Pharmacological Reports 69 (2017) 438–447

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Neuromedin: An insight into its types, receptors and therapeutic opportunities

Saumitra Gajjar, Bhoomika M. Patel*

Institute of Pharmacy, Nirma University, Ahmedabad, India

ARTICLE INFO

Article history:
Received 9 August 2016
Received in revised form 26 December 2016
Accepted 18 January 2017
Available online 22 January 2017

Keywords:
Neuromedin
Neuromedin receptors
Cancer
Pain

ABSTRACT

Neuropeptides are small protein used by neurons in signal communications. Neuromedin U was the first neuropeptide discovered from the porcine spinal and showed its potent constricting activities on uterus hence was entitled with neuromedin U. Following neuromedin U another of its isoform was discovered neuromedin S which was observed in suprachiasmatic nucleus hence was entitled neuromedin S. Neuromedin K and neuromedin L are of kanassin class which belong to tachykinin family. Bombesin family consists of neuromedin B and neuromedin C. All these different neuromedins have various physiological roles like constrictive effects on the smooth muscles, control of blood pressure, pain sensations, hunger, bone metastasis and release and regulation of hormones. Over the years various newer physiological roles have been observed thus opening ways for various novel therapeutic treatments. This review aims to provide an overview of important different types of neuromedin, their receptors, signal transduction mechanism and implications for various diseases.

Contents

Abbreviations: ACTH, Adrenocorticotrophic hormone; CRH, Corticotrophin releasing hormone; FSH, Follicle stimulating hormone; GIT, Gastrointestinal tract; GPCRs, G-Protein Coupled Receptors; GRP, Gastrin releasing peptide; LH, Luteinizing hormone; NMB, Neuromedin B; NMC, Neuromedin C; NMK, Neuromedin K; NML, Neuromedin L; NMS, Neuromedin S; NMU, Neuromedin U; NMULIR, NMU like immunoreactivity; PVN, Paraventricular nucleus; RIA, Radioimmunoassay; RT-PCR, Reverse Transcriptase-Polymer Chain Reaction; SCN, Suprachiasmatic nucleus; TRH, Thyroid releasing hormone.

* Corresponding author.
E-mail addresses: drbhoomikampatel@gmail.com, bgoyal@rediffmail.com (B.M. Patel).

http://dx.doi.org/10.1016/j.pharep.2017.01.009
1734-1140/

Introduction

Neuropeptides are small protein related structures (peptides) which are used by the neurons to communicate with each other. Neuropeptides present in the brain influence the brain in many aspects by neuronal signaling thus implicating themselves in various physiological processes. A search of novel neuropeptides has been a newer interest for researchers or scientists in this decade. Although many neuropeptides have been isolated with defined functions, a powerful method of isolating novel neuropeptides took place in the early nineties [1]. Human genomic sequence study shows that there are hundreds of G protein coupled receptors present and matter of fact is that yet their ligands are yet to be discovered [2]. The unidentified GPCRs have same alikeness with the known GPCRs ligands which has opened the ways for the discovery of newer neuropeptide agents. The biggest advantage of human genomic sequencing is that it helps in identifying neuropeptides with its related receptors, leading to the development of novel neuropeptides over a large scale in this decade. Ten newer neuropeptides have been discovered being endogenous ligands for orphan GPCRs [3] "Neuromedin" one such novel discovery.

Neuromedin peptides are basically divided into 4 classes (1) Bombesin comprising of Neuromedin B and Neuromedin C, (2) Kanassin comprises of Neuromedin K and Neuromedin L, (3) Neurotensin comprises of Neuromedin N, (4) Neuromedin U and Neuromedin S. Isolation of the first neuromedin took place in the 1980s from porcine spinal cord which had large amount of vasoconstrictor properties which was Neuromedin U [4–9] the first neuropeptide of all, later on its different isoforms were discovered. Neuromedin U was found in brain and periphery and has many physiological aspects which include constrictive effects on the smooth muscles, control of blood pressure, pain sensations, hunger, bone metastasis and release and regulation of hormones [10–17]. This review aims to provide an overview of important different types of Neuromedin, their receptors, signal transduction mechanism and implications for various diseases.

Types of neuromedins, structure, location, receptors, signal transduction

A brief overview of Neuromedin U, Neuromedin B and Neuromedin S has been summarized in Table 1.

Neuromedin U

Neuromedin U a novel neuropeptide having various physiological roles is obtained from the spinal cord of the porcine species which had the ability to cause potent constriction of skeletal smooth muscle. It was first administered in the uterus and caused potent vasoconstriction hence was entitled with Neuromedin U. Being synthesized in vasculature of endothelial cells on being released operates in paracrine fashion. NMU is a highly conserved neuropeptide. Purification of NMU led to the discovery of two of its isoforms having same biological activity. This consisted of NMU-25 (icosapentapeptide) other one NMU-8 (octapeptide). The rodents which include rat consist of NMU-23. In recent times many newer types such as NMU-17 is isolated of Chinese red belly toad, *Bombina maxima* from their skin secretions [18], different variants NMU-21, NMU-38 have been isolated from goldfish brain. One of the peptides produced by *Drosophila hugin* gene pyrokinin-2 possessing myostimulatory activity resembles mammalian NMU-8 [19]. The human NMU-25 is icosapentapeptide having 174 amino acid precursors which contain NMU peptide inside C-terminus (carboxy terminus) which is split into 25 amino acids. NMU is obtained from various species having different amino acid homology. The SAR has been preserved against evolutionary pressures.

The amino acid sequence of human which is contained in the C-terminus NMU-25-Phe-Arg-Val-Asp-Glu-Glu-Phe-Gln-Ser-Pro-Phe-Ala-Ser-Gln-Ser-Arg-Gly-Tyr-Phe-Leu-Phe-Arg-Pro-Arg-Asn-NH_2.

Immunocytochemistry or Radioimmunoassay (RIA) studies show that neuromedin receptors are widely distributed in the regions of the brain and also the gastrointestinal tract (GIT). Radioligand studies did not detect any circulating NMU-like

Table 1
Comparisons of different types of Neuromedin.

	Neuromedin U	Neuromedin B	Neuromedin S
Structure	Octapeptide/Icosapentapeptide	Decapeptide	Hexatricontapeptide
Location	Pituitary and GIT	Pituitary and GIT	Suprachiasmatic nucleus of Brain
Receptors	NMU receptors	BB receptors	NMU receptors
Subtypes	NMU-1 and NMU-2	BB-1 and BB-2	NMU-2
Type	G-protein coupled receptors	G protein coupled receptors	G protein coupled receptors
Signalling	Phosphoionositol pathway/MAP-ERK pathway	Phosphoionositol pathway/ Adenyl cyclase pathway	Phosphoionositol pathway
Molecular Formula	$C_{141}H_{203}N_{41}O_{38}$	$C_{52}H_{73}N_{15}O_{12}S_1$	$C_{173}H_{265}N_{53}O_{44}$
Molecular Weight	3080.37	1132.300	3791.33
Agonist	Nonselective-NMU Selective-NMS for NMU-2 receptor, Hexapeptide analogues, icariin, EUK2010	NMB, Bradykinin, Leptin	NMU, NMS, Leptin a-melanocyte stimulating hormone, corticotrophin releasing hormone
Antagonist	R-PSOP, [D-Pro^6]-HMU-8, [D-Leu^3, D-Pro^6]-MNU-8,Astressin	Somatostatin analogues (SS-14. SS-28), PD 168368, BIM-23127	R-PSOP, SHU9119 (antagonist for α-MSH), α-helical corticotropin-releasing factor-(9–41) (antagonist for CRH)

immunoreactivity (NMULIR) defining neuromodulatory roles of NMU [20]. The brain and the spine regions showed high levels of NMULIR. In the spinal cord, the dorsal horn was found to be rich in NMU which suggested its role in pain pathways. In the brain, NMULIR was detected in the anterior pituitary, hypothalamic regions, septum, amygdala, nucleus accumbens and the globus pallidus regions [21–23]. Very high levels of NMULIR by Northern Blot analysis technique [24] was detected in the GIT along with neurons of calcitonin gene related peptides, substance P, vasoactive intestinal peptide and neuropeptides Y in the regions which includes duodenum, jejunum, caecum, colon and the rectum part concluding its role in the GIT. NMULIR was also found in the genital system which included ureter, vas deference, prostate, fallopian tubules, urethra, testis and the ovaries. NMULIR was observed in the stomach in the nerve cells of the submucosal, mucosal and myenteric plexus region [25–28], spleen, lymphocytes, bone marrow, and the adrenal medulla [29].

