA (Fig. 3). However, the full implication of the neuroendocrine regulation in CCA remains to be elucidated. Many questions of how the neuroendocrine-tumor cell network functions in CCA are being generated and to be confirmed in future extensive experimental and clinical studies.

First issue to remark is the innervation of tumor cells. It has been established that activated nerves in tumor microenvironment could secrete neurotrophic factors on CCA cells, which facilitates migration and metastasis of tumor cells along the nerve fibers. However, there is also converse evidence suggesting that tumor denervation or decreased nerve activity is associated with tumor metastasis and advanced stage [78]. Since limited facts available thoroughly explain the interaction between CCA cells and surrounding nerve fibers, more basic experiments should be conducted exploring how tumors are innervated and the specific mechanism of tumor cells invasion into nerve fibers. Another important part in neuroendocrine system which cannot be ignored is the role of sensory nerve fibers. As known, tumor-associated pain is caused by innervated sensory fibers into tumors or metastases. In pancreatic and prostate cancers, inhibition of neurotrophic peptide NGF has been shown to relieve neuropathic pain [79,80]. Since NGF also functions as a promoting factor in CCA growth, therapies of inhibiting NGF may provide dual effect against both tumor growth and accompanied pain. Therefore, further studies are needed to investigate the potential role of sensory nervous system in CCA. Finally, several reports described before have provided therapeutic approaches for treatment of CCA in use of neuroendocrine inhibitors or analogs. However, current evidence are only based on initial experiments and investigations, future clinical trials which simulate the regulation of neuroendocrine factors and target on tumor inhibition are eagerly encouraged and anticipated. Development of anti-CCA strategies based on neuroendocrine regulation may lead to improvement in survival outcomes of patients with CCA.

Conflict of interests

All authors have declared no conflict of interest.

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