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Review

An Insight into Neuropeptides Inhibitors in the Biology of Colorectal Cancer: Opportunity and Translational Perspectives

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Abstract: Neuropeptides are mainly secreted from the human central and peripheral nervous systems. Neuropeptides bind to its cognate rhodopsin-like G-protein coupled receptor (GPCR) and perform various physiological functions. Conventional cancer treatments in clinical practice still present many drawbacks due to the lack of selectivity toward the target cell, drug-resistance, and side-effects, thus pushing for the development of new therapeutic agents and therapies. Recent research suggests that neuropeptides influence cancer cell proliferation, invasion, metastasis, and angiogenesis and, therefore, they could be exploited as a target for novel anticancer therapies. Very recently, targeted approaches that inhibit neuropeptides and their associated receptors are being developed in cancer treatment. This review focuses on various neuropeptides and their potential utility as drug targets by different inhibitors as a recently identified approach to cancer prevention, with particular emphasis on colorectal cancer.

Keywords: neuropeptide; receptor; inhibitors; cancer; therapeutic agents; bombesin; neurotensin; vasoactive intestinal peptide; substance P

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1. Introduction

Neuropeptides (NPs) are small chains of amino acids that serve as chemical messengers and are released by neurons as neurotransmitters and neurohormones. Over 100 diverse classes of NPs with neuromodulatory, neuroinflammatory, and nerve cell proliferation properties have been characterized [1]. At a cellular level, NPs are ribosomally synthesized as larger protein-like macromolecules, which are further processed post-translationally into the vesicle for transportation to their broad range of targets. NPs act mainly by binding to the single seven-pass transmembrane receptor-like G-Protein Coupled Receptor (GPCR); however, in exceptional cases, they can also activate more than one GPCRs [2]. Based on their precise chemical nature and physiological functions, neurotransmitters fall into three major types (peptidergic, biogenic, and amino acids) of which NPs are an excellent example of peptidergic neurotransmitters, as schematically shown in Figure 1 and briefly described in Table 1.

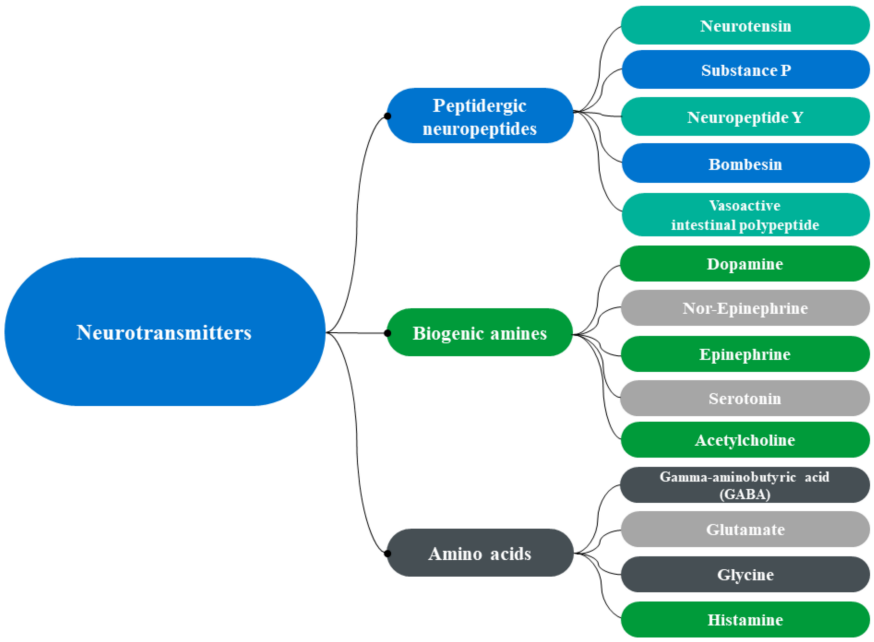

Figure 1. Chemical classification of neurotransmitters.

Broadly speaking, NPs include neuropeptide Y, calcitonin gene-related peptide (CGRP), opioids, galanin, vasoactive intestinal peptide (VIP), cannabinoids, substance P, bombesin, neurotensin, etc., and their essential physiological functions are related to tissue homeostasis, energy metabolism, and development of tumor microenvironment [27,28].

NPs have been meticulously investigated in recent years due to their aberrant behavior in cancer development. Their increased expression levels have been associated with the progression of colorectal, breast, lung, glioblastoma, prostate, and head and neck cancers [29]. Moreover, plenty of studies have also evaluated aberrantly expressed NP receptors in various human cancers. The consideration that the NP-receptor complex is coupled with different signaling pathways, including cAMP/EPACs recently related to cancer cell growth and development, leads to new biological and diagnostic targets [30].

Despite the progress made by research in finding new drugs and optimizing those already known [31–41] and exploiting new techniques [42–45], exploring novel approaches might lead to unexpected positive results. In that regard, targeting the receptors with suitable drugs or inhibitors may help counteract its physiological and pathological role in cancer initiation and progression through the ligand–receptor complex [46]. Hence, it has been confirmed that NPs and their receptors are significantly involved in various human tumors, making them an ideal druggable target in cancer theranostics. Among top-cited cancers, colorectal cancer (CRC) is one of the most common cancers worldwide. Among the symptoms, individuals experience changes in bowel habits, stool consistency, rectal bleeding, abdominal discomfort and pain, anemia, and weight loss. Our most intriguing observation is that various important NPs (such as amylin, bombesin, and ghrelin) regulate gastrointestinal functions; however, deviation from the normal functioning of these NPs may increase the risk of CRC onset, which represents one of the major growing concerns that need urgent attention. Therefore, mechanistic insight into the function of NPs in the tumorigenic process might suggest novel strategies for discovering novel inhibitors exploitable in antitumor therapy. In this review, we will address the possible implication of NPs in the pathophysiology of CRC and other cancers, and the possibility of their inhibition by specific molecules utilizable in cancer treatment with particular emphasis on CRC.

Table 1. List of neurotransmitters with corresponding sources, expression, and their brief description.