NMU consists of G protein coupled receptors which include NMU receptor-1 and NMU receptor-2 which resemble seven transmembrane helix structures. NMU-receptor-1 is highly present in the peripheral regions including the gastrointestinal tract. They are especially expressed in the goblet cells. NMU-receptor-2 is highly expressed in CNS specific in regions which include the thalamic regions, the spine, medulla oblongata, and the reticular system present in the pontine regions.

NMU-R1 and NMU-R2 cause activation of Gaq/11 and Gas, resulting into increase permeability of intracellular Ca^{2+} and inhibition of forskolin stimulated cAMP generation. NMU receptors cause activation and release of arachidonic acid, which is calcium dependent as a result of activation of phospholipase A2. NMU also is responsible for activation of protein kinase ERK1 and ERK2 pathway.

Neuromedin S

Neuromedin S is an isoform of NMU was originally isolated from the rat brain from suprachiasmatic nucleus (SCN) as a result of this was entitled Neuromedin S or NMS. It is considered as an additional endogenous ligand for NMU receptors. Two isoforms NMS-17, NMS-33 are discovered and isolated of the bombina frogs *Bombina Maxima* from the venoms present in their organ [30]. The rat NMS peptide inside C-terminus (carboxyl terminus) is amidated into 36 amino acids. The structures of NMS and NMU have very close structure resemblance. The 7 terminus C-terminal amidated sequencing of NMU closely relates the structure with NMU, which plays an important role for agonists of NMU to bind. The N terminal part of NMS is having totally unique sequencing which is not related to peptide and not by any chance variant of NMU, as in Homo sapiens NMU along with NMS genes are situated on altogether a different chromosome 2q11.2 and 4q12. It has been observed that pro-proteins and genes reside same structure with that of NMU [31]. NMU and NMS by proteolytic processing are produced from the precursor protein factors. This process takes place at the third and fourth site. Their exhibits a homology between 1st and 2nd sites of their amino acid sequences. NMS gene composition consists of ten exons, there is a high amount of conservation between exon and intron boundaries in NMU and NMS precursor proteins.

Reverse transcriptase-polymerase chain reaction was carried out and NMS mRNA was highly found in the hypothalamus of the CNS. In the brain of the rodents NMS is predominantly detected in the SCN of the hypothalamus, very small amount of NMS is expressed in the other regions of the brain. SCN containing NMS is located on the side of the third ventricle just above the optic chiasma [32]. The SCN present consists of two regions first being the ventrolateral part and other being the dorsomedial part in which vasoactive intestinal peptide and other being arginine vasopressin are present. NMS which is highly found in ventrolateral SCN is in a similar matter to VIP mRNA. NMS is detected in left ventricle together with NMU1 Receptors in both vascular endothelial and smooth myocytes of intramyocardial vessels. It is also detected in spleen and testis.

NMS binds to NMU receptors. NMU-1 is present in the periphery while NMU-2 receptor is present in the brain thus NMS has more selectivity for NMU-2 receptors. NMU and NMS consist of similar structural resemblance which plays important role in binding with their related receptors. NMS has specificity for NMU-2 receptor that is FM-4/TGR1. It is a G-protein coupled receptor. In late 1990s FM-3/GPR66 developed as an orphan GPCR resembled similarity with the neurotensin along with growth hormone secretagogue receptors [33] which are highly present in the peripheral region [34]. The second receptor FM-4/TGR1 was discovered [35] which is largely present in CNS. In rodent brain, FM-4/TGR1 is detected in the paraventricular nucleus (PVN) located within the third ventricle of the hypothalamic region, CAI regions which are present in the hippocampus. NMS is present in SCN which has high extent of specificity for FM-4/TGR1.

NMS consisting of GPCR protein receptor induces an increase in intracellular Ca^{2+} influx and cause an increase in calcium levels especially on CHO cells which express FM-3/GPR66 and FM-4/TGR1 receptors.

Neuromedin B

Neuromedin B is obtained from the skin portions of European toad species *Bombina bombina* [36] which plays various physiological roles in the mammalian CNS [37,38]. It has a structure resembling to that of bombesin hence was entitled the name neuromedin B or NMB. It was originally isolated from porcine gastric tissue and the spinal cord [39]. There are two types of bombesin like peptides. The first being the mammalian forms of bombesin the other being amphibian forms of bombesin [40]. The mammalian form of bombesin consists of BN like peptides (1) Gastrin releasing peptide (GRP), (2) Neuromedin B. The amphibian form of bombesin has various bombesin like peptides such as bombesin, alytesin, ranatensin, litorin, and phyllolitorin. Gastrin releasing peptide (GRP) has a leucine residue whereas second being NMB like ranatensin and litorin consists of phenylalanine residue. NMB has a C-terminal amidated sequence which is highly conserved across mammalian species, Gly-Asn-Leu-Trp-Ala-Thr-Gly-His-Phe-Met-NH_2 [41,42].

As mammals, BN like peptides are of two types the first being Gastrin releasing peptide (GRP) and other being neuromedin B (NMB). NMB is largely present in the pituitary gland, pancreas, and adrenal medulla and of GIT. NMB are found in both CNS as well as periphery [43]. NMB receptors are known as BB1 receptors which G-protein coupled receptors which consist of the endogenous ligand as NMB. The NMB receptors are subdivided into 4 subtypes. Mammalians consists of two family classes first Gastrin releasing peptide the other being neuromedin B (NMB) are specific for BB_1 and BB_2 receptors. Bombesin receptors subtype 3 and 4 (BRS-3) and (BRS-4) have been discovered in amphibian tissues.

NMB binds to GPCR. The process starts with the exchange of GTP for GDP with Ga subunit. The free Ga activates adenyl cyclase which converts ATP to cAMP resulting into activation of protein kinase A. Protein kinase A as a result enters the nucleus and activates cAMP response binding protein which in turn activates the CRE region of DNA of the nucleus which leads to activation of various cascades. NMB also activate Protein kinase C and increase the intracellular influx.

In mammals, BN like peptides Gastrin releasing peptide and neuromedin B has a significant relation with respect to their various physiological functions. GRP has shown to reduce food intake. It is considered more potent in the reduction of food intake

than NMB [44]. GRP causes an increase in plasma gastrin and gastric acid secretion which has been observed in humans, dog and pigs whereas NMB causes a decrease in gastric motility [45–47]. GRP causes secretion of various peptides pancreatic polypeptide, enteroglucan, pancreatic glucagon, motilin, vasoactive intestinal peptide and insulin and thus plays an important role in glucose homeostasis NMB on the other hand only causes hyperglycemia [48–50]. GRP has played an important role in circadian rhythm through the suprachiasmatic nucleus [51]. NMB on the other hand as pruritogenic properties NMB is also responsible for local flare and wheal [52]. GRP also regulates stress by controlling anxiety and fear responses whereas NMB is a thyroid stimulating hormone inhibitor [53,54]. GRP causes smooth muscle contraction in rats and humans and causes stimulation of myenteric and submucosal neurons [55–59]. Gastrin releasing peptide (GRP) and NMB play a very important role on immune cells such as lymphocytes, leukocytes [60–64] and they promote growth and proliferation in various colon cancer [64], small cell lung carcinoma [65] and prostate cancer [66]. Thus the roles of NMB and GRP do differ partially.

A brief overview of Neuromedin C, Neuromedin N, Neuromedin K and Neuromedin L has been summarized in Table 2.

Neuromedin C

Neuromedin C is a tetradecapeptide which was first isolated from the skin of amphibian species and then from the porcine spinal cord. It is of Bombesin class of family. It has a structural resemblance to that of neuromedin B but with slight difference in structure hence was entitled with next letter to that of B that is Neuromedin C. In mammals BN like peptides are of two types the first being Gastrin releasing peptide (GRP) and other being Neuromedin B (NMB). Neuromedin C comes under Gastrin releasing peptide group, is known as GRP^{-} [18–27] as well as GRP 10.

