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A Mini-Review on Potential of Neuropeptides as Future Therapeutics

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Abstract

Neuropeptides are small protein like messenger molecules that are involved in regulation of various activities in living species. These neuropeptides have been isolated from variety of sources ranging from small insects to mammals. They regulate multiple activities and functions of body in both vertebrates and invertebrates. A wide range of neuropeptides have been isolated from different invertebrate species like insects, bees, beetles, drosophila to understand role of peptide sequences in controlling homeostasis and behavior. Along with more than 100 peptides have been identified in mammals and most of them are synthesized and secreted by hypothalamus. Neuropeptides not only act via nervous system but some of them also act peripherally through endocrine systems to regulate various functions. Further, they are involved in regulation of functions like cell signaling, respiration, growth, social behavior, reproduction, inflammation, stress, anxiety, sexual activity, glucose homeostasis, feeding behavior, memory and learning. Common known neuropeptides, involved in different regulation mechanisms, are oxytocin, vasopressin, orexins, bradykinin, neuropeptide Y, tachykinins, opiod neuropeptides, angiotensin, somatostatin, ghrelin, galanin and hemokinins. Not only this, neuropeptides are also involved in management of diseases like Alzheimer's, Parkinsonism, Seizures and epilepsy, diabetes, high blood pressure, obstructive sleep apnea and various skin diseases. Diversified roles of neuropeptides make them promising candidates for prospective therapeutics. A lot of research has been done on antimicrobial peptides but research works related to neuropeptides has received attention of researchers recently only. This review sheds light on various neuropeptides involved in regulation and control of body functions in living species.

Keywords Neuropeptides · Regulation · Hormones · Neurons · Oxytocin · Kisspeptin · Peptidomimetics · Somatostatin · Angiotensin · Galanin

Abbreviations

BBB	Blood brain barrier
CCAP	Crustacean cardioactive peptide
GnRH	Gonadotropin releasing hormone
GnIH	Gonadotropin inhibitory hormone
DM	Diabetes mellitus
AT2R	Angiotensin II type 2 receptor

Introduction

The concept of neuropeptides came into light in late 1960s and early 1970s; during this time various scientists working either independently or in groups gave this concept, that neuropeptides are the peptides that are produced in the brain and gut that directly affect the neuron. Some neuropeptides were even found to affect the non-neural tissues and organs; that gave an indication that the major role of neuropeptides is the integration of brain functions and systems of the body. Major contributors to the neuropeptides concept were De Wied et al. 1969 and Kastin et al. 1979. But, other researchers took many years to accept this concept. As a result, many peptides with neurogenic activities were isolated from various sources like sharks, frogs, invertebrates, plants and mammals; to gain more insights on neuropeptides (De Wied 1969, Kastin et al. 1979, Strand 1999). With expansion of neuropeptides research area in subsequent years different researchers have tried to explain neuropeptides in their own

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style; as per Burbach et al. 2011 neuropeptides are small protein-like molecules that are synthesized and secreted by neurons; comprising subfamilies like granins, cerebellins, neural chemokines and neurexophillins (Burbach 2011). Similarly another group defined neuropeptides as chemical messengers that are released from nerve cells and act in endocrine and paracrine manner. Where in, they directly reach their target cells via blood in endocrine route and co transmitters modulate their functions following paracrine pathway (Elewa et al. 2013).

Moreover, it is the largest class of signaling molecules that contributes to diverse physiological processes (Fricker and Devi 2018); these molecules modulate signaling between cells in endocrine and nervous system, along with regulation of homeostasis, immunomodulation and neuroprotection (Catalani et al. 2017). Neuropeptides play key role in transfer of information and regulation of growth, development, reproduction and metabolism in multi cellular animal organisms (Derst et al. 2016). For research purpose neuropeptides have been chemically extracted from tissues (Stemmler et al. 2013). Since ages, Crustaceans have been used as major source for neuropeptide research. First fully characterized neuropeptide from an invertebrate was also isolated from a shrimp. Crustacean cardiac, nervous and somatogastric systems are used as models to understand neural circuit functioning and modulation by peptides (Christie et al. 2010). The sinus gland of crustacean is a well-reported site of endocrine signaling neuropeptides secretion. There are over seventy different neuropeptides that have been isolated from this species, few are: proctolin, RYamides, RFamides, orcomyotropin, pigment dispersing hormone and orcokinins etc. (Hui et al. 2011). Crustacean cardioactive peptide (CCAP) and its related peptides are involved mainly in the regulation of ecdysis and act as neuro-hormone secreted into the haemolymph. A CCAP-related peptide named conoCAP-a, from cone snail acts as cardio-active peptide and CCAP isolated from arthropod acts as cardio-accelerator (Moller et al. 2010).

In parallel, about 250 neuropeptides have been identified in nematodes (Knickelbine et al. 2018). In nematode systems such neuropeptide operate within a structurally simple nervous system comprising of 300 neurons (Marks and Maule 2010). Other well-known sources for neuropeptides are echinoderms and cicadas. Echinoderms are known for SALFamides neuropeptides like S1 and S2 neuropeptides; they have been isolated from starfish, while more neuropeptides have recently been isolated from *P. miniata* (Elphick et al. 2013, Jones et al. 2014). These neuropeptides act as muscle relaxants in echinoderms (Jones et al. 2014). Another rich source of neuropeptides includes neurosecretory glands of the cicadas. The *corpora cardiac*, have been known for more than 20 years as source of isobaric peptides with hypertrehalosemic activity (Konig et al. 2017). Few more sources that have been used to study nature of neuropeptides are *C. elegans* (Holden-Dye and Walker 2013), *Beetles* (Marciniak et al. 2013), *Chelicerata* (Christie et al. 2011), *Burying beetles* (Urbanski et al. 2018), and *Drosophila* (Kahsai et al. 2010).