Neurotransmitters	Sources	Expressed	Description	Refs.
Peptidergic neuropeptides				
Neurotensin ($C_{78}H_{121}N_{21}O_{20}$)	Hypothalamus and intestine	Hypothalamus, bronchial epithelial cell, lymph node, anterior pituitary, jejunal mucosa, superficial temporal artery, hippocampus proper, duodenum, appendix and gallbladder.	Neurotensin is thought to regulate the luteinizing hormone, prolactin release and brain dopamine system. Involved in a wide variety of biological effects, such as histamine release, vasodilation, gastrointestinal (GI) muscle modulation and motility, and stimulation of intestinal secretion.	[3,4]
Vasoactive intestinal polypeptide	Gut, pancreas, and hypothalamus	Appendix, rectum, gastric mucosa, endothelial cell, transverse colon, cingulate gyrus and prefrontal cortex	It performs several functions in the body, such as relaxation of muscle in digestive tract and heart, control of fluid secretion, increase in glycogenolysis and reduction of the blood pressure.	[5,6]
Substance P ($C_{63}H_{98}N_{18}O_{13}S$)	Brain, spinal cord and intestine	Hypothalamus, amygdala and periaqueductal gray	Substance P is associated with inflammation, pain, anxiety, mood, cell migration and angiogenesis.	[7,8]
Bombesin ($C_{71}H_{110}N_{24}O_{18}S$)	Brain	-	It mediates gastrin release and was also termed gastrin-releasing peptide. It participates in various processes, such as glucose homeostasis, circadian rhythm, thermoregulation, and many GI processes.	[9,10]
Neuropeptide Y ($C_{190}H_{287}N_{55}O_{57}$)	Brain and circulating platelets	Cerebral cortex, thalamus, brainstem, hypothalamus, amygdala, prostate, and hippocampus	Neuropeptide Y plays a crucial role in food intake, reducing stress and pain, lowering blood pressure, and storing of energy.	[11,12]
Calcitonin gene-related peptide (CGRP)	Peripheral and central neuron	placental syncytiotrophoblast, villous vascular endothelial cells, and decidua	Calcitonin gene-related peptide is implicated in vasodilation, appetite suppression, stem cell mobilization, and homeostasis.	[13,14]
Biogenic neurotransmitter				
Dopamine ($C_8H_{11}NO_2$)	Substantia nigra ventral brain	Brain, blood vessels, kidneys, pancreas, and gastrointestinal tract	Dopamine regulates norepinephrine inhibition, vasodilation, increases sodium excretion, reduces insulin production and gastrointestinal motility.	[15,16]
Epinephrine and Norepinephrine ($C_9H_{13}NO_3$)	Adrenal gland and medulla oblongata	Heart, liver, lungs, muscles, and brain	Epinephrine has effects on increasing blood sugar, heart rate, smooth muscle contraction, and pupil dilation	[17,18]
Serotonin ($C_{10}H_{12}N_2O$)	Enteric nervous system located in the GI tract and brain	-	Sleep, emotion, mood, wound healing, immune regulation, and insulin secretion are some of the important cognitive and peripheral functions modulated by serotonin.	[19,20]
Acetylcholine (Ach, $C_7NH_{16}O_2+$)	Motor neurons, parasympathetic nervous system and brain	Skeleton muscle, brain, and other organs	Ach is a well-known neurotransmitter of the neuronal system, it is also synthesized in non-neuronal cells including mesothelial, adipocytes, fibroblast, epithelial, endothelial, and cancer cells.	[21,22]
Amino acids				
Gamma-aminobutyric acid-GABA, ($C_4H_9NO_2$)	Brain	-	GABA is an inhibitory neurotransmitter that blocks messages or nerve signals between nerves and CNS, though its function is well defined in reducing the feeling of stress, anxiety, and fear.	[23,24]
Glycine ($C_2H_5NO_2$)	Kidneys and liver	-	Glycine is an inhibitory neurotransmitter of the central nervous system CNS, produced naturally in the body and important for the healthy development of bones, muscles, and tissues.	[25]
Histamine ($C_5H_9N_3$)	Basophils and mast cells	-	It plays a central role in inflammatory response and as itching mediator.	[26]

2. Most Significant Neurotransmitters in Cancer Development and Progression

Cancer incidence sometimes arises due to stress-like conditions under the influence of released neurotransmitters or hormones, which are increased during stressful events. Studies have demonstrated a strong and consistent link between cancer and the expression of stress-induced neurotransmitters that are identified as potent mediators for cancer initiation and progression.

Prior research has explored the relationship between cancer and dopamine and found that decreased dopamine expression can result in tumor development [47]. Knockdown of the expression of dopamine results in the inhibition of IGF-1 (insulin-like growth factor-1), which is responsible for the proliferation of gastric cancer cells and angiogenesis. Meanwhile, upregulating the Krüppel-like factor 4 (KLF4) gene, a well-known cell cycle regulator, can also inhibit proliferation [16]. In another study, it was demonstrated that dopamine could exert an antagonistic action in colon, breast, and stomach cancer, which means its stimulation could inhibit the growth of tumors [48]. However, the effect of dopamine is not clear yet as, in some cases, it also proved its inability to inhibit the proliferation and migration of cancer cells, indicating that its action is either dose-dependent or expression-based in different cancers [49].

Serotonin is another important neurotransmitter that exerts a mitogenic function in the development and progression of several cancers, such as lung, prostate, liver, melanoma, and pancreas [50–52]. An in vitro study showed that tryptophan hydroxylase 1 (TPH1), an enzyme catalyzing serotonin production, is highly expressed and facilitates breast cancer onset by sustaining mammary epithelial cells' growth [53]. Similarly, serotonin secretion concurrently enhances cell proliferation in the liver and pancreatic cancer. Therapeutically, inhibition of serotonin receptors, such as the hydroxytryptamine receptor 2B (HTR2B) in pancreatic cancer and the 5-hydroxytryptamine receptor 2B (5-HT2B) in the liver, has been shown to prevent cancer cell proliferation, angiogenesis, and metastasis [54,55].

In recent years there has been a rise in the number of studies targeting the complex of neurotransmitters, i.e., epinephrine (E) and norepinephrine (NE), and their GPCR, which drive several biological processes in cancer onset and progression, including proliferation, survival, angiogenesis, and invasion [56]. In addition, much research has been carried out on the genes encoding GPCR receptors in the context of cancer pathogenesis through the activation of the signaling cascade via the β1/2-adrenoreceptor (β-AR)—cyclic-AMP (cAMP)—protein kinase A (PKA). The underlying mechanism of promoting cancer initiation and development by E and NE through β-AR has been correlated to many cancers, including lung, ovarian, colon, and breast cancer, suggesting that E, NE, and the GPCR represent a potential diagnostic and therapeutic target in these types of cancer [57–61].