Neuromedin C is widely distributed in the CNS region and the gastrointestinal tissues. NMC was observed in the brain regions such as the hippocampus, olfactory bulbs, thalamus, and spinal cord and in the adrenal gland. In the gastrointestinal tract, it is highly observed in the stomach and the duodenum parts.

Neuromedin C receptors are the Bombesin receptors. They are present in the CNS and the GI regions. They are G protein coupled receptors. NMC acts on bombesin receptors BB_1 as well as BB_2. They work through the inositol pathway.

Neuromedin C is identical with C-terminal of GRP, homologous to bombesin. NMC is conserved in the C-terminal decapeptide of bombesin. Amino acid sequence of NMC is Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-NH2 [67–69].

Neuromedin N

Neuromedin N is a type of neurotensin like tridecapeptide which was isolated from the bovine hypothalamus as well as a porcine spinal cord. It has similar properties that of neurotensin peptide hence was entitled with Neuromedin N. Neuromedin N is widely distributed in the CNS regions and gastrointestinal tract of mammals. Neuromedin N and neurotensin are products of the same precursor are present in the hippocampus, forebrain and midbrain of the rat [70,71]. Neuromedin N has a high affinity for the neurotensin receptors which are widely distributed in the brain regions. Neuromedin N acts as agonists on these receptors. They are G protein coupled receptors following the calcium signaling pathway [72].

Neuromedin N consists of COOH terminal region, with four amino acids being shared similar as that of neurotensin. Neurotensin and neuromedin N are separated by a Lys-Arg sequence. Lys-Arg are connected to N-terminus of the neuromedin N. The amino acid sequence of neuromedin N is Lys-lle-Pro-Tyr-IIe-Leu [73].

Neuromedin K

Neuromedin K is a type of neuropeptide of the neuromedin family is of kanassin class. It was found in the spinal cord of the vertebrates. Tachykinin family consists of substance P, which was believed to be the only tachykinin present in the mammalian until the development of Neuromedin K which is also known as Neurokinin b and Neuromedin L which is also known as Neurokinin a [74]. It is a type of kanassin class hence was entitled with Neuromedin K.

Neuromedin K is widely distributed in CNS regions. In the CNS it is observed in the olfactory lobes, hypothalamus, and hippocampus. It is also present in the dorsal half of the spinal cord. Neuromedin K acts through tachykinin receptor known as NK_3 receptors. The receptors are widely present in the brain regions of the mammalians. They are G protein coupled receptors. Neuromedin K has a similar homology with respect to amphibian kanassin. Neuromedin K is a decapeptide with the amino acid sequence Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH2 [75].

Neuromedin L

Neuromedin L is a type of neuropeptide of the neuromedin family is of kanassin class. It was found in the spinal cord of the vertebrates. It was isolated along with its second isoformic form Neuromedin K. Neuromedin L is also known as neurokinin a. It is of kanassin class and differs slightly with neuromedin K as a result of which was entitled the letter next to K that is neuromedin L. Neuromedin L is widely distributed in CNS regions and various parts of the periphery. In the CNS the highest concentrations were

Table 2
Details of other Neuromedins.

	Neuromedin K	Neuromedin C	Neuromedin L	Neuromedin N
Structure	Undecapeptide	Decapeptide	Undecapeptide	Hexapeptide
Type of Receptor	G protein coupled receptors (GPCRs)	G protein coupled receptors (GPCRs)	G protein coupled receptors (GPCRs)	G protein coupled receptors (GPCRs)
Receptors	Tachykinin receptor 3 closely associated to neurokinin B	Bombesin like and closely associated to gastrin releasing peptide	Tachykinin receptor 1, closely associated to neurokinin A	Neurotensin Receptors specific to NTS1 very closely related to Neurotensin
Pathway	Calcium signalling pathway, Neuroactive ligand-receptor interaction	Phosphoionositol pathway/ Adenyl cyclase pathway	Calcium signalling pathway	Calcium signalling pathway
Physiological Functions and Pathological Significance	Aging, Constrictive action on smooth muscles, Heart rate	Gastrin and Somatostatin release, increase in blood pressure	Contraction of smooth muscles	Hypotension in rats, contraction of ileum of guinea pig
Under Research	It is observed to be associated with cholinergic system	Indirect association with cancer growth	Related to Substance P and consisting of similar properties	It is observed to have modulatory effect on dopamine D2 receptors

found in the hypothalamus, thalamus, medulla, pons and the hippocampus regions and somewhat in the cerebral cortex. It is also present in the dorsal half region of the spinal cord.

Neuromedin L acts as an agonist on SP-E type receptors. The receptors are widely present in the brain regions. They are G protein coupled receptors following the calcium signaling pathways. Neuromedin L is conserved in the C terminal decapeptide of Kanassin, except three amino acid residues in the N-terminal half differ. Amino acid sequence of neuromedin L is His-Lys-Thr-Asp-Ser- Phe-Val-Gly-Leu-Met-NH2 [76]. An overview of locations of different Neuromedins has been summarized in Table 3.

Pharmacological actions

A brief overview of pharmacological actions and its therapeutic implications of neuromedin and its isoforms have been summarized in Table 4.

Smooth muscle contraction

NMU and NMS are potent vasoconstrictors. NMU causes concentration dependent contraction of rat circular smooth muscles from the fundus region, it neither involves cholinergic transmission and also not nervous stimulation [77]. It was also discovered that NMU causes contraction of longitudinal muscles of the ileum and urinary bladder which has got a high amount of resistance to atropine as well as tetrodotoxin [78], it has a direct constrictor action on human ascending colon [79]. NMU exhibits both *in vivo* and *in vitro* properties which result in contraction of ileum, colon, stomach and bladder of canine. NMU possesses positive prokinetic properties on mouse colon as it causes mark reduction between two successive peristaltic waves [80]. NMS causes potent vasoconstriction of smooth muscles. NMS acting as a partial agonist caused contraction of the isolated saphenous vein. NMK is found to have a contractile function on the smooth muscles. It produced contraction on the guinea pig ileum, in the rat duodenum and urinary bladder of the hamster [81]. NML is found to have a contractile function on the guinea pig ileum. NMC produces a contractile effect on the uterus of guinea pig [82].

NMU-8 causes an increased level of electrogenic ion transport mechanism, by exhibiting a positive mechanism by causing contractions of longitudinal muscles in the porcine jejunal mucosa. Electrogenic ions consist of Ca^{2+}, Na^{2+}, K^{+} for this electrogenic pumps play a very important role. The whole process is mediated by external Cl^{-} and is controlled by noncholinergic enteric neurons [83].

Immunomodulation

NMU-R1 receptors are present in immune cells which suggest of NMU playing an important role in immunomodulation. NMU is present in the dendrite cells; monocyte B-cells, In the T cells and the natural killer cells, presence of NMU-R1 receptors indicate an interaction between effector population and helper antigen-presenting cells. NMU stimulates Gaq/11 signaling cascade which significantly causes an increase in production of cytokine which includes interleukin [4–6,10,13]. NMU-R1 receptors are expressed in mast cells through which degranulatory process are induced in inflammatory mediators. NMU plays an important role in allergy induced anti-inflammatory conditions like asthma the mechanism being considered is eosinophilic infiltration into inflammatory sites. NMU has a protective role in lipopolysaccharide which causes inflammation which results into neuronal cell death in mice. Agents which target NMU-Receptors can prove effective results.NMB are proposed to have pruritogenic properties which lead to intense scratching behavior in rodents when administered centrally [84,85].

NMC plays a major role in the immune system by acting as a chemo attractant, by stimulating phagocytic function in phagocytic cells, and potentiating the effect of lipopolysaccharide in alveolar macrophages [86].

Hormonal regulation

When NMU is administered intravenously there occurs an increase in levels of oxytocin and vasopressin mechanism believed to be its effects *via* FOS like immunoreactivity which occurs in supraoptic nuclei and para ventricular nucleus, it was observed that in the anterior pituitary their occurred large amount of decrease in the release levels of FSH and LH. It was observed that the rodents which were deficient of NMU caused an early vaginal opening [87,88].

NMS causes oxytocin release [89]. NMS plays a vital role in the female gonadotropic axis. It was observed that NMS levels in female adults fluctuate throughout estrous phase which a high amount of expression was seen during the proestrus phase. When NMS is administered i.c.v. this caused an increase in levels of LH in the estrus phase whereas only slight LH secretion is seen in diestrus phase.