More than thirty families of neuropeptides having different structures and functions have been discovered so far in insects. Most of the molecules affect the insect's physiology. However activity of these molecules depends on type of species and age of species. While as far as animals are concerned, neuropeptides control various complex behavioral actions in animals (Chowanski et al. 2016). Gonadotropin releasing hormone (GnRH) was discovered in mammals at beginning of 1970s, at that time it was believed that (GnRH) was the only neuropeptide in hypothalamus that regulated gonadotropin release in vertebrates. Later on in year 2000, a new hypothalamic hormone, gonadotropin inhibitory hormone (GnIH) was discovered that inhibited the gonadotropin release (Tsutsui 2016). In humans neuropeptides influence multiple activities; there are more than 100 well known neuropeptides that have been identified till date in humans and more than 1000 predicted neuropeptides encoded in genome that are yet to be identified (Russo 2017). Humans have approximately more than 90 neuropeptide genes; while a relatively simple organism like nematode possesses a slightly higher quota of neuropeptide genes (Chang et al. 2015). Recently two RF amide peptides have been cloned in humans. RF- amide neuropeptides spans from corner to corner in the entire life of organism. They play important roles in regulation of reproduction and feeding behavior in vertebrates as well as invertebrates (Quillet et al. 2016). RF amide neuropeptides affect diverse functions in vertebrates and invertebrates that influence the pituitary hormone secretion (Qaiser et al. 2012). Examples of C-terminal RFamide motif are gonadotropin-inhibitory hormone, kisspeptin, neuropeptide FF, prolactin-releasing peptide, and pyroglutamylated RFamide peptide (Elphick and Mirabeau 2014).

Mechanism of Action of Neuropeptides and their Fragments

The interaction between host and pathogen involves countless host proteins and various peptide families. Neuropeptides is one such family that is integral part of nervous system and host defense system (Augustyniak et al. 2012). Various evidences suggest that when the nervous system is challenged by any stress, injury, or drug abuse; neuropeptides have been found to play important role (Hökfelt et al. 2003). The mechanism of action of neuropeptides still remain indescribable, evidence suggest that peptides may exert their main actions under specific conditions (Hökfelt et al. 2000). There are three different ways by which neurons handle peptides. Mode 1: when there are substantial levels

under normal conditions. Mode 2: when there are very low levels under normal conditions. Mode 3: transient expression during development. One such common example that gives explanation of these modes is Galanin. As Galanin in hypothalamic neurons acts by Mode 1, Galanin in sensory neurons acts by Mode 2 and Galanin in primary sensory neurons acts by Mode 3 (Tohyama 1992).

On the other hand interaction of neuropeptides with their receptors has been explained in a unique way, as the neuropeptides have been found to undergo proteolysis into fragments; these peptide fragments interact with those receptors that are not recognized by their parent peptides from which fragments are formed. For example, neuropeptides like bradykinin, substance P, angiotensin I and II, neuropeptide Y, and dynorphin A are all degraded into bioactive fragments. Most of neuropeptides degrade into bioactive fragments that contain amino acid residues; hence they can become useful starting points for developing drugs that have the ability to mimic the effects of these fragments. Therefore such substances could serve as a rich source of novel drugs (Hallberg 2015). Mechanism of action of neuropeptides as suggested by Merighi, Adalberto is described in Fig. 1 (Merighi et al. 2011).

Role of Neuropeptides

Neuropeptides not only regulate physiological functions but they also play a major role in pathology of diseases. These roles of neuropeptides have been explained below.

Regulation of Body Functions by Neuropeptides

These are distinct protein based small molecules that are present in animals. They control growth, digestion, development and various other processes. They regulate the wide variety of behavioral actions associated with sleep, feeding, memory, addiction, courtship, social interactions, learning and stress (Schoofs et al. 2017). Brief account of regulation of body functions by neuropeptides is given below:

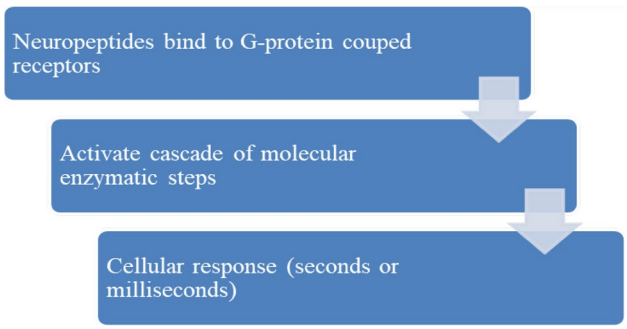

Fig. 1 Mechanism of action of neuropeptides

Regulation of Blood Pressure

Bradykinin is a polypeptide that is found in higher concentration in body tissues as compared to blood plasma. Bradykinin is formed by conversion of kininogens into plasma kallikrein (bradykinin) and glandular kallikrein (tissue kallikrein) via enzymatic actions of kininogenases enzymes. It is a vasoactive kinin that regulates pressure of blood. Kinins are involved in numerous biologic actions like inflammation, nociception, reactive hyperemia, capillary permeability and glucose uptake (Palkhiwala et al. 2001). Neuropeptide Y is yet another 36 amino acid polypeptide. It regulates blood pressure and angiogenesis. It also acts as orexigenic agent to regulate eating behavior. Various activities like fasting, glucosuria and energy loss stimulate neuropeptide Y-ergic arcuate—paraventricular nucleus pathway (Kokot and Ficek 1999).

Regulation of Sodium Water Intake

Angiotensin II is a hormone that is produced locally within the kidney. Main actions of Angiotensin II are regulation of sodium water intake, formation and release of hormones and regulation of sympathoadrenal systems. It works via feedback mechanism by detecting changes in hormone, electrolyte and sympathetic systems to modulate activity of the brain (Malpas et al. 2006), (Durvasula and Shankland 2006), (Wassmann and Nickenig 2006), (Saavedra 2005).