It is now well recognized that acetylcholine (ACh) also has tumor-promoting activity, including proliferation, differentiation, migration, and angiogenesis in the colon and gastric cancer via increased expression of vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) [62,63]. This association was also investigated in another study showing that inhibition of nicotinic ACh (n-ACh) receptors (n-AChR), which are upregulated in squamous cell lung carcinomas (SCC), limited basal and nicotine-stimulated growth of SCC [64]. In a different study, it was observed that n-ACh served as a potent mediator of the nuclear factor kappa B (NFkB) inflammatory pathway by activating the sympathetic nervous system in stressful events, leading to a cancer-like condition [65,66]. Researchers suggested novel cancer therapies based on targeting the ACh receptors [67]. The most common ACh receptors identified in different types of cancer are the α7-nAChR and the M3-mAChR receptors, which can be inhibited by antagonists, namely D-tubocurarine, α-bungarotoxin, and secreted Ly-6/uPAR-related protein 1 (SLURP-1) drug [68]. Similarly, the pharmacological efficacy of M3-mAChR antagonists (e.g., darifenacin and tiotropium) was exploited to arrest tumor initiation and progression by minimizing cell proliferation, survival, and angiogenesis in small cell lung cancer, as well as colon and gastric cancer [69,70].

Clear, strong, and well-documented evidence supports the expression of glutamate and its receptors as a prognostic biomarker in several cancers [71,72], including prostate, glioma, melanoma, colorectal, and gastric cancer, suggesting that aberrant glutamate signaling is one of the key factors for cancer development and progression [73,74]. One prospective study showed that treatment of colon cancer cells with an antagonist inhibited cell growth by downregulating the level of the metabotropic glutamate receptor 4 (mGluR4), whereas the opposite effect was observed by treatment with an agonist, possibly because of

the increased expression of mGluR4 in the presence of 5-fluorouracil (5-FU), suggesting that mGluR4 antagonists may reduce the chance of cancer onset as well as improve the health of patients undergoing cancer treatments [75,76].

Along the same lines of information, it is also well documented that gamma-aminobutyric acid (GABA) and its receptors play a dominant role in cancers, as confirmed by its modified activity in colon, glioma, breast, ovarian, and gastric cancers [77,78]. A number of studies suggest that GABA receptors are overexpressed in several cancers, including breast [46], prostate [53], and pancreatic cancer [50,51]. In contrast, low expression of GABA receptors was found in liver cancer [79–81]. Increased cell division was likely due to activation of the mitogen-activated protein kinase (MAPK) pathway in gastric cancer cells under the effect of muscimol, a potent agonist for the $GABA_A$ receptors [82]. Similarly, Takehara and colleagues showed that pancreatic cancer was developed due to activation of the MAKP/ERK pathway via an increase in secondary messengers, such as Ca^{2+} ions, in a GABA independent manner [83,84].

3. Neuropeptides: Peptidergic Neurotransmitters

Neuropeptides are peptide hormones that the neuroendocrine system uses as chemical signals to communicate among cells. They are a set of signaling messengers that regulate exocrine and endocrine secretion, smooth muscle contraction, blood pressure, and inflammation by acting as neurotransmitters, paracrine regulators, and hormones. Numerous NPs are localized in the brain and co-released with neurotransmitters to reach their target, where they perform a wide variety of functions.

NPs are said to serve as modulators depending on the condition in which they are challenged; however, they generally function in the brain in a paracrine manner. Growing evidence supports that during stress, injury, and pain, they act as potent neurotransmitters and trophic factors that mediate the inhibitory or stimulatory action of the nervous system. In recent years, several biomolecules, such as neurotensin, substance P (SP), vasoactive intestinal polypeptide (VIP), bombesin, opioids, and neuropeptide Y have emerged as potential forms of NPs whose action as neuronal mediators has been extensively studied in different pathological conditions, including cancer [80,85]. As discussed earlier, severe consequences of stress are often correlated with oncogenesis in different cancers. However, NPs related to cancer development and progression are listed in Table 2.

Table 2. NPs related to cancer development and progression and their main characteristics.

Neuropeptides	Number of Amino Acids	Discovery	Related Cancers	Tumorigenic Properties	Refs.
Neurotensin	13	Carraway and Leeman in 1973	Pancreatic, lung, breast, prostate, and colorectal cancer	Increased cell proliferation and migration	[86,87]
Vasoactive intestinal polypeptide (VIP)	28	Said and Mutt in 1970	Neuroblastoma, pituitary adenomas, colorectal cancer, endometrial, and lung cancer	Increased cell proliferation, metastasis, invasion, and angiogenesis	[88,89]
Substance P	11	Von Euler and Gaddum in 1931	Glioblastoma, breast, acute lymphoblastic Leukemia, colorectal cancer, melanoma, and gastric cancer	Increased cell proliferation, migration, invasion, and angiogenesis; pro-inflammatory effect	[90,91]
Bombesin	14	Battey and Wada in 1991	Prostate, gastric, lung, breast, colorectal cancer, renal cell carcinoma, small cell lung carcinoma, neuroendocrine, squamous, colon, and pituitary cancer	Promoted vascularization, tumor growth, and differentiation	[92–95]
Neuropeptide Y	36	Tatemoto and Mutt in 1982	Neuroblastoma, colorectal cancer, breast, Ewing sarcoma, and prostate cancer	Induced cell growth, vascularization, and angiogenesis; pro-inflammatory effect	[46,96,97]
Calcitonin gene-related peptide (CGRP)	37	Amara and colleagues in 1982	Prostate, lung, colorectal cancer, pancreatic, ovarian, endometrial, pituitary, renal, and hepatic cancer	Promoted angiogenesis, lymphangiogenesis, cell growth, neovascularization, proliferation, and migration	[98–101]