Table 3
Locations of Neuromedin and its isoforms present in various tissues.

Neuromedins	Central Nervous System	Gastrointestinal Tract	Reproductive System	Other
NMU	anterior pituitary, hypothalamic regions, septum, amygdale, nucleus accumbens, globus pallidus, dorsal horn	duodenum, jejunum, caecum, colon, rectum part, submucosal, mucosal and myeteric plexus region of stomach	ureter, vas deference, prostate, fallopian tubules, urethra, testis, ovaries	spleen, lymphocytes, bone marrow, and the adrenal medulla
NMS	suprachiasmatic of the hypothalamus, third ventricle above the optic chiasma	–	testis	spleen
NMB	Present	Present		pituitary gland, pancreas, adrenal medulla
NMC	hippocampus, olfactory bulbs, thalamus, spinal cord	stomach, duodenum parts	–	–
NMN	hippocampus, forebrain, midbrain	Present	–	–
NMK	the olfactory lobes, hypothalamus, hippocampus, dorsal half	–	–	–
NML	hypothalamus, thalamus, medulla, pons, hippocampus, cerebral cortex, dorsal half	–	–	–

Table 4
Pharmacological Actions and Therapeutic implications of Neuromedin.

Neuromedin	Physiological Roles	Therapeutic Potentials
NMU/NMS/NMC/ NML/ NMK	Constrictive effect on smooth muscles	Inhibitory actions can applied for various smooth muscle disorders like overactive bladder syndrome. (Antagonist)
NMU/NMB/NMC	Immune Regulation (Releasing of cytokines)	Allergic inflammatory Diseases like Asthma and Rheumatoid Arthritis (Agonists)
NMU/NMS/NMN	Hormone Release (1. Release of Corticotrophin Hormone) (2. Suppression of LH/FSH play roles in puberty onsets) (3. Decrease in release of Insulin)	1. Decrease in Stress (Antagonist) 2. Used in Females with delayed puberty (Agonist) 3. Hypoglycaemia (Antagonist)
NMU/NMS	Circadian Rhythm	Agonists can be used in Jet Lag
NMU/NMB/NMS	Appetite and Feeding (Decrease in Food intake)	Agonists can be used as Anti-obesity agent Anorexic Agent
NMU/NMB/NMN	Pain (Excites the Nociceptive Pain)	Agonists can be used in Neuropathic Pain
NMU/NMS/ NMN/NMK/ NML	Cardiovascular And Regional Blood Flow (Increase in blood pressure and heart pumping)	Agonists can be used in Hypertension and controlling the blood flow rate in particular region.
NMU	Alleviation of tumour growth	Agonist in Oral Cancers Lung Cancer Breast Cancer Pancreatic Ductal Carcinoma
NMU	Decrease in Bone mass	Osteoporosis (Antagonist)
NMS	Antidiuretic	Agonists can be used in Diabetes Insipidus

In rat pancreatic islets there was detection of NMU-R1 receptors. NMU causes a decrease in insulin release in isolated pancreatic islets which is totally dose dependent [90]. Further evaluation is still needed to be established. NMB causes hyperglycemia [91,92]. NMN also is found to play an important role in hormone secretion [93].

Circadian regulation

NMU through the receptors present in hypothalamic suprachiasmatic nucleus (SCN) mediates an important role in circadian rhythm. The gene of NMU closely resembles that of the biological clock. On *iv* injection, NMU activates expressions of Fos proteins present in SCN and results into phase dependent circadian locomotor activity like rhythm [94]. Thus NMU receptors can be targeted and novel drugs could be discovered to help in conditions of jetlag.

NMS in SCN regulates the circadian cycle in a paracrine or autocrine fashion proving its potential in circadian rhythm. A one day circadian cycle is generated through an auto regulatory transcription or translation feedback way which is constituted of families consisting of clock genes. The circadian cycle is controlled by environmental conditions such as environmental temperatures and other being photic and nonphotic signals.

Stress and behavioral response

Receptors of NMU which are present in hypothalamic PVN is chiefly responsible for the release of corticotrophin releasing hormone. The release of CRH takes places due to stimulus in the form of stress which in turn helps in the release of ACTH in the anterior pituitary, ACTH, as a result causes stimulation of cortisol and thus PVN is an important connection which is known as hypothalamo-pituitary adrenal axis. Subcutaneous injection of NMU in rats resulted into ACTH level increase in plasma blood concentration, corticosterone and glucocorticoids [95]. NMU is also responsible for stress type behavior [96].

NMB is a thyroid stimulating hormone release inhibiting peptide. TRH causes NMB to reduce in the pituitary region up to 45% on peripheral administration in rats [97]. There is occurrence of reduction in the Serum T3 levels of the NMB knockout mice suggesting it roles in pituitary thyroid regions [98].

GI functions

NMU results into a decrease of food intake thus inhibiting feeding behavior in rats on single *iv* administration. NMU causes decrease of food intake as well as body weight has been demonstrated [99–103]. Leptin is considered as a hunger hormone and plays very important role in feeding homeostasis, weight gain and the metabolism associated activities [104,105]. It has been observed that leptin have significant interactions with NMU receptors. There occurs a decrease in NMURNA in ob/ob strain of mice which are leptin deficient in the hypothalamic regions as well as decrease of NMURNA in ventromedial hypothalamic of rodents. Receptors of NMU are present in the arcuate nucleus in the hypothalamic region plays important role in food intake [106,107]. Thus NMU can consider as a target for novel therapies as anti-obesity and anorexic agents.

When NMU is administered *iv* in the PVN region it causes an increase in various physiological properties including the locomotion, thermal regulation, increase in the O2 consumption of the rodents. When NMU is administered intravenously it causes a reduction in the feeding homeostasis and increase the physical activity and thus resulting into increase energy loss. Gastric emptying is reduced by NMU. The gastric emptying property considered as a result of inhibition of food intake [108].

NMB receptors are detected in the visceral adipocyte cells through various studies [109] proving itself as an effective peptide in a gene related eating disorders [110]. NMB causes inhibition of food intake and thus resulting into a decrease in IL6 which is considered as important cytokine obesity associated inflammatory response [111,112]. NMB has proved to produce mitogenesis in adipocyte 3T3 cells which lead to decrease in obesity [113]. On injecting NMB produces a dose dependent hypothermia and an increase in metabolism in rats [114–118]. NMB have been found to play important role in gastric motility by decreasing motility [119], there occur gastric acid secretion [120] and causes secretion of a number of hormones in the stomach [121].

There occurs a decrease in 12-h food intake in dark period when NMS is administered *iv* the response obtained is total dose dependent. It was observed that the food intake due to various hormones such as ghrelin, neuropeptide Y, and agouti-related proteins was reduced when NMS was administered *icv*. It was observed that two anorexigenic neuropeptide agents

corticotrophin releasing hormone and a- melanocyte stimulating hormone are important for NMS to impart its action.

Pain

NMU with its receptors are expressed in lamina-1 and outer region of lamina-2 of the spinal cord which are essential in the regulation of nociceptive pathways. NMU-R2 receptors are highly expressed. When NMU was administered as intrathecally rodents produced a hyperalgesia like condition and typical behavioral responses like licking, biting of the lower body, continuous scratching due to the activation of nociceptive pathways. In rats NMU unregulated the flexor motor neuron activity due to slight touching or pinching whereas their also occurred an increase of miniature excitatory post-synaptic currents (mEPSCs) in substantia gelatinosa region and deeper regions of neurons. When mice were exposed to NMU intrathecally hyperalgesia like condition with morphine sensitive behavioral changes were obtained [122]. NMU did not cause any effect on miniature inhibitory post-synaptic currents which proved the fact that it is effective on pre-synaptic terminals of the afferent fibers and acts like an important autocrine/paracrine neuromodulator which cause an increase in excitatory post synaptic current (EPSC) in regions including substantia gelatinosa and its deeper neurons which resulted in hyperalgesia like condition. As future prospective, NMU has shown positive results in pain pathways and can be developed as a novel entity for neuropathic pain.

NMB are involved in nociceptive pain [123]. The observational studies have shown that on intravenous administration of NMB causes local heating, wheal and flare like responses due to stimulation of the nociceptive pathways present in the dorsal horn of the spinal cord, this condition is defined as neurogenic inflammation. NMN is found to play an important role in the analgesia and producing hypothermia [124,125].