Perception of Pain

Tachykinin and opioid neuropeptides play a major role in perception of pain (Saidi and Beaudry 2015). The proteolysis control of these endogenous neuropeptides has a significant influence on pain perception (Saidi and Beaudry 2017). Examples of tachykinins involved in pain perception are neurokinin A, neurokinin B, and substance P (Mostafa et al. 2016). All tachykinins are known to interact with NK1, NK2, and NK3 receptors. Among all tachykinins Substance P express the highest selectivity for NK1 receptors. This receptor plays a major role in neurogenic plasma extravasation and in the transmission of nociceptive signals (Folkers et al. 1982). Tachykinins and their corresponding peptidomimetics form a very attractive approach to design a new series of analgesics (Lipkowski et al. 2004). Peptidomimetic approach has also been utilized to design antagonists to substance P. Example of peptide based peptidomimetic having antagonistic activity to substance P is FR 113,680 Fig. 2 (Morimoto et al. 1992) and examples of non peptide based peptidomimetics (Fig. 3) having antagonistic activity

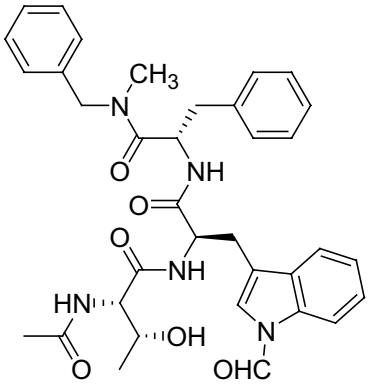

Fig. 2 FR 113,680, a peptide based peptidomimetic having antagonistic activity to substance P

to substance P are RP67580 (Garret et al. 1991), CP96345 (Snider et al. 1991), CP9994 (Rosen et al. 1993).

Cell–Cell Communication

Neuropeptides are able to signal to neighboring cells or are released as neurohormones into the blood flow (Galoian and Patel 2017). Proteolytic processing of proneuropeptide precursors in secretory vesicles produces active neuropeptides (Funkelstein et al. 2010). Neuropeptides are vital signaling molecules that participate in the regulation of various physiological activities in invertebrates and vertebrates (Gui et al. 2017).

Regulation of Glucose, Growth and Pancreatic Functions

Neuropeptides released from brain along with peptides and hormones released from other body parts like GIT and muscles, regulate secretions from pancreas which in turn regulate endocrine function of islets within exocrine pancreatic tissue that is responsible for release of hormones like glucagon, insulin, ghrelin, pancreatic polypeptide, and somatostatin. Ghrelin, somatostatin, glucose dependent insulinotropic polypeptide and glucagon like peptide regulate exocrine as well as endocrine functions of pancreas (Gesmundo et al. 2017).

Somatostatin regulates growth in vertebrates (Liu et al. 2010). Somatostatin and its receptor have distinctive functional complexity and versatility. It is widely distributed and frequently co-expressed with its subtypes. It has multiple functions like central nervous system functions, cell proliferation and endocrine-exocrine secretions (Gahete et al. 2010). It is a peptide made up of 14 amino acids that inhibit exocrine and endocrine secretions of pancreas. It has a very short half-life and hence limited clinical applications. However its synthetic analogue octreotide, a peptide made up of 8 amino acids has a longer duration of action and possesses similar pharmacological effects. It inhibits secretions of glucagon, insulin, gastrin, pancreatic polypeptide and gastric inhibitory polypeptide. Along with this, it regulates release of thyroid stimulating hormone and growth hormone secretion in response to insulin induced hypoglycemia, exercise and arginine stimulation. It regulates gastric emptying and gall bladder emptying. This is regulated via the absorption of water and electrolytes (Harris 1994).

Regulation of Feeding Behavior

Hypothalamic neurons release neuropeptides that regulate feeding by acting at various appetite centres and hypothalamus in the brain. Neuropeptides have the ability to diffuse over greater distances as compared to classical neurotransmitters, hence affecting neuronal extra synaptic receptors expressed by neuron and triggering behavioral output (Parker and Bloom 2012). For example: glucagon like peptide-2 has been hypothesized to affect appetite via hypothalamus (Dalvi and Belsham 2012) and another glucagon like peptide-1 receptor agonist neuropeptide, exendin-4,

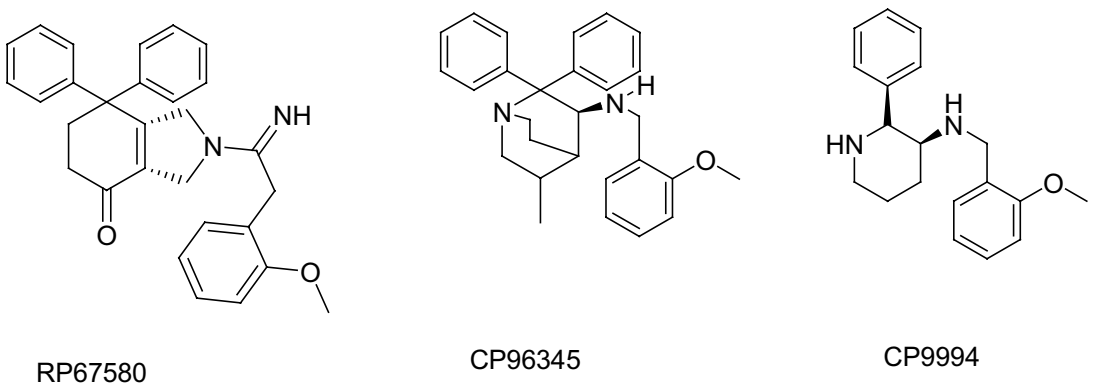

Fig. 3 Non-peptide peptidomimetics having antagonistic activity to substance P neuropeptide

induce satiety and reduce food intake to regulate feeding behavior (Dalvi et al. 2012). Orexins and neuromedins are other two neuropeptides that regulate feeding behavior. Orexins affect energy balance by stimulating both feeding and energy expenditure. While on the other hand neuromedins suppress feeding behavior and give anorectic action. It reduces appetite and increases physical activity to produce a negative energy balance. These two neuropeptides along with other substances act on the appetite system and balance the feeding and physical activity behaviors. Overall orexins and neuromedins regulate body weight (Nixon et al. 2012).

Regulation of Social Behavior

Oxytocin is a well-known neuropeptide that controls social behavior (Hashimoto et al. 2012). Oxytocin and vasopressin like peptides are present in most of vertebrates. They are produced and released by the pituitary gland. Oxytocin and vasopressin regulate various physiological functions in vertebrates (Gruber 2014). These two peptides are also involved in mediating various aspects of social behavior like social recognition and responses to noticeable social threats (Kavaliers and Choleris 2011). Oxytocin regulates bonding, attachment, parental behaviors, trust, lactation, and various other functions like touch, pain, homeostasis of cardiovascular system, analgesia and satiety. Social bonds are associated with the stimulation of cell signaling pathways that promote neurotrophic and synaptic maturation. While on the other hand any abnormality in these cells signaling pathway or any defect in function of neurotransmitters in brain leads to antisocial behavior; factors that lead to improper social behavior are stress, chemical, diet, noise, and air pollution (Vargas-Martinez et al. 2014).