NPs and their associated receptors have been extensively investigated to identify their critical role in complex diseases such as obesity, diabetes, Alzheimer's, and other nervous system disorders. Moreover, the presence of NPs in several disease pathogenesis has been widely described. Still, the critical role of NPs and their associated receptors in the development of cancers and their potential implication for specific therapy and prevention of cancer is not well-defined [102]. NPs have been studied by several researchers who provided mechanistic insight into the biological significance of the neuronal system in tumor progression [101,102]. NPs have been found to bind to multiple receptors expressed in endothelial cells and induce cell proliferation, migration, survival, and differentiation, as well as promote angiogenesis, thus suggesting that NPs are tumor-promoting factors during cancer development and progression. Galli and colleagues demonstrated that a higher serum concentration of neuropeptide Y (NPY) in neuroblastoma patients was significantly correlated with poor prognosis and survival outcomes [97]. Moreover, elevated NPY circulation in serum was linked to metastasis and angiogenesis. This study supports the higher expression of NPY in patients with neuroblastoma and suggests its potential exploitation as a therapeutic biomarker for monitoring cancer progression. The diagnostics potential of NPY was also evaluated in CRC patients in different samples, such as tissue, cell lines, and feces. Interestingly, the results showed a significantly hypermethylated promoter region of NPY in CRC tissues as well as fecal exfoliated cells. Moreover, treatment with 5-aza-2′-deoxycytidine (a demethylating agent) suppressed the methylation level of NPY in CpG Island at the promoter region and normalized its transcriptional expression in vivo, indicating that tissue and fecal NPY methylation could be a potential biomarker in CRC patients [103]. NPs, such as neurotensin (NTS) and its cognate low-affinity receptors NTSR1 and NTSR2, mediate several biological functions, including gastric acid secretion, bowel motility, and fatty acid absorption. Growing evidence shows that NTS is also strongly implicated in a number of mechanisms involved in tumor growth, proliferation, survival, metastatic spread, and invasiveness. The recent resurgence of NTS and NTSR1 and NTSR2 complexes in cancer-inducing cell proliferation and development by pathway deregulation, such as the Wnt/β-catenin signaling pathway, enlightens its role in the carcinogenesis process. In fact, it has been suggested as a potential prognostic biomarker in head and neck squamous cell carcinoma, lung, colon, and breast cancers [104,105].

It has been shown that the substance P-neurokinin-1 receptor SP/NK-1R complex is frequently dysregulated in cancer, confirming its role as a growth-promoting and anti-apoptotic factor in CRC, breast, and prostate cancer. In gastrointestinal (GI) cancer, the NK-1 receptor was also found to be overexpressed in GI tumor cells, and the binding of SP to the NK-1 receptor was implicated in many biological functions, such as proliferation, migration, metastasis, and angiogenesis [106,107]. Therefore, a therapeutic approach against the NK-1 receptor could potentially inhibit the growth-promoting activity of the GI tumor cells. For example, NK-1 receptor inhibition with antagonists, such as fosaprepitant, L-732,138, aprepitant, and L-733,060, induced an antineoplastic effect against GI tumors by inhibiting cell migration and angiogenesis, inducing apoptosis, and counteracting the Warburg effect [108,109].

Aberrant expression of galanin receptors (GalRs) could be also considered a risk factor for human GI cancers, in particular stomach epithelial cells and gastric cancer cells. GalRs (GalR1, GalR2, and GalR3) belong to the GPCRs family that interacts with galanin (Gal) and regulate a range of biological processes, including tumorigenesis [110,111]. A study demonstrated that elevated Gal expression in samples from CRC patients along with high serum concentration can be considered a serious risk of invasion and metastasis [112]. Despite a clear understanding of the role of Gal in CRC cases, its receptors have been less explored except GalR1, but this does not overwhelmingly support the role of GalRs in the pathogenesis of CRC. The possible role of GalRs in CRC tissue and colon epithelial cells was also evaluated in a recent study showing that GalR2, GalR1, and GalR3 present stronger immunoreactivity in human colon cancer cells compared to epithelial cells (enterocytes and goblet cells) in the large intestine of CRC patients. Furthermore, GalR3 with significantly

higher immunoreactivity and survival rate in CRC patients was suggested to be an excellent prognostic biomarker for CRC patients [113]. A close association between Gal and CRC occurrence has been also reported by other researchers who observed a differential expression of Gal at different stages of the CRC in addition to GalR1 expression measured with the help of the IHC method. Their study concluded that underexpressed Gal is directly correlated with an advanced CRC stage [114].

4. Promising Neuropeptides Inhibitors for the Development of Effective Cancer Therapy

Numerous therapeutic approaches targeting NPs and their receptors have been established to counteract the effect of these peptides, especially in cancer [81]. Several antagonists, inhibitors, and antibodies have been developed against each NP and their receptors, directly or indirectly disrupting their function and downregulating their potential activity in cancer development. Therefore, a wide range of novel enhanced combination therapies and various inhibitors may serve as a promising strategic therapeutic option for the treatment of cancer patients [115].

4.1. Emerging Neuropeptides Inhibitors in Colorectal Cancer

Colorectal cancer (CRC) is one of the most common cancers, mainly due to alterations in genetic and epigenetic factors that lead to tumor progression and development [116,117]. Several NPs have been identified that play a significant role in stimulating various important signaling pathways, thus leading to CRC development [118]. Therefore, the development of specific inhibitors targeting these NPs may serve as a potential therapeutic approach for CRC treatment. The following section briefly describes various NPs and their specific inhibitors used for therapeutic purposes in the treatment of CRC.

4.1.1. Bombesin

Bombesin (BB) and its receptors (BBR) have been reported to be overexpressed in many cancers, including CRC. Two commonly known BB-related peptides, including gastrin-releasing-peptide (GRP) and neuromedin-B (NMB) and their respective GPCR receptors, i.e., GRPR (also known as BB2) and NMBR (also known as BB1), are expressed at a higher level in CRC patients [119]. Stimulation of these NPs has been shown to increase tumor differentiation and progression, acting mainly as morphogenetic molecules. Therefore, various therapeutic options have been developed for regulating the expression of BB-related peptides and their receptors in CRC. Researchers in their study highlighted the potential inhibitory effect of various BBR antagonists in affecting the development and progression of tumors in patients with CRC [94]. Various combinational therapies, including the use of a suitable antagonist together with a potent inhibitor, have been reported to have even more inhibitory effects on CRC cancer cells [120]. With the help of experimental analysis, it was observed that the application of RC-3095, a GRPR antagonist, together with several cytotoxic agents, such as 5-FU and irinotecan, results in downregulation and growth inhibition of CRC xenografts. Another study reported the antitumor activity and inhibitory tendency of AN-215, a BB-conjugated analog containing doxorubicin, in CRC [121]. These compounds help target and regulate the growth and proliferation of cancer cells.