Cardiovascular actions

Quantitative RT-PCR demonstrated upregulation of NMU-25 in the left ventricle of patients suffering from heart failure due to dilated cardiomyopathy or ischemic heart disease. NMU causes an increase in heart rate of rats [126] and localization of NMU-R1 receptors to intramyocardial vessels suggesting a potential role in hemodynamic control. Infact, NMU is also associated with cardiac remodeling [127].

Intravenous administration of NMU in rats caused very quick and very high amount of increase in the levels of blood pressure in the arteries. NMU increases the heart rate and also plasma concentration of norepinephrine is increased suggesting its role in the increase of sympathetic activity especially in the paraventricular nucleus (PVN) in the hypothalamic region. On *iv* administration of NMU causes an increase in blood pressure of arteries for a very small amount of time indicating a potential role in affecting cardiovascular system [128]. The hypotensive situation developed by NMU was also observed when it was administered in rats in the nucleus tractus solitarus region [129]. Thus NMU receptors can be considered as a new target for novel therapies for treating hypertension. It was observed that NMU affects the splanchnic circulation, in which at smaller doses there occurred a reduction in superior mesenteric blood flow which suggested vasoconstrictor effects. In anesthetized dogs when *iv* NMU was administered it caused a high amount of decrease in the blood flow of superior mesenteric artery and of the portal vein. Thus these observations suggesting that NMU plays an important role in the regulation of the blood flow of the intestines. NMS on *iv* administration caused an increase in the blood pressure of the rodents. NMK produces hypotensive state on its administration [130]. NML produces a hypotensive state in rabbit [131].

Cancer

The mammalian gene is localized on chromosome 4q12 and has shown to alleviate the transformation having a strong association with cancer [132]. In colony focus assays which used esophageal squamous cell carcinoma (ESCC) cell line, NMU inhibited showed potential role in tumour suppression by down regulation of genes highlighting its role in Oral cancer [133]. It was observed that exogenous NMU curbed the growth suppression of K562-dominant negative Myb protein (MERT) cells and was found to increase growth in primary acute myeloid leukemia cells. NMU is said to involve in HGF-c-MET paracrine loop which regulated the very important cell migration and has shown positive potential in the treatment of pancreatic ductal adenoma carcinoma. NMU has also shown therapeutic potentials for HER2 positive cancers.NMU plays an important role in the release of important cytokines which play important role in the growth, differentiation and stimulation of the T and B cells [134]. Thus NMU receptors can be developed as a target for novel therapeutics for treating cancer of various origins.

Miscellaneous

NMU-Receptor agonists were found to decrease the density of bone mass in mice. Recent cellular studies have revealed that NMU shows effects in CNS through leptin or via the sympathetic nervous system to regulate bone remodeling [135]. It was observed that NMU proliferate rodent cultured calvarial osteoblast cells. It is believed that NMU-R2 is involved in this [136]. NMS cause the increase of the plasma concentration of arginine and vasopressin and caused a decrease in nocturnal urine volume. NMU-R2 receptors are said to be involved. NMB causes compulsive grooming. NMU plays an important role in photoperiodism. NMN plays an important role in activation of dopamine receptors suggesting its role in the development of novel antipsychotic drugs for treating depression [137] (Fig. 1).

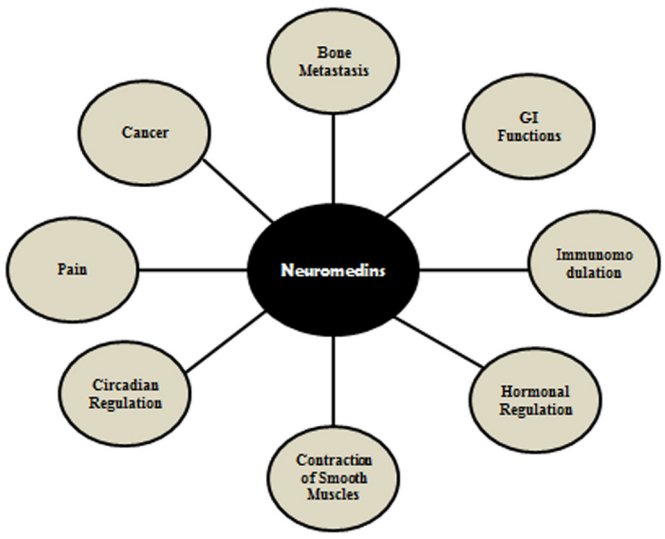

Fig. 1. Pharmacological Functions of Neuromedin.

Conclusion

Research has led to improved understanding of neuromedins in various diseases like cardiovascular diseases, gastrointestinal disorders, immune regulations, CNS disorders and cancer. On one side, advancements in technology have led to the better understanding of disease pathogenesis and on other side, research on such endogenous peptides lead to a good co-relation between the two. Moreover, with the specific receptors of neuromedins being identified, novel drugs can be designed targeting them. Although, currently very few drugs modulating the actions of neuromedin are under clinical trials, many drugs are being investigated at the pre-clinical level. This provides a hope that neuromedins may emerge out as a novel targets in future for severely deadly diseases including cancer.

Funding

None.