Sexual Behaviour

Neuropeptides like adrenocorticotropin, oxytocin, opioid peptides, and alpha-melanocyte stimulating hormone are few examples of most studied neuropeptides in brain that regulate the sexual behavior. Studies on some of mammalian species suggest that among these neuropeptides all expedite sexual behavior except opioid peptides that inhibit sexual performance. Others neuropeptides that are also involved in regulating sexual behavior are: neuropeptide Y, cholecystokinin, vasopressin, substance P, hypocretins/orexins, vasoactive intestinal peptide, angiotensin II, and corticotrophin releasing factor. Neuropeptides that regulate sexual activity act via hypothalamic nuclei, spinal cord, and medial preoptic area. Well it is still not clear that whether these neuropeptides act on sexual arousal phase or sexual performance phase during sexual activity except in cases of oxytocin and opioid peptides. Apart from most studied neuropeptides that affect the sexual behavior, very less information has been gathered in last few years on mechanism of action of neuropeptides regulating sexual behavior (Argiolas and Melis 2013).

Reproduction

Neuropeptides and receptors that are involved in reproduction of vertebrate species are gonadotropin-releasing hormone and kisspeptin, and their receptors gonadotropin-releasing hormone receptor and kisspeptin receptor (Kim et al. 2012). Hormones affect most tissues of body and play an important role in regulating reproduction at all stages of life. Gonadotropin releasing hormone is synthesized in the hypothalamus that regulates reproduction by stimulating the secretion of gonadotropins. Therapeutics based on these neuropeptides are being developed to treat hormone based diseases in humans (Newton et al. 2016). Different body functions that are regulated by neuropeptides are given in Table 1 and Fig. 4.

Role of Neuropeptides in Different Ailments and Diseases

Diabetes

According to a report of year 2010 diabetes has affected 285 million adults. Patients affected with diabetes have a risk of developing neuropathy and delayed wound healing that can lead to diabetic foot ulcers and sometimes amputation of foot. Another complication that is associated with diabetes is diabetic retinopathy. Various considerable efforts have been made in the recent years to find solutions for this condition. Neuropeptides that are released from autonomous nervous system and skin cells play a significant role in healing of wounds in diabetes (da Silva et al. 2010).

Migraine

Migraine is a common disabling neurovascular primary headache condition that affects people and can last for days. It can often strike multiple times in a month. It is often characterized by throbbing pain in head, fatigue, yawning and irritability. There is a diversity of symptoms associated with migraine. The exact mechanism behind migraine's pathology is still not clear (Tajti et al. 2015). Trigeminovascular system neuropeptides may act as potential biomarkers for chronic primary headaches and migraine (Riesco et al. 2017).

Table 1 Different body functions that are regulated by neuropeptides

S. No	Peptide	Function/role	Reference
1	Angiotensin	Regulate blood pressure via vasoconstriction	(Basso and Terragno 2001)
2	Neuropeptide Y	Regulation of arousal and anxiety	(Kask et al. 2002)
3	Oxytocin	Play a role in mammalian behavior and health	(Carter et al. 2020)
4	Brain opioid peptides	Play a vital role in attachment, emotion, motivation, stress, pain, and feeding behavior	(Rebillard et al. 1977)
5	Bradykinin	Regulate blood pressure via vasodilation	(Marcos-Contreras et al. 2016)
6	Ghrelin	Regulation of appetite and energy	(Magrill 1973)
7	Galanin	Regulation of sleep, cognition, feeding, blood pressure, and mood	(Mechenthaler 2008)
8	Kisspeptin (Kp)	Regulation of reproductive functions	(Dudek et al. 2018)
9	Somatostatin	Regulation of growth in vertebrates	(Liu et al. 2010)
10	Neurokinin B	Pregnancy in females and maturation in young adults	(Navarro 2013)
11	Hemokinin	Regulation of respiratory, endocrine, inflammatory, and immune system	(Borbély and Helyes 2017)
12	Ghrelin	Anticonvulsant activity	(Portelli et al. 2012)
13	Neuropeptide Y	Regulation of itching	(Jakobsson et al. 2019)
14	Neuropeptide W	Regulation of energy homeostasis	(Li et al. 2018)
15	Vasopressin	Central Autonomic Control and Blood Pressure Regulation	(Lozić et al. 2018)
16	Galanin, spexin and kisspeptin	Regulation of metabolism, mood and behaviour	(Mills et al. 2021)