4.1.2. Neurotensin

Neurotensin (NTS), together with its receptor, plays a pivotal role in stimulating oncogenesis and tumorigenesis in CRC cells and significantly influences many signaling pathways, such as Wnt/β-catenin, MAPK, PI3K/AKT, and Src/Raf dependent pathway. Growing evidence indicates that the NTSR1-NTS interaction activates RAS and PLC, further stimulating other downstream signaling processes. Remarkably, activation of the RAS gene induces an increase in the production of NTS, which exhibits autocrine and paracrine properties and simultaneously upregulates the AKT gene, which has been found to inhibit apoptosis in colon cells [85–87]. On the other hand, PLC plays a critical role in convert-

ing PIP2 to IP3, which increases calcium ion production. The increased concentration of calcium ions stimulates several downstream regulatory genes, such as AKT, c-Fos, EGFR, NF-κB, and CAMKII, which further promote various cellular metabolic processes, such as apoptosis, signal transduction, activation of MAP Kinase, AKT pathway, ion channels modulation, tumor cell proliferation and survival, cell invasion and metastasis. The regulatory role of NTS in promoting CRC through signaling processes has been depicted in Figure 2.

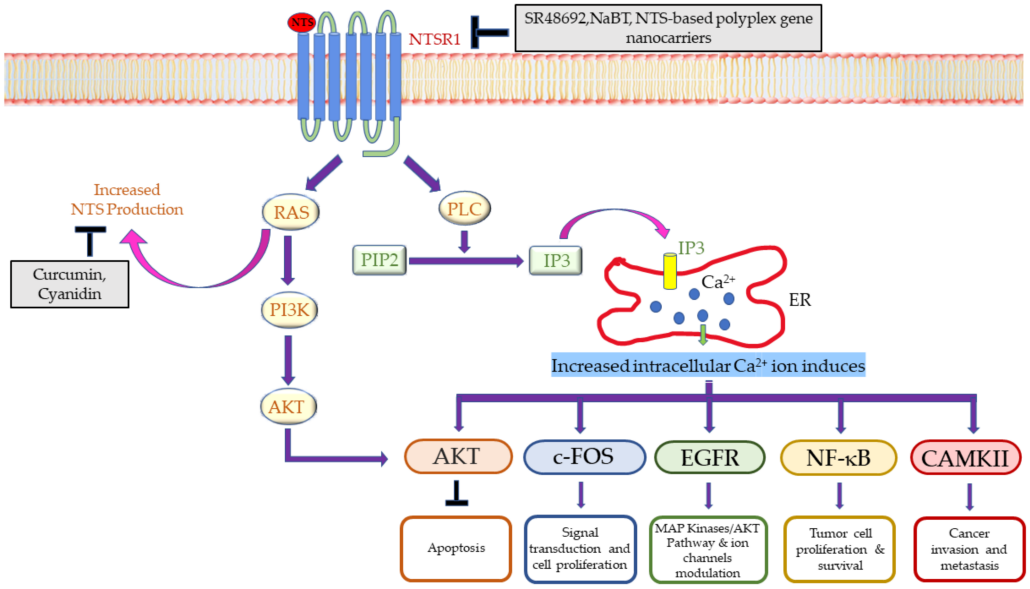

Figure 2. Signaling cascade driven by NTS interacting with NTSR1. This complex is involved in the gene regulation of various biological processes via activating the RAS-PI3K-AKT and PLC-IP3-Ca^{2+}, finally contributing to cancer progression. Abbreviations: NTSR1: neurotensin receptor type 1; PI3K: phosphatidylinositol-3-kinase; PLC: protein lipase C; PIP2: phosphatidylinositol-4,5-bisphosphate; IP3: inositol trisphosphate; ER: endoplasmic reticulum; AKT, protein kinase B; EGFR: epidermal growth factor receptor; NF-kB: nuclear factor of kappa-light-chain-enhancer of activated B-cells; CAMKII: calcium/calmodulin-dependent protein kinase II.

Researchers highlighted the elevated expression of more than 40% of NTS receptors in human CRC cell lines and activation of the Wnt/APC signaling pathway, which led to the upregulation of their oncogenic activity. It is clear that the NTS-NTSR1 complex in CRC cell lines (HT29, HCT116, SW620, SW480) raises the possibility that this complex increases the risk of CRC progression [122]. Thus, the expression of NTS/NTSR1 directly influences CRC progression and development and can serve as a potential molecular biomarker in CRC diagnosis and prognosis. Several treatments have already been proposed for targeting the expression of NTS/NTSR in CRC. Sodium butyrate (NaBT) was reported to have a beneficial effect in downregulating the NTS and NTSR activity [123]. NaBT is a histone deacetylase inhibitor that directly hinders the functional activity of NTSR mRNA, protein, and promoter function, thereby suspending the growth and proliferation of CRC cells and increasing their apoptosis. In another study, Iwase et al. 1996 identified a potent NTSR antagonist, SR48692, which downregulates the expression of NTS and inhibits tumor growth and development [124]. Concurrent work by Maoret et al. also considered a similar approach based on a non-peptidic NTSR antagonist, i.e., SR 48692. In vitro experiments revealed that SR48692 markedly reduces colony formation by interacting with the NTSR expressed in colon cancer cells [109]. Further support for this positive result was obtained in vivo. Treatment with SR 48,692 (1.7 µmol/kg every 24 h) reduced the tumor formed by xenografted SW480 and HCT116 cells in nude mice, suggesting that SR 48,692 deserves further attention as it could be an antagonist with potential anticancer activity in the treatment of colon cancer. Another therapeutic approach exploited the use of various antioxidants and dietary compounds on the activity and function of NTS in

CRC. For example, natural products, such as curcumin, effectively inhibited the secretion of NTS-mediated IL-8 protein and downregulated the migration activity of colon cells [125]. Cyanidin, another dietary product, has also been shown to have an inhibitory effect on NTS and other pathways related to cancer cell metabolism induced by the epidermal growth factor (EGF) [126]. A nanotechnological approach proposed by Hernandez and coworkers exploited NTS-based polyplex gene nanocarriers targeting specifically the NTSR, demonstrating its feasibility as an effective therapeutic approach for treating CRC [127].