References

[1] Civelli O. Functional genomics: the search for novel neurotransmitters and neuropeptides. FEBS Lett 1998;430:55–8.
[2] Vassilatis DK, Hohmann JG, Zeng H, Li F, Ranchalis JE, Mortrud MT, et al. The G protein coupled receptor repertories of human and mouse. Proc Natl Acad Sci U S A 2003;100:4903–8.
[3] Civelli O, Saito Y, Wang Z, Nothacker HP, Reinscheid RK. Orphan GPCRS and their ligands. Pharmacol Ther 2006;110:522–5.
[4] Kangawa K, Minamino N, Fukuda A, Matsuo H. Neuromedin-K – a novel mammalian tachykinin identified in porcine spinal-cord. Biochem Biophys Res Commun 1983;114:533–40.
[5] Minamino N, Kangawa K, Fukuda A, Matsuo H. Neuromedin-L – a novel mammalian tachykinin identified in porcine spinal-cord. Neuropeptides 1984;4:157–66.
[6] Minamino N, Kangawa K, Matsuo H. Neuromedin-C – a bombesin-like peptide identified in porcine spinal-cord. Biochem Biophys Res Commun 1984;119:14–20.
[7] Minamino N, Kangawa K, Matsuo H. Neuromedin-N – a novel neurotensin-like peptide identified in porcine spinal-cord. Biochem Biophys Res Commun 1984;122:542–9.
[8] Minamino N, Kangawa K, Matsuo H. Neuromedin-U-8 and neuromedin-U-25 – novel uterus stimulating and hypertensive peptides identified in porcine spinal-cord. Biochem Biophys Res Commun 1985;130:1078–85.
[9] Minamino N, Sudoh T, Kangawa K, Matsuo H. Neuromedins—novel Smooth-muscle stimulating peptides identified in porcine spinal-cord. Peptides 1985;6:245–8.
[10] Brighton PJ, Szekeres PG, Willars GB. Neuromedin U and its receptors: structure, function, and physiological roles. Pharmacol Rev 2004;56(2):231–48.
[11] Brighton PJ, Wise A, Dass NB, Willars GB. Paradoxical behaviour of neuromedin U in isolated smooth muscle cells and intact tissue. J Pharmacol Exp Ther 2008;325(1):154–64.
[12] Torres R, Croll SD, Vercollone J, Reinhardt J, Griffiths J, Zabski S, et al. Mice genetically deficient in neuromedin U receptor 2, but not neuromedin U receptor 1, have impaired nociceptive response. Pain 2007;130(3):267–78.
[13] Novak CM, Zhang M, Levine JA. Sensitivity of the hypothalamic paraventricular nucleus to the loco motor-activating effects of neuromedin U in obesity. Brain Res 2007;1169:57–68.
[14] Vigo E, Roa J, Pineda R, Castellano JM, Navarro VM. Aguilar E, et al. Novel role of the anorexigenic peptide neuromedin U in the control of LH secretion and its regulation by gonadal hormones and photoperiod. Am J Physiol Endocrinol Metab 2007;293(5):E1265–73.
[15] Iwai T, Iinuma Y, Kodani R, Oka J. Neuromedin U inhibits inflammation-mediated memory impairment and neuronal cell-death in rodents. Neurosci Res 2008;61(1):113–9.
[16] Tanida M, Satomi J, Shen J, Nagai K. Autonomic and cardiovascular effects of central neuromedin U in rats. Physiol Behav 2009;96(2):282–8.
[17] Mitchell JD, Maguire JJ, Kuc RE, Davenport AP. Expression and vasoconstrictor function of anorexigenic peptides neuromedin U-25 and S in the human cardiovascular system. Cardiovasc Res 2009;81(2):353–61.
[18] Lee WH, Liu SB, Shen JH, Jin Y, Lai R, Zhang Y. Identification and molecular cloning of a novel neuromedin U analogue from the skin secretions of toad Bombina maxima. Regul Pept 2005;129:43–7.
[19] Austin C, Lo G, Nandha KA, Meleagros L, Bloom SR. Cloning and characterization of the cDNA encoding the human neuromedin U (NmU) precursor: NmU expression in the human gastrointestinal tract. J Mol Endocrinol 1995;14:157–69.
[20] Domin J, Ghatei MA, Chohan P, Bloom SR. NmU – a study of its distribution in the rat. Peptides 1987;8:779–84.
[21] Shan L, Qiao X, Crona JH, et al. Identification of a novel neuromedin U receptor subtype expressed in the central nervous system. J Biol Chem 2000;275:39482–6.
[22] Raddatz R, Wilson AE, Artymyshyn R. Identification and characterization of two neuromedin U receptors differentially expressed in peripheral tissues and the central nervous system. J Biol Chem 2000;275:32452–9.
[23] Guan XM, Yu H, Jiang Q, Van Der Ploeg LH, Liu Q. Distribution of neuromedin U receptor subtype 2 mRNA in the rat brain. Brain Res Gene Expr Patterns 2001;1:1–4.
[24] Austin C, Oka M, Nandha KA, Legon S, Khandannia N, Lo G, et al. Distribution and developmental pattern of neuromedin-U expression in the rat gastrointestinal-tract. J Mol Endocrinol 1994;12:257–63.
[25] Augood SJ, Keast JR, Emson PC. Distribution and characterization of neuromedin-U-like immunoreactivity in rat-brain and intestine and in guinea-pig intestine. Regul Pept 1988;20:281–92.
[26] Ballesta J, Carlei F, Bishop AE, Steel JH, Gibson SJ, Fahey M, et al. Occurrence and developmental pattern of neuromedin U-immunoreactivity nerves in the gastrointestinal-tract and brain of the rat. Neuroscience 1988;25:797–816.
[27] Bishop AE, Ballesta J, Carlei F, Steel JH, Gibson SJ, Fahey M, et al. The distribution and development of a new brain and gut peptide, neuromedin-U. J Pathol 1988;154:A99–A100.
[28] Honzawa M, Sudoh T, Minamino N, Kangawa K, Matsuo H. Neuromedin U-like immunoreactivity in rat intestine – regional distribution and immune histochemical study. Neuropeptides 1990;15:1–9.
[29] Hedrick JA, Morse K, Shan L. Identification of a human gastrointestinal tract and immune system receptor for the peptide neuromedin U. Mol Pharmacol 2000;58:870–5.
[30] Chen TB, Zhou M, Walker B, Harriot P, Mori K, Miyazato M. Structural and functional analogs of the novel mammalian neuropeptide, neuromedin S (NmS), in the dermal venoms of Eurasian bombinid toads. Biochem Biophys Res Commun 2006;345:377–84.
[31] Mori K, Miyazato M, Ida T, Murakami N, Serino R, Ueta Y. Identification of neuromedin S and its possible role in the mammalian circadian oscillator system. EMBO J 2005;24:325–35.
[32] Reppert SM, Weaver DR. Molecular analysis of mammalian circadian rhythms. Ann Rev Physiol 2001;63:647–76.
[33] Tan CP, McKee KK, Liu Q, Palyha OC, Feighner SD, Hreniuk DL, et al. Cloning and characterization of a human and murine T-cell orphan G-protein coupled receptor similar to the growth hormone secretagogue and neurotensin receptors. Genomics 1998;52:223–9.
[34] Fujii R, Hosoya M. Fukusumi Identification of neuromedin U as the cognate ligands of the orphans G protein coupled receptor FM3. Biochem Biophys Res Commun 2000;275:21068–74.
[35] Hosoya M, Moriya T, Kawamata Y, Ohkubo S, Fujii R, Matsui H, et al. Identification and functional characterization of a novel subtype of neuromedin U receptor. Biochem Biophys Res Commun 2000;275:29528–32.
[36] Anastasi A, Erspamer V, Bucci M. Isolation and structure of bombesin and alytesin, 2 analogues active peptides from the skin of the European amphibians Bombina and Alytes. Experientia 1971;27:166–7.
[37] Tacht Y, Brown M. On the role of bombesin in homeostasis. Trends Neurosci 1982;5:431–3.
[38] Spindel E. Mammalian bombesin-like peptides. Trends Neurosci 1986;9:130–3.
[39] McDonald TJ, Jornvall H, Nilsson G, Vagne M, Ghatei M, Bloom SR, et al. Characterization of a gastrin releasing peptide from porcine non-antral gastric tissue. Biochem Biophys Res Commun 1979;90:227–33.
[40] Erspamer V, Erpamer GF, Inselvini M. Some pharmacological actions of alytesin and bombesin. J Pharm Pharmacol 1970;22:875–6.
[41] Ohki-Hamazaki H, Iwabuchi M, Maekawa F. Development and function of bombesin-like peptides and their receptors. Int J Dev Biol 2005;49:293–300.
[42] Minamino N, Kangawa K, Matsuo H. Neuromedin B and neuromedin Ca two mammalian bombesin-like peptides identified in porcine spinal cord and brain. Ann N Y Acad Sci 1988;547:373–90.
[43] Merali Z, McIntosh J, Anisman H. Role of bombesin-related peptides in the control of food intake. Neuropeptides 1999;33:376–86.
[44] Ghatei MA, Jung RT, Stevenson JC, Hillyard CJ, Adrian TE, Lee YC, et al. Bombesin: action on gut hormones and calcium in man. J Clin Endocrinol Metab 1982;54:980–5.
[45] Bertaccini G, Erspamer V, Melchiorri P, Sopranzi N. Gastrin release by bombesin in the dog. Br J Pharmacol 1974;52:219–25.
[46] Delle Fave G, Kohn A, de Magistris L, Mancuso M, Sparvoli C. Effect of Bombesin stimulated gastrin on gastric acid secretion in man. Life Sci 1980;27:993–9.
[47] Walsh JH, Wong HC, Dockray GJ. Bombesin-like peptides in mammals. Fed Proc 1979;38:2315–9.
[48] Kirkham TC, Perez S, Gibbs J. Prefeeding potentiates anorectic actions of neuromedin B and gastrin releasing peptide. Physiol Behav 1995;58:1175–9.
[49] Ladenheim EE, Taylor JE, Coy DH, Moore KA, Moran TH. Hindbrain GRP receptor blockade antagonizes feeding suppression by peripherally administered GRP. Am J Physiol 1996;271:R180–4.
[50] Kawai K, Mukai H, Yuzawa K, Suzuki S, Kuzuya N, Fujii K, et al. Effects of neuromedinB and GRP-10 on gastrin and insulin release from cultured tumor cells of a malignant gastrinoma. Endocrinol Jpn 1990;37:857–65.