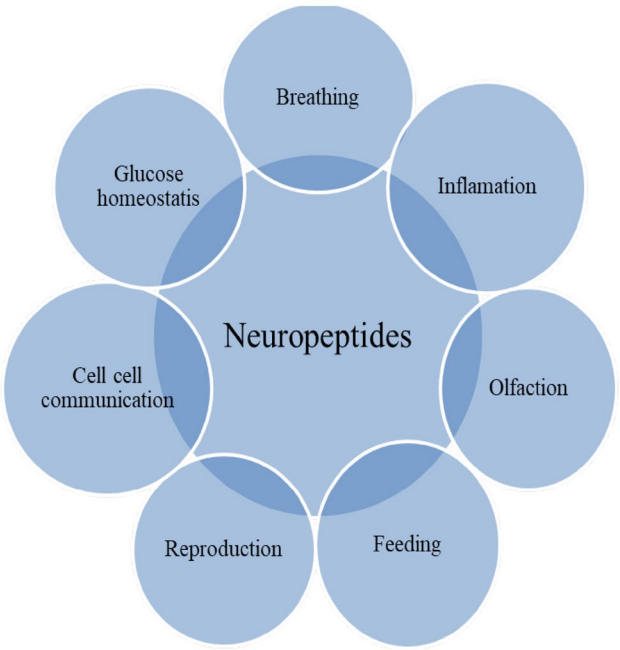

Fig. 4 Regulation of different body functions by neuropeptides

Seizures and Epilepsy

Seizures are neurological disorders that affect nearly 50 million people worldwide. Balance between excitatory and inhibitory neurotransmitters gets imbalanced which leads to abnormal and repetitive firing of the neurons in seizures. Neuropeptides regulate these seizures by resolving imbalance of excitatory and inhibitory neurotransmitters. Such neuropeptides are released on excitation from dense core synaptic vesicles (Menon et al. 2017). Epilepsy is another neuronal disorder in which recurrent seizures occurs. It is caused by imbalance between inhibition and excitation. Neuropeptides act by modulating the effect of excitatory and inhibitory neurotransmitters in maintaining this imbalance. Neuropeptides like somatostatin, ghrelin, cortistatin, galanin, adrenocorticotropic hormone, cholecystokinin, neuropeptide Y, dynorphin, thyrotropin-releasing hormone, neurotensin, and angiotensin, have the ability to suppress such seizures in the brain (Clynen et al. 2014). Anticonvulsant neuropeptides like neuropeptide Y, galanin, neurotensin, somatostatin, dynorphin have been validated as potential anti-epileptic compounds in animal models of epilepsy. These neuropeptides can serve as attractive templates for developing novel neurotherapeutics (Robertson et al. 2011). Adrenocorticotropic hormone neuropeptide is already in use in clinical practice to suppress seizures (Kovac and Walker 2013).

Depression

According to world health organization depression is the most common disability that has affected western population. Stress related type of mood disorders not only has a deleterious effect on patients but they also affect healthcare system. Information on neurobiology of such conditions is scarce as the high percentages of patients do not respond to currently existing medications that target monoaminergic systems. Studies indicate that brain neuropeptides not only participate in stress physiology but are also clinically

important in treatment of depression (Kormos and Gaszner 2013).

Parkinsonism

It is a disorder in which neurons of midbrain nigral dopaminergic neurons are deteriorated. Its etiology is not known exactly but various factors like neuroinflammation, protein misfolding, oxidative stress and mitochondrial dysfunction are involved in its pathology. Presently Parkinsonism is treated with replacement of dopamine with levodopa. Various therapeutic approaches are being explored; therapy with neuropeptides is one such approach that offers wide-ranging effects in the nervous system. A neuropeptide named pituitary adenylate cyclase-activating polypeptide belonging to secretin/glucagon superfamily has shown beneficial effects in models of neuro-degeneration, they have shown protective effect in dopaminergic neurons. Thus, neuropeptides are novel therapeutic candidates that have potential to treat Parkinson's disease (Reglodi et al. 2017).

Alzheimer's Disease

It is a brain disorder associated with abnormal cognition and behavior. Neuropeptides are distributed throughout the whole nervous system as neuromodulators, neurohormones, and neurotransmitters. They play a vital role in regulation of cognition and behavior (Van et al. 2015). Tachykinin also plays a major role in amyloid formation and hence might decrease the toxic effects of amyloids associated with this disease (Singh and Maji 2012).

Obstructive Sleep Apnea

It is a sleep disorder associated with obesity and other metabolic disorder. Its major symptoms are excessive sleepiness during daytime and snoring. Neuropeptides like neuropeptide Y, Hypocretin-1, ghrelin, adiponectin, and leptin have been found to play a role in sleep regulation (Sanchez-de-la-Torre et al. 2011). Different neuropeptides play different roles in management of diseases (Fig. 5). Along with advantages Neuropeptides also suffer from certain limitations, which restrict their use. Their limitations (in brief) have been described in below.

Limitations of Neuropeptides

Peptides are useful in treatment of brain disorders, but the treatment option is limited due to their inability in crossing BBB. Various drug delivery strategies have been designed so far to target neuropeptides to brain, in most brain targeting approaches prodrug concept has been used by covalently

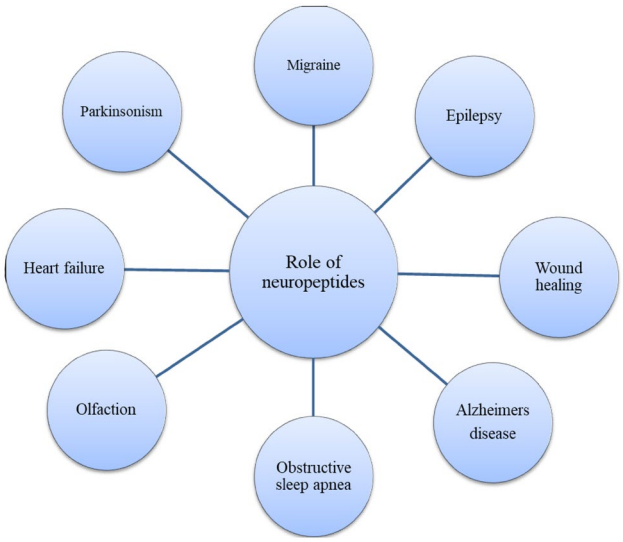

Fig. 5 Role of neuropeptides in different diseases

linking the lipophilic and bio reversible moieties to peptides. This improves the metabolic stability in body fluids and brain uptake of peptide drugs but on the other hand it results in loss of activity of parent peptide. The moment peptide prodrug conjugates reach BBB; the parent active peptide is released from its prodrug due to enzymatic action (Prokai-Tatrai and Prokai 2011). Another concept that is used as an alternative route for administration of peptides to brain is via intra nasal route. This route is a preferred route due to existence of a direct pathway between brain and olfactory neuroepithelium (Veronesi et al. 2011). Neuropeptides that are hydrophilic in nature are ineffective in crossing BBB; like thyrotropin releasing hormone is unstable as well as hydrophilic due to its peptidic nature and hence somewhat ineffective to enter the blood brain barrier (Kaur et al. 2016).