4.1.3. Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) has been reported to contribute significantly to CRC progression and development, although in some cases it inhibited it. Nevertheless, VIP antagonists have been used as potential inhibitors to limit the neoplastic progression of several cancer cell lines. Levy and colleagues demonstrated the in vitro antineoplastic activity of VIP hybrid antagonists, such as $NTS_{6–11}VIP_{7–28}$, in CRC cell lines (HCT-15) expressing functional VIP receptors [128]. $NTS_{6–11}VIP_{7–28}$ was able to inhibit cancer growth and proliferation at nanomolar concentrations, showing its potential as a potent preventing agent in cancer therapy and confirming that the VIP hybrid antagonist could be efficiently utilized as a potential therapeutic approach for treating and preventing CRC.

4.1.4. Substance P

Substance P (SP) supports the proliferation and development of cancer cells in CRC, mainly due to the activation of NK1R with the help of various proinflammatory cytokines. Application of Spantide 1, an antagonist of NK1R, resulted in a decreased expression of cancer cells in CRC [94]. Aprepitant, another NK1R antagonist, also significantly downregulated cellular growth and proliferation of two colon cancer cell lines, i.e., LiM6 and DLD1 [90]. Inactivation of the SP/NK1R signaling pathways led to aberrant inhibition of the Wnt signaling pathway, thus resulting in the downregulation of various cellular processes [90,91]. However, SP/NK2R signaling in CRC has not been explored well yet [129]. The influential work of Xiang and colleagues gave rise to a renewed interest in understanding the higher expression of NK2R, which was demonstrated to be associated with tumorigenesis, metastasis, and poor survival of CRC patients. The higher expression of NK2R in colon cancer was observed due to interferon (IFNα/β) stimulation and polyinosinic-polycytidylic acid (poly I:C) administration in vitro and in vivo, respectively. However, the use of a potent and selective antagonist (GR 159897) against the NK2R, inhibited the tumor cell proliferation in vitro and the tumor formation in cancer-bearing mice, suggesting it is an optimistic target in patients with colon cancer [130].

4.1.5. Neuropeptide Y

Neuropeptide Y is secreted from tumor cells and acts through multiple receptors, especially the Y2 receptor (Y2R). It mediates proliferation and angiogenesis during cancer development. However, in some cases, it mediated chemoresistance by virtue of its Y5 receptor under various pathological conditions. Consequently, it was observed that altered expression of NPY and its receptors are directly correlated with poor clinical manifestations, low survival, and enhanced cell proliferation in different types of cancer, suggesting NPY as a remarkable drug target [131]. Overexpression of NPY activates the Y2 receptor on colonic endothelial cells and has a direct impact on angiogenesis and tumor growth following activation of the ERK/MAPK pathway in colon adenocarcinoma. However, it was demonstrated that the use of a specific Y2R antagonist inhibited the NPY-induced angiogenesis and orthotopic HT29 tumor growth in colon adenocarcinoma [132].

4.1.6. Orexins

Orexin-A and orexin-B are two new NPs that interact with their respective receptors (OX1R and OX2R) and are involved in different pathophysiologic processes, including inflammation, ulcerative colitis, and cancer [133,134]. Previous studies have demonstrated

a strong and consistent link between OX1R and OX2R expression in cancer. The high prevalence of OX1R in GI cancer is responsible for metastasis to the lung and liver from the colon [135]. It is noteworthy that orexins and their receptors' antagonists were found to exert an antitumor effect on the growth of colon cancer cells, possibly due to the induction of mitochondrial apoptosis [136]. Circumstantial evidence supported that orexin treatment reduces the cell proliferation in colon cancer cell lines (HT-29, Caco-2, and LoVo) by promoting apoptosis, and diminishes the tumor growth in tumor-bearing mice and xenografted tumor in nude mice. However, the antitumor activity of orexin can be reversed by using suitable inhibitors, such as NSC-87877 and PD169316 [137].

4.2. Neuropeptides Inhibitors: A Promising Approach also for Other Cancers

In addition to CRC, neuropeptides have also been identified as significant cell growth factors for various other cancers [90]. As our understanding of the impact of neuropeptide growth factors in other cancer improves, new strategies in translational research for diagnosing and predicting the disease and its treatment have appeared. Similarly, to the case of CRC, several NPs, such as substance P, neurotensin, and bombesin, have been reported to initiate signaling pathways that lead to the development and progression of other tumors. Thus, inhibitory mechanisms against specific NPs and their receptors must be developed to regulate oncogenic mechanisms. In terms of treatment, antibodies, antagonists, and selective inhibitors could target neuropeptides, growth factors, receptors, and signaling pathways that regulate their mitogenic effects [85]. Further on in this review, we briefly highlighted some inhibitors of specific NPs and their receptors in several prominent cancers.

4.2.1. Breast Cancer

Breast cancer is a heterogeneous disease resulting mainly from a mutation in BRCA1, BRCA2, and other important regulatory genes. It is one of the most common malignancies affecting women worldwide. Various novel therapeutic approaches, including bioactive lipids, plant-derived secondary metabolites, multi-omics approach, next-generation sequencing (NGS), and precision medicine, have been exploited for its treatment; however, the search for successful clinical therapy is still active [138–140]. Substance P (SP) has been associated with activation of the neurokinin-1 receptor system (NK1R), which upregulates various intracellular processes responsible for tumor initialization and development in breast cancer [90]. The inhibitory effects of various NK1R antagonists, such as Aprepitant, L-732,138, L-733, 060, CP-96345, C-9994, MEN 11467, and SR14033, on different breast cancer cell lines have been identified experimentally and their role in inducing apoptosis and inhibiting cellular growth has been established [141–143].