[51] Moody TW, Carney DN, Cuttitta F, Quattrocchi K, Minna JD. High affinity receptors for bombesin/GRP-like peptides on human small cell lung cancer. Life Sci 1985;37:105–13.
[52] Moody TW, Merali Z. Bombesin-like peptides and associated receptors within the brain: distribution and behavioral implications. Peptides 2004;25:511–20.
[53] Bedard T, Mountney C, Kent P, Anisman H, Merali Z. Role of gastrin-releasing peptide and neuromedin B in anxiety and fear-related behavior. Behav Brain Res 2007;179:133–40.
[54] Roesler R, Henriques JA, Schwartsmann G. Gastrin-releasing peptide receptor as a molecular target for psychiatric and neurological disorders. CNS Neurol Disord Drug Targets 2006;5:197–204.
[55] Linari G, Linari MB. Effect of bombesin on pancreatic secretion and gall bladder motility of the chicken. Eur J Pharmacol 1975;34:305–10.
[56] Mayer EA, Elashoff J, Walsh JH. Characterization of bombesin effects on canine gastric muscle. Am J Physiol 1982;243:G141–7.
[57] Zafirov DH, Palmer JM, Nemeth PR, Wood JD. Bombesin, gastrin releasing peptide and vasoactive intestinal peptide excite myenteric neurons. Eur J Pharmacol 1985;115:103–7.
[58] Washington MC, Sayegh AI. Gastrin releasing peptides increase Fos-like immunoreactivity in the enteric nervous system and the dorsal vagal complex. Peptides 2012;32:1600–5.
[59] McDonald TJ, Ghatei MA, Bloom SR, Adrian TE, Mochizuki T, Yanaihara C, et al. Dose–response comparisons of canine plasma gastroenteropancreatic hormone responses to bombesin and the porcine gastrin-releasing peptide (GRP). Regul Pept 1983;5:125–37.
[60] Ruff M, Schiffmann E, Terranova V, Pert CB. Neuropeptides are chemoattractants for human tumor cells and monocytes: a possible mechanism for metastasis. Clin Immunol Immunopathol 1985;37:387–96.
[61] De la Fuente M, Del Rio M, Ferrandez MD, Hernanz A. Modulation of phagocytic function in murine peritoneal macrophages by bombesin, gastrin-releasing peptide and neuromedin C. Immunology 1991;73:205–11.
[62] van Tol EA, Verspaget HW, Hansen BE, Lamers CB. Neuroenteric peptides affect natural killer activity by intestinal lamina propria mononuclear cells. J Neuroimmunol 1993;42:139–45.
[63] Del Rio M, Hernanz A, de la Fuente M. Bombesin gastrin-releasing peptide, and neuromedinC modulate murine lymphocyte proliferation through adherent accessory cells and activate protein kinase C. Peptides 1994;5:15–22.
[64] Narayan S, Guo YS, Townsend Jr. CM, Singh P. Specific binding and growth effects of bombesin-related peptides on mouse colon cancer cells in vitro. Cancer Res 1990;50:6772–8.
[65] Viallet J, Minna JD. Gastrin-releasing peptide (GRP, mammalian bombesin) in the pathogenesis of lung cancer. Prog Growth Factor Res 1989;1:89–97.
[66] Bologna M, Festuccia C, Muzi P, Biordi L, Ciomei M. Bombesin stimulates growth of human prostatic cancer cells in vitro. Cancer 1989;63:1714–20.
[67] Walsh JH, Wong HC, Dockray GJ. Bombesin Like peptides in mammals. Fed Proc 1979;2:2315–9.
[68] Moody TW, Thoa NE, O'Donohue L, Jacobowitz DM. Reduced Gastrin releasing peptide in CSF after recovery from bulimia. Life Sci 1981;2:2273–9.
[69] Kimura S, Goto K, Ogawa T, Sugita Y, Kanazawa I, Munekata E. Novel neuropeptides, Neurokinin α and β, isolated from porcine spinal cord. Proc Jpn Acad 1983;59:101–4.
[70] Dobner PR, Barber DL, Villa-Komaroff L, McKiernan C. Cloning and sequence analysis of cDNA for the canine neuro- tensin/neuromedin N precursor. Proc Natl Acad Sci U S A 1987;54:3516–20.
[71] Checler F, Vincent JR, Kitabgi R. Neuromedin N: high- affinity interaction with brain neurotensin receptors and rapid inactivation by brain synaptic peptidases. Eur J Pharmacol 1986;126:239–44.
[72] Tanaka K, Masu M, Nakanishi S. Structure and functional expression of the cloned rat neurotensin receptor. Neuron 1990;4:847–54.
[73] Erspamer VGBJ Glass. Gastrointestinal Hormones. New York: Raven Press; 1980. p. 343–61.
[74] Harmar AJ. Three tachykinins in mammalian brain. Trends Neurosci 1984;7:57.
[75] Ding YQ, Shigemoto R, Takada M, Ohishi H, Nakanishi S, Mizuno N. Localization of the neuromedin K receptor (NK3) in the central nervous system of the rat. J Comp Neurol 1996;364:290–310.
[76] Minamino N, Kangawa K, Matsuo H. Neuromedin N: a novel neurotensin-like peptide identified in porcine spinal cord. Biochem Biophys Res Commun 1984;122:542–9.
[77] Benito-Orfila MA, Domin J, Nandha KA, Bloom SR. The motor effect of Neuromedin-U on rat stomach in vitro. Eur J Pharmacol 1991;193:329–33.
[78] Maggi CA, Patacchini R, Giuliani S, Turini D, Barbanti G, Rovero P, et al. Motor response of the human isolated small-intestine and urinary-bladder to porcine neuromedin U-8. Br J Pharmacol 1990;99:186–8.
[79] Jones NA, Morton MF, Prendergast CE, Powell GL, Shankley NP, Hollingsworth SJ. Neuromedin U stimulates contraction of human long saphenous vein and gastrointestinal smooth muscle in vitro. Regul Pept 2006;136:109–16.
[80] Dass NB, Bassil AK, North-Laidler VJ, Morrow R, Aziz E, Tuladhar BR. Neuromedin U can exert colon-specific, enteric nerve-mediated prokinetic activity, via a pathway involving NMU receptor activation. Br J Pharmacol 2007;150:502–8.
[81] Gerfen CR. Substance P (neurokinin-1) receptor mRNA is selectively expressed in cholinergic neurons and basal forebrain. Brain Res 1991;556:165–70.
[82] Del Rio M, De La Fuente M. Chemoattractant capacity of bom- besin, gastrin-releasing peptide and neuromedin C is mediated through PKC activation in murine peritoneal leukocytes. Regul Pept 1994;49:185–93.
[83] Brown DR, Quito FL. Neuromedin-U octapeptide alters ion-transport in porcine jejunum. Eur J Pharmacol 1988;155:159–62.
[84] Katz R. Grooming elicited by intracerebroventricular bombesin and eledoisin in the mouse. Neuropharmacology 1980;19:143–6.
[85] Gmerek DE, Cowan A. Studies on bombesin-induced grooming in rats. Peptides 1983;4:907–13.
[86] Lemaire I. Bombesin-related peptides modulate interleukin-1 production by alveolar macrophages. Neuropeptides 1991;20:217–23.
[87] Ozaki Y, Onaka T, Nakazato M, Saito J, Kanemoto K, Matsumoto T, et al. Centrally administered neuromedin U activates neurosecretion and induction of C-Fos messenger ribonucleic acid in the paraventricular and supraoptic nuclei of rat. Endocrinology 2002;143:4320–9.
[88] Fukue Y, Sato T, Teranishi H. Regulation of gonadotropin secretion and puberty onset by neuromedin U. FEBS Lett 2006;580:3485–8.
[89] Rokkaku K, Onaka T, Okada N. Neuromedin U facilitates oxytocin release from the pituitary via beta adrenoceptors. Neuroreport 2003;14:1997–2000.
[90] Sakamoto T, Mori K, Miyazato M, Kangawa K, Sameshima H, Nakahara K. Involvement of neuromedin S in the oxytocin release response to suckling stimulus. Biochem Biophys Res Commun 2008;375:49–53.
[91] Kaczmarek P, Malendowicz LK, Pruszynska-Oszmalek E. Neuromedin U receptor 1 expression in the rat endocrine pancreas and evidence suggesting neuromedin U suppressive effect on insulin secretion from isolated rat pancreatic islets. Int J Mol Med 2006;18:951–5.
[92] Brown M, Rivier J, Vale W. Bombesin: potent effects on thermoregulation in the rat. Science 1977;196:998–1000.
[93] Brown M, Rivier J, Vale W. Bombesin affects the central nervous system to produce hyperglycemia in rats. Life Sci 1977;2(1):1729–34.
[94] Jin GF, Guo YS, Smith ER, Houston CW. The effect of Bombesin-related peptides on the phagocytic function of mouse phagocytes in vitro. Peptides 1990;I(I):393–6.
[95] Nakahara K, Hanada R, Murakami N. The gut brain peptide neuromedin U is involved in the mammalian circadian oscillator system. Biochem Biophys Res Commun 2004;318:56–61.
[96] Malendowicz KA, Nussdorfer GG, Nowak KW, Mazzocchi G. Effects of neuromedin U-8 on the rat pituitary-adrenocortical axis. In Vivo 1993;7:419–22.
[97] Hanada R, Nakazato M, Murakami N, Sakihara S, Yoshimatsu H, Toshinai K, et al. A role for Neuromedin U in stress response. Biochem Biophys Res Commun 2001;289:225–8.
[98] Ortiga-Carvalho TM, Oliveira KJ, Soares BA, Pazos-Moura CC. The role of leptin in the regulation of TSH secretion in the fed state: in vivo and in vitro studies. J Endocrinol 2002;174:121–5.
[99] Oliveira KJ, Ortiga-Carvalho TM, Cabanelas A, Veiga MA, Aoki K, Ohki-Hamazaki H, et al. Disruption of neuromedin B receptor gene results in dysregulation of the pituitary?thyroid axis. J Mol Endocrinol 2006;36:73–80.
[100] Kojima M, Haruno R, Nakazato M, Date Y, Murakami N, Hanada R, et al. Purification and identification of neuromedin U as an endogenous ligand for an orphan receptor GPR66 (FM3). Biochem Biophys Res Commun 2000;276:435–8.
[101] Nakazato M, Hanada R, Murakami N, Date Y, Mondal MS, Kojima M, et al. Central effects of neuromedin U in the regulation of energy homeostasis. Biochem Biophys Res Commun 2000;277:191–4.
[102] Niimi M, Murao K, Taminato T. Central administration of neuromedin U activates neurons in ventrobasal hypothalamus and brainstem. Endocrine 2001;16:201–6.
[103] Ivanov TR, Lawrence CB, Stanley PJ, Luckman SM. Evaluation of neuromedin U actions in energy homeostasis and pituitary function. Endocrinology 2002;143:3813–21.
[104] Hanada T, Date Y, Shimbara T, Sakihara S, Murakami N, Hayashi Y, et al. Central actions of neuromedin U via corticotrophin-releasing hormone. Biochem Biophys Res Commun 2003;311:954–8.
[105] Considine RV, Caro JF. Leptin and the regulation of body weight. Int J Biochem Cell Biol 1997;29:1255–72.
[106] Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature (Lond) 1998;395:763–70.
[107] Wren AM, Small CJ, Abbott CR, Jethwa PH, Kennedy AR, Murphy KG, et al. Hypothalamic actions of neuromedin U. Endocrinology 2002;143:4227–34.
[108] Graham ES, Turnbull Y, Fotheringham P. Neuromedin U and Neuromedin U receptor-2 expression in the mouse and rat hypothalamus: effects of nutritional status. J Neurochem 2003;87:1165–73.
[109] Duggan JP, Booth DA. Obesity, overeating and rapid gastric emptying in rats with ventromedial hypothalamic lesions. Science (Wash. D.C.) 1980;231:609–11.
[110] Yang YS, Song HD, Li RY, Zhou LB, Zhu ZD, Hu RM, et al. The gene expression profiling of human visceral adipose tissue and its secretory functions. Biochem Biophys Res Commun 2003;300:839–46.
[111] Bouchard L, Drapeau V, Provencher V, Lemieux S, Chagnon Y, Rice T, et al. Neuromedin b: a strong candidate gene linking eating behaviors and susceptibility to obesity. Am J Clin Nutr 2004;80:1478–86.
[112] Ladenheim EE, Knipp S. Capsaicin treatment differentially affects feeding suppression by bombesin-like peptides. Physiol Behav 2007;91:36–41.
[113] Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 2004;92:347–55.