Current Status

Natural peptides found in various organisms perform different biological functions; therefore they have the ability to become ideal therapeutic candidates. But their success as therapeutic moieties is hindered by their poor pharmacokinetic profiles. This problem can be solved by developing nonpeptide peptidomimetics, as they overcome these limitations as well as retain the activity of the parent peptide (Smith et al. 2011). Different strategies have been exploited so far to develop peptidomimetics and neuropeptide ligands, such strategies are: use of unnatural amino acids (Fig. 6) (Bihel et al. 2015), by placing ring constrained spacers (Sivertsen et al. 2011), grafting of pharmacophoric amino acid side chains to a scaffold (Gouin and Murphy 2005) and utilization of nonhydrolizable amide bond surrogates

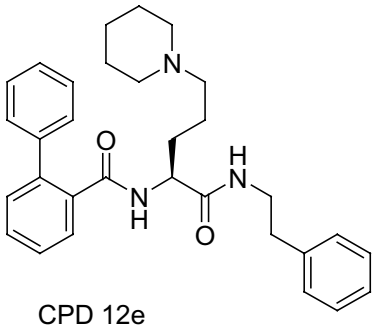

Fig. 6 Neuropeptidomimetic Compound 12e

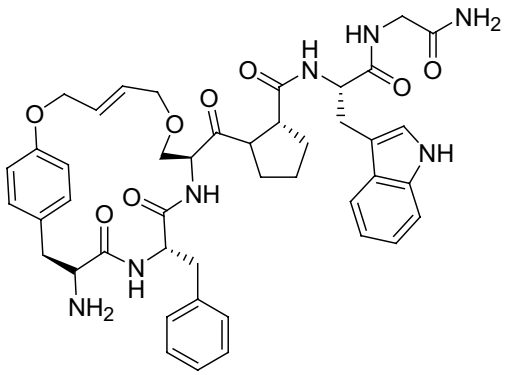

Fig. 7 Alkenyl-bridged macrocycle of Heicokinin I

(Valverde et al. 2014). These peptidomimetics distribute well in the space and mimic the bioactivity of parent peptide. Both linear and oligoheterocyclic peptidomimetics of parent peptide can be synthesized via solid phase synthesis (Hammami et al. 2014). One such example is mimetic of insect diuretic neuropeptide Helicokinin I. Strategy that was used to prepare this neuro-peptidomimetic was ring closing metathesis reaction. The alkenyl-bridged macrocycle (Fig. 7) retained the activity of parent peptide helicokinin I (Van et al. 2015).

Peptidomimetics not only bind to neuropeptide receptors but also show activity at low nanomolar ranges. In a study by Karad SN et al., a fluoroalkene and trifuoroethylamine peptidomimetics of opioid neuropeptide Leu-enkephalin was synthesized. Synthesized analogue not only bound to δ- and μ-opioid receptors but also displayed low nanomolar functional activity. On the other hand the trifluoroethylamine peptidomimetic with a bulky CF3 substituent was not able to activate these receptors (Karad et al. 2017).

Peptidomimetics have also been designed to enhance the stability and prolong the bioactivity. In a study, neurokinin 3 receptor agonist was developed to regulate reproductive functions. These peptidomimetics were designed based upon their degradation profiles. The alteration of senktide with (E)-alkene dipeptide isostere produced a NK3R agonist that enhanced the stability and prolonged the bioactivity (Misu et al. 2014).

Peptidomimetic approach can also be utilized for neuropeptides that have a short half-life. An example is the neuropeptide kisspeptin that regulates the growth by stimulating gonadotrophin-releasing hormone secretion. But it suffers from a drawback that is has a short half-life, proteolytic degradation and rapid renal clearance. However, their modified analogs have the tendency to open new possibilities for the treatment of reproductive disorders in humans (Decourt et al. 2016). Another neuropeptide, neurotensin suffers with a drawback of short biological half-life due to rapid proteolysis in vivo. A strategy that has been utilized to stabilize this peptide is utilization of nonhydrolizable 1,4-disubstituted, 1,2,3-triazoles as amide bond surrogates (Mascarin et al. 2015).

Neuropeptides and Neuropeptide Agonists in Clinical Trials

AT2R (Angiotensin II Type 2 Receptor) Agonist

Peptidomimetics like AT2R agonists are in clinical trial and nonpeptide selective angiotensin II type 2 receptor agonist (C21) was reported in 2004, this nonpeptide agonist has shown anti-inflammatory and antifibrotic actions in vivo. It is one of the most explored nonpeptide agonist and it is currently under clinical trials (Hallberg et al. 2017).

Apelin-13

It is a neuropeptide that plays an important role in memory, learning and neuroprotection. It is generally isolated from bovine stomach. It is currently under clinical trial to study its effect in Alzheimer's disease. No treatment options are available till date that cures this disease completely. Different studies have shown apelin as potential therapeutic that can prevent the production of Aβ cells or may increase its degradation directly or indirectly. Various in vitro and in vivo studies on apelin have shown that it prevents the death of neurons (Masoumi et al. 2018).

Kisspeptin

It is a reproductive hormone whose effect has been studied on limbic brain activity and behavior. Its effect has been evaluated in heterosexual men; kisspeptin administration not only regulated sexual and emotional behaviors but they also reduced the negative moods of individuals. Results of this study suggested that kisspeptin has the potential to act as therapeutic agent in patients suffering from disorders of

reproductive functions (Comninos et al. 2017). Another form of kisspeptin that has been studied in humans is kisspeptin-54. It stimulates the secretion of reproductive hormones in humans (Jayasena et al. 2014a, b). Since this neuropeptide is essential for human reproduction, as it acts on the hypothalamus to stimulate secretion of gonadotrophin-releasing hormone. It is presently under evaluation as a novel therapeutic for treatment of infertility conditions in women (Jayasena et al. 2014a, b).

Somatostatin Analogues

Octreotide is a somatostatin analog that is used in treatment of hypoglycemia caused by congenital hyperinsulinisim. It was evaluated in a clinical trial in Japanese population. Its efficacy was determined in patients with diazoxide-unresponsive congenital hyperinsulinism; this analogue was well tolerated by majority of patients when given by subcutaneous route (Hosokawa et al. 2017). Another somatostatin analogue that has been evaluated in clinical trials is lantreotide, its structure is given in (Fig. 8) (Pandit et al. 2008). This analogue was found to possess efficacy against enteropancreatic neuroendocrine tumor in the phase III study. This was also evaluated in Japanese population, by single arm study. Results of study suggested that lanreotide can be used as treatment option for patients suffering with neuroendocrine tumor (Ito et al. 2017).