Another therapeutic approach targeting SP took advantage of Spantide III, which effectively caused cell death and reduced cell proliferation [144]. Neurotensin and its receptors are directly correlated to the size of the tumor, recurrence, and survival rate in breast cancer patients [105]. Possible treatments with a previously developed radiolabeled neurotensin analog, Tc-NT-XI, were inefficient and inaccurate [145]. Therefore, new generations with more stable compounds, such as ^{99m}Tc-NT-XIX (^{99m}Tc-(*N*-His)Ac-(Arg-*N*-CH_3)-Arg-Pro-(dimethyl-Tyr)-(*tert*-Leu)-Leu, ^{188}Re-NT-XIX, and ^{18}F-DEG-VS-NT (^{18}F-(2-(2-(2-fluoroethoxy)ethoxy)ethylsulfonyl)ethene-neurotensin), have been developed which mainly target the NTSR receptor and efficiently inhibit tumor development and progression in BC [146]. Bombesin/gastrin-releasing peptide (GRP) and GRPR have been found to be elevated in 62% of breast cancer patients. A study highlighted the role of two BB/GRP antagonists, i.e., RC-3095 and RC-3940-II, in significantly reducing the growth and proliferation of BC cells. These antagonists directly downregulated the secretions of bFGF, IGF-II, and VEGF-A in breast cancer cells, thereby inhibiting angiogenesis [92]. Similarly, there is a well-recognized association between neuropeptide Y and its receptors and human breast cancer, which has been demonstrated to promote cell proliferation, migration, and vascularization. Investigation through the Y5R agonist resulted in an increased proliferation rate and further application of Y5R blockade L-152,804 led to attenuation in

a concentration-dependent manner, which resulted in the inhibition of the proliferative impact of the Y5R agonist treatment [147].

4.2.2. Prostate Cancer

Prostate cancer is one of the most common cancers in men and occurs mainly due to genetic and environmental factors [148]. Various NPs involved in the development and progression of prostate cancer have been identified. Therefore, specific inhibitors against these NPs have been developed. For example, a specific GRPR antagonist ^{68}Ga-RM2, also known as BAY 86-7548 (^{68}Ga-DOTA-4-amino-1-carboxymethyl-piperi- dine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2), has been developed and frequently used for inhibiting prostate cancer progression [149]. ^{64}Cu-CB-TE2A-AR-06 (CB-TE2APEG4-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2), another GRPR antagonist, was recently developed and found to be metabolically stable and efficient for cancer treatment and inhibition. Neuropeptide Y and its receptors have also been found to play a prominent role in prostate cancer development and progression. Specific inhibitors targeting NPY, such as BIBP32226, a recently discovered Y1R antagonist, could be used effectively in the treatment of prostate cancer by inhibiting cellular proliferation and growth [150].

4.2.3. Glioblastoma

Primary central nervous system (CNS) tumors account for about 2% of all adult malignancies. Gliomas account for 40% to 67% of initial tumors in adult CNS cancers [151]. Glioblastoma (GBM) is the most aggressive malignant primary brain tumor of the astrocytic lineage and, according to the WHO classification, it is a grade IV glioma [152]. Gastrin-releasing peptide (GRP) released from presynaptic terminals regulates synaptic plasticity, memory, and fear responses by binding to GRPR specifically localized at postsynaptic membranes. GRP is a BB-like peptide found in mammals that regulates a variety of biological responses by activating the GRPR. Many forms of human peripheral tumors have an abnormal expression of both GRP and GRPR. Human glioma has been shown to have extensive expression and a high quantity of GRPR [153–155]. The development of selective GRPR antagonists as potential targeted anticancer drugs has been motivated by the finding that GRP and GRPRs play a role in cancer progression. For example, the GRPR antagonist RC-3095 induced a reduced proliferation of C6 rat glioma cells in vitro [156]. Furthermore, RC-3095 alone or in combination with TMZ inhibited the growth of C6 gliomas both in vitro and in vivo [157]. These findings lend credence to the idea that GRPR antagonists could be helpful in the treatment of glioma. VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) are structurally related neuropeptides operating through GPCR subtypes named vasoactive intestinal peptide receptors VPAC1, VPAC2, and PAC1. Human GBM tumors and GBM cell lines have these receptors [158,159]. Thus, targeting of the VIP receptor system and associated signaling pathways could also be an interesting therapeutic option in combination therapy with anti-proliferative drugs.

4.2.4. Lung Cancer

Lung cancer remains the top cause of cancer-related fatalities in both men and women worldwide [160]. BBR is a class of GPCR consisting of the neuromedin B receptor (NMBR), the gastrin-releasing peptide receptor (GRPR), and the orphan bombesin-receptor subtype-3 (BRS-3). These receptors are frequently overexpressed in various cancers, including non-small cell lung cancer (NSCLC) [161]. Research investigations showed that VIP receptors (VPAC1/2) are overexpressed in various cancers (e.g., breast, prostate, and neuroblastoma cancers), gaining attention as targets for potential therapy. Moreover, VPAC1 receptors were found in high amounts in 58% of biopsy samples from patients with lung cancer, indicating their high pathogenicity in vitro [162,163]. VPAC1/2 are GPCR receptors on which VIP and PACAP-27 bind with high affinity, increasing the activity of adenylyl cyclase and cAMP in small cell lung cancer (SCLC) cells through stimulatory (Gs) subunits, subsequently increasing the secretion rate of BB-like peptides. In numerous cases, VPAC1 antagonists, in

combination with chemotherapeutic drugs, inhibited lung cancer growth in many SCLC and NSCLC cells, representing a promising antitumor approach. BB-like peptides have been observed in the dense core neurosecretory vesicles of SCLC cells. With the addition of VIP, the secretion of BB-like peptides from SCLC cells increases, which then bind to the BB2 receptor [163–166]. Due to the overexpression of BB2 in tumors, various radiolabeled BB analogs have been developed to target tumors with cytotoxic drugs for therapy [121]. NTS is highly expressed in SCLC cells [166]. NTS increases cancer cell survival by activating the PI3K/Akt/mTOR pathway [167]. NTS also induces overexpression of the EGFR, HER2, and HER3 genes in lung cancers [168]. However, addition of 2-([1-{7-chloro-4-quinolinyl}-5-{2,6-dimethoxyphenyl}pyrazole-3-yl]carboxylamino)tricyclo(3.3.1.1.[3.7]) decan-2-carboxylic acid (SR48692) reversed the signal transduction driven by NTS and reduced clonal growth and xenograft proliferation in SCLC cells [163]. In this context, inhibitors targeting various neuropeptides in different cancer types, especially CRC, have been discussed below and are summarized in Table 3.

Table 3. List of neuropeptides, corresponding receptors, and relative drugs/antagonists useful for preventing cancer progression.