[114] Zachary I, Rozengurt E. High-affinity receptors for peptides of the bombesin family in Swiss 3T3 cells. Proc Natl Acad Sci U S A 1985;82:7616–20.
[115] Wunder BA, Hawkins MF, Avery DD, Swan H. The effects of bombesin injected into the anterior and posterior hypothalamus on body temperature and oxygen consumption. Neuropharmacology 1980;19:1095–7.
[116] Babcock AM, Baker DA, Moody TW. Bombesin-induced hypothermia: a dose? response and receptor antagonist study. Pharmacol Biochem Behav 1992;43:957–60.
[117] Itoh S, Takashima A, Itoh T, Morimoto T. Effects of neuromedins and related peptides on the body temperature of rats. Jpn J Physiol 1995;45:37–45.
[118] Tsushima H, Mori M, Fujiwara N, Moriyama A. Pharmacological characteristics of bombesin receptor mediating hypothermia in the central nervous system of rats. Brain Res 2003;969:88–94.
[119] Even PC, de Saint Hilaire Z, Nicolaidis S. Peripheral administration of bombesin increases metabolism in the rat. Physiol Behav 1991;49:439–42.
[120] Porreca F, Burks T. Centrally administered bombesin affects gastric emptying and small and large bowel transit in the rat. Gastroenterology 1983;853:313–7.
[121] Tacht Y, Vale W, Rivier J, Brown M. Brain regulation of gastric secretion: influences of neuropeptides. Proc Natl Acad Sci U S A 1980;77:5515–9.
[122] Yu XH, Cao CQ, Mennicken F, Puma C, Dray A, O'Donnell D, et al. Pro-nociceptive effects of neuromedin U in rat. Neuroscience 2003;120:467–74.
[123] Cao CQ, Yu XH, Dray A, Filosa A, Perkins MN. A pro-nociceptive role of neuromedin U in adult mice. Pain 2003;104:609–16.
[124] Zhang X, Xu ZQ, Bao L, Dagerlind A, Hok Felt T. Complementary Distribution of Receptors for neurotensin and NPY in small neurons in Rat lumbar DRGs and regulation of the receptors and peptides after peripheral axotomy. J Neurosci 1995;15:2733–47.
[125] Kalivas PW, Richardson-Carlson R, Duffy P. Neuromedin N mimics the actions of neurotensin in the ventral tegmental area but not in the nucleus accumbens. J Pharmacol Exp Ther 1986;238:1126–31.
[126] Bissette G, Manberg P, Nemeroff CB, Prange A. Neurotensin a biologically active peptide. Life Sci 1978;23:2173–82.
[127] Gardiner SM, Compton AM, Bennett T, Domin J, Bloom SR. Regional hemodynamic effects of neuromedin-U in conscious rats. Am J Physiol 1990;258:R32–8.
[128] Dahlof B. Left ventricular hypertrophy and angiotensin II antagonists. Am J Hypertens 2001;14:174–82.
[129] Chu C, Jin Q, Kunitake T. Cardiovascular actions of central neuromedin U in conscious rats. Regul Pept 2002;105:29–34.
[130] Tsubota Y, Kakimoto N, Owada-Makabe K. Hypotensive effects of neuromedin U microinjected into the cardiovascular related region of the rat nucleus tractus solitarius. Neuroreport 2003;14:2387–90.
[131] Khawaja AM, Rogers DF. Tachykinin: receptor to effector. Int J Biochem Cell Biol 1996;28:721–38.
[132] Dubuc I, Nouel D, Coquerel A, Menard JF, Kitabgi P, Costentin J. Hypothermic effect of neuromedin N in mice and its potentiation by peptidase inhibitors. Eur J Pharmacol 1988;151:117–21.
[133] Yamashita K, Upadhyay S, Osada M, Hoque MO, Xiao Y, Mori M, et al. Pharmacologic unmasking of epigenetically silenced tumour suppressor genes in oesophageal squamous cell carcinoma. Cancer Cell 2002;2:485–95.
[134] Alevizos I, Mahadevappa M, Zhang X. Oral cancer in vivo gene expression profiling assisted by laser capture micro dissection and microarray analysis. Oncogene 2001;20:6196–204.
[135] Johnson EN, Appelbaum ER, Carptenter DC. Neuromedin U elicits cytokine release in murine Th2 type T cell clone D10. G4.1. J Immunology 2004;173:7230–8.
[136] Sato S, Hanada R, Kimura A. Central control of bone remodeling by neuromedin U. Nat Med 2007;13:1234–40.
[137] Rucinski M, Ziolkowska A, Tyczewska M, Szyszka M, Malendowicz LK. Neuromedin U directly stimulates growth of cultured rat calvarial osteoblast-like cells acting via the NMU receptor 2 isoform. Int J Mol Med 2008;22:363–8.