Oxytocin

Oxytocin is one of the widely studied neuropeptide. It modulates social behavior of individuals. However the mechanism behind social bonding and affection via oxytocin are still not clear. A clinical study on male healthy volunteer has shown that oxytocin affects key center in brain for social cognition and introspective processing, the precuneus (Kumar et al. 2014). Another role of oxytocin is control of feeding behavior. Preclinical studies have shown that oxytocin acts on hypothalamus to limit food intake that is why it has the potential to control obesity. Clinical study of oxytocin in normal and obese young men has shown that oxytocin has a higher inhibitory effect on food intake in obese men in comparison to men with normal weights. From this type of action, this study suggests that oxytocin has the potential to control this metabolic disorder (Thienel et al. 2016).

Neurokinin B

It is a neuropeptide that acts via hypothalamus and it preferentially binds to the neurokinin 3 receptor. Preclinical studies in rodents suggest that NKB signaling mediates hot flushes in menopausal women. Therefore its effects were also evaluated in healthy women. Results suggested that administration of NKB in women may lead to hot flushes. However further studies are required to understand the role of NKB signaling in inhibition of hot flushes in menopausal women (Jayasena et al. 2015).

Conclusion

Neurons communicate information via different chemical signals. There are more than 100 different peptides; most of them evoke precise behavior (Ludwig 2011). Central nervous system integrates peripheral and autonomic signals to sense energy homeostasis and responds to them by releasing

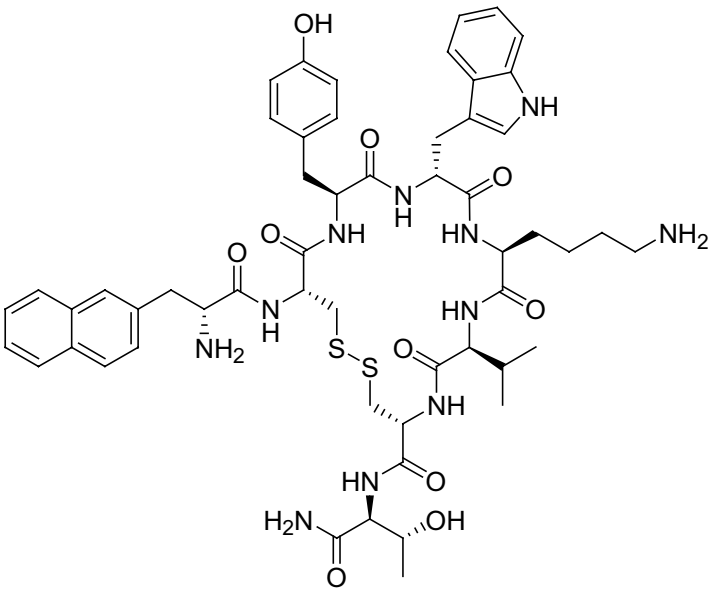

Fig. 8 Chemical structure of Lanreotide

neurotransmitters and neuropeptides (Maldonado-Ruiz et al. 2017). Instinctive behavior is controlled via limbic system, brainstem and hypothalamus. Studies on different appetite and energy homeostatis models in rodents suggest that hypothalamic neuropeptides are responsible for maintaining appetite. Some of these neuropeptides also influence locomotor or psychomotor activity in rodents (Matsuda et al. 2011). Neuropeptides along with some peptide hormones are involved in the regulation of most if not all physiological functions (Kunz, Chen et al. 2018). Most of neuropeptides are abundantly expressed in brain regions to control anxiety and emotional behavior (Lin 2012).That is why, in past few years, there has been a remarkable growth in the number of identified neuropeptides. There are about 3455 and 2406 neuropeptides in invertebrates and vertebrates in neuropeptide database, NeuroPep (Wang et al. 2015). During the past half century research related to neuropeptides has emerged at an enormous rate. These neuropeptides have opened the gates for designing new therapeutic strategies for the management of various neurological disorders (Nyberg and Hallberg 2011).

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Declarations

Conflict of interest There is no conflict of interest.

Ethical Approval Not applicable.

References

Argiolas A, Melis MR (2013) Neuropeptides and central control of sexual behaviour from the past to the present: a review. Prog Neurobiol 108:80–107

Augustyniak D, Nowak J, Lundy FT (2012) Direct and indirect antimicrobial activities of neuropeptides and their therapeutic potential. Curr Protein Pept Sci 13(8):723–738

Basso N, Terragno NA (2001) History about the discovery of the renin-angiotensin system. Hypertension 38(6):1246–1249

Bihel F, Humbert JP, Schneider S, Bertin I, Wagner P, Schmitt M, Laboureyras E, Petit-Demouliere B, Schneider E, Mollereau C, Simonnet G, Simonin F, Bourguignon JJ (2015) Development of a peptidomimetic antagonist of neuropeptide FF receptors for the prevention of opioid-induced hyperalgesia. ACS Chem Neurosci 6(3):438–445

Borbély É, Helyes Z (2017) Role of hemokinin-1 in health and disease. Neuropeptides 64:9–17

Burbach JP (2011) What are neuropeptides? Methods Mol Biol 789:1–36

Carter CS, Kenkel WM, MacLean EL, Wilson SR, Perkeybile AM, Yee JR, Ferris CF, Nazarloo HP, Porges SW, Davis JMJPR (2020) Is oxytocin "nature's medicine? Pharmacol Rev 72(4):829–861

Catalani E, De Palma C, Perrotta C, Cervia D (2017) Current evidence for a role of neuropeptides in the regulation of autophagy. Biomed Res Int 2017:5856071

Chang YJ, Burton T, Ha L, Huang Z, Olajubelo A, Li C (2015) Modulation of locomotion and reproduction by FLP neuropeptides in the nematode *Caenorhabditis elegans*. PLoS One 10(9):e0135164

Chowanski S, Lubawy J, Urbanski A, Rosinski G (2016) Cardioregulatory functions of neuropeptides and peptide hormones in insects. Protein Pept Lett 23(10):913–931

Christie AE, Stemmler EA, Dickinson PS (2010) Crustacean neuropeptides. Cell Mol Life Sci 67(24):4135–4169

Christie AE, Nolan DH, Ohno P, Hartline N, Lenz PH (2011) Identification of chelicerate neuropeptides using bioinformatics of publicly accessible expressed sequence tags. Gen Comp Endocrinol 170(1):144–155

Clynen E, Swijsen A, Raijmakers M, Hoogland G, Rigo JM (2014) Neuropeptides as targets for the development of anticonvulsant drugs. Mol Neurobiol 50(2):626–646

Comninos AN, Wall MB, Demetriou L, Shah AJ, Clarke SA, Narayanaswamy S, Nesbitt A, Izzi-Engbeaya C, Prague JK, Abbara A, Ratnasabapathy R, Salem V, Nijher GM, Jayasena CN, Tanner M, Bassett P, Mehta A, Rabiner EA, Honigsperger C, Silva MR, Brandtzaeg OK, Lundanes E, Wilson SR, Brown RC, Thomas SA, Bloom SR, Dhillo WS (2017) Kisspeptin modulates sexual and emotional brain processing in humans. J Clin Invest 127(2):709–719

da Silva L, Carvalho E, Cruz MT (2010) Role of neuropeptides in skin inflammation and its involvement in diabetic wound healing. Expert Opin Biol Ther 10(10):1427–1439

Dalvi PS, Belsham DD (2012) Glucagon-like peptide-2 directly regulates hypothalamic neurons expressing neuropeptides linked to appetite control in vivo and in vitro. Endocrinology 153(5):2385–2397

Dalvi PS, Nazarians-Armavil A, Purser MJ, Belsham DD (2012) Glucagon-like peptide-1 receptor agonist, exendin-4, regulates feeding-associated neuropeptides in hypothalamic neurons *in vivo* and *in vitro*. Endocrinology 153(5):2208–2222

De Wied D (1969) "Effects of peptide hormones on behavior. Front Neuroendocrinol 1:97

Decourt C, Robert V, Anger K, Galibert M, Madinier JB, Liu X, Dardente H, Lomet D, Delmas AF, Caraty A, Herbison AE, Anderson GM, Aucagne V, Beltramo M (2016) A synthetic kisspeptin analog that triggers ovulation and advances puberty. Sci Rep 6:26908

Derst C, Dircksen H, Meusemann K, Zhou X, Liu S, Predel R (2016) Evolution of neuropeptides in non-pterygote hexapods. BMC Evol Biol 16:51

Dudek M, Ziarniak K, Sliwowska JH (2018) Kisspeptin and metabolism: the brain and beyond. Front Endocrinol (Lausanne) 9:145

Durvasula RV, Shankland SJ (2006) The renin-angiotensin system in glomerular podocytes: mediator of glomerulosclerosis and link to hypertensive nephropathy. Curr Hypertens Rep 8(2):132–138

Elewa R, Makrantonaki E, Zouboulis CC (2013) Neuropeptides and skin aging. Horm Mol Biol Clin Investig 16(1):29–33

Elphick MR, Mirabeau O (2014) The evolution and variety of RFamide-type neuropeptides: insights from deuterostomian invertebrates. Front Endocrinol (lausanne) 5:93

Elphick MR, Achhala S, Martynyuk N (2013) The evolution and diversity of SALMFamide neuropeptides. PLoS One 8(3):e59076

Folkers K, Hörig J, Rampold G, Lane P, Rosell S, Björkroth UJACS (1982) Design and synthesis of effective antagonists of substance P. Acta Chem Scand 36:389–395

Fricker LD, Devi LA (2018) Orphan neuropeptides and receptors: Novel therapeutic targets. Pharmacol Ther 185:26–33

Funkelstein L, Beinfeld M, Minokadeh A, Zadina J, Hook V (2010) Unique biological function of cathepsin L in secretory vesicles for biosynthesis of neuropeptides. Neuropeptides 44(6):457–466

Gahete MD, Cordoba-Chacon J, Duran-Prado M, Malagon MM, Martinez-Fuentes AJ, Gracia-Navarro F, Luque RM, Castano JP

(2010) Somatostatin and its receptors from fish to mammals. Ann N Y Acad Sci 1200:43–52
Galoian K, Patel P (2017) Epigenetic control of cancer by neuropeptides. Biomed Rep 6(1):3–7
Garret C, Carruette A, Fardin V, Moussaoui S, Peyronel J-FO, Blanchard J-C, Laduron PM (1991) Pharmacological properties of a potent and selective nonpeptide substance P antagonist. Proc Natl Acad Sci U S A 88(22):10208–10212
Gesmundo I, Villanova T, Banfi D, Gamba G, Granata R (2017) Role of melatonin, Galanin, and RFamide neuropeptides QRFP26 and QRFP43 in the neuroendocrine control of pancreatic beta-cell function. Front Endocrinol (Lausanne) 8:143
Gouin SG, Murphy PV (2005) Synthesis of somatostatin mimetics based on the 1-deoxymannojirimycin scaffold. J Org Chem 70(21):8527–8532
Gruber CW (2014) Physiology of invertebrate oxytocin and vasopressin neuropeptides. Exp Physiol 99(1):55–61
Gui SH, Jiang HB, Smagghe G, Wang JJ (2017) The neuropeptides and protein hormones of the agricultural pest fruit fly Bactrocera dorsalis: What do we learn from the genome sequencing and tissue-specific transcriptomes? Peptides 98:29–34
Hallberg M (2015) Neuropeptides: metabolism to bioactive fragments and the pharmacology of their receptors. Med Res Rev 35(3):464–519
Hallberg M, Savmarker J, Hallberg A (2017) Angiotensin peptides as AT2 receptor agonists. Curr Protein Pept Sci 18(8):809–818
Hammami S, Mighri Z, Dooley CT, Nefzi A (2014) Synthesis and analgesic activity of alkylated, reduced and constrained oligoheterocyclic peptidomimetic analogs of Leu-enkephalin. Bioorg Med Chem Lett 24(18):4482–4485
Harris AG (1994) Somatostatin