Neuropeptide	Cancer	Drugs/Antagonists	Targeted Receptors	Refs.
Bombesin (neuromedin B/gastrin-releasing peptide)	Small cell lung carcinoma	PD176252, PD168368	Gastrin-releasing peptide receptors-GRPR, neuromedin B receptor-NMBR	[169,170]
		Bantag-1	Bombesin-receptor subtype-3	
	Breast	RC-3095, RC-3940-II	Gastrin-releasing peptide receptors-GRPR	[92,171,172]
	CRC	RC-3095, AN-215	Gastrin-releasing peptide receptors-GRPR	[121,154]
	Prostate	BAY 86-7548, 64Cu-CB-TE2A-AR-06, RC-3095	Gastrin-releasing peptide receptors-GRPR	[149,173]
	Ovary	PD176252	Gastrin-releasing peptide receptors-GRPR, neuromedin B receptor-NMBR	[174]
	Glioma	PD176252, PD168368	Neuromedin B receptor-NMBR	[175]
	Pancreatic	RC-3095, RC-3925-II, RC-3940-II and RC-3950-II	Gastrin-releasing peptide receptors-GRPR	[173,176]
Neurotensin	Breast	^{99m}Tc-NT-XIX, ^{188}Re-NT-XIX, ^{18}F-DEG-VS-NT	Neurotensin receptor-NTSR	[145,146]
	Pancreatic adenocarcinoma	177 Lu-3BP-227	Neurotensin receptor-1 NTSR-1	[177]
	CRC	Sodium butyrate, SR48692, Curcumin, Cyanidin, SR 48692, 177 Lu-3BP-227	Neurotensin receptor-NTSR	[109,124]
	Small cell lung carcinoma	SR48692	Neurotensin receptor-1 NTSR-1	[178]
Vasoactive intestinal peptide-VIP	CRC	$NTS_{6-11}VIP_{7-28}$	Vasoactive intestinal peptide receptor-VPAC1/2	[128]
	Breast	VIP hybrid	Vasoactive intestinal peptide receptor VIP receptor	[179]
Substance P	Breast	Aprepitant, L-732,138, L-733,060, CP-96345, C-9994, MEN 11467, SR14033, Spantide III	Neurokinin 1 receptor-NK1R	[91,142–144]
	CRC	Spantide 1, Aprepitant, Fosaprepitant, GR 159897	Neurokinin 1 receptor-NK1R	[90,129,130]
Neuropeptide Y	Breast	BIBP3226 BIIE0246 L-152,804	Y1R Y2R Y5R	[131]
	Colon adenocarcinoma	-	Y2R	[132]
	Prostate	BIBP32226	Y1R	[150]
Orexin	Gastrointestinal tumors and CRC	NSC-87877, PD169316	Orexin receptor -OX1R	[136,137]

5. Conclusions and Future Perspectives

Neurotransmitters, including NPs, often exhibit modified expression in several cancers. However, the utility of NPs as therapeutics in cancer treatment remains largely unclear. As knowledge of the nervous system and its implication in tumor development is constantly evolving, the involvement of neuropeptides in the onset and progression of cancer has also undergone significant advances. In the last few decades, NPs have therefore provided new opportunities to examine, identify, and characterize their potential therapeutic exploitation for the diagnosis and treatment of cancer. It is interesting to note that agonists and antagonists of different types of neurotransmitters and NPs have become increasingly

available as drugs. For example, serotonin, dopamine, ACh and their receptors, GABA and β-AR antagonists, and dopamine and its agonists have been exploited for diagnostic purposes and as potential drug candidates. Finally, NPs and their receptors regulate several biological processes of the tumor microenvironment; therefore, they may represent a new targetable approach for cancer therapy.

Based on the knowledge gained from cited studies, the potential of various neuropeptides and their receptor as novel therapeutic targets for cancer treatment has been demonstrated in several cancers, including colorectal, breast, prostate, glioblastoma, and lung cancer. Nevertheless, despite the promising results reported in the literature, it becomes difficult to determine efficient and specific inhibitors that target neuropeptides due to limited resources, limited efficacy, and a lack of complete understanding of the functional role of various neuropeptides in cancer development and progression. In order to significantly increase the efficacy of various anticancer therapeutic drugs and reduce their side effects in humans, a combined drug therapy system, e.g., including a selective drug delivery approach along with the application of modified neuropeptides, could potentially serve as a promising therapeutic approach for cancer treatment [180,181]. For better clinical application of specific neuropeptide inhibitors, it has become important to determine at which cancer stage the respective neuropeptide receptors respond well. Given these findings and the challenging perspective, it becomes important to address such limitations, and perhaps more advanced research on neuropeptides would help in the better clinical management of cancers, including CRC.

As a result of recent advances in this area, the situation may soon change. Further improvements in the area of cancer research are expected to provide an enhanced understanding of drug selectivity and efficacy for better cancer management.

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Abbreviations

Ach, Acetylcholine; BB, Bombesin; β-AR, β-Adrenergic receptors; COX-2, Cyclooxygenase-2; CRC, Colorectal cancer; CGRP, calcitonin gene-related peptide; GABA, Gamma-aminobutyric acid; GPCR, G-Protein Coupled Receptor; GRP, Gastrin-releasing peptide; GI, Gastrointestinal; IGF-1, HTR2B, Hydroxytryptamine receptor 2B; Insulin-like growth factor-1; IP3, Inositol trisphosphate; KLF4, Krüppel-like factor 4; MAPK, Mitogen-activated protein kinase; NSCLC, Non-small cell lung cancer; NMB, Neuromedin-B; NPs, Neuropeptides; NPY, Neuropeptide Y; NTS, Neurotensin; NF-κB, Nuclear factor of kappa-light-chain-enhancer of activated B-cells; NaBT, Sodium butyrate; NK1R, Neurokinin 1 Receptor; NGS, Next-generation sequencing; PACAP, Pituitary adenylate cyclase-activating polypeptide; PKA, Protein kinase A; PIP2, Phosphatidylinositol-4,5-bisphosphate; PGE2, Prostaglandin E2; SCC, Squamous cell lung carcinomas; SLURP-1, Secreted Ly-6/uPAR-related protein 1; SP, substance P; TPH1, Tryptophan hydroxylase 1; TMZ, Trimetazidine; VPAC, Vasoactive intestinal peptide receptor; VIP, Vasoactive intestinal peptide; VEGF, Vascular-Endothelial Growth

Factor; WHO, World Health Organization.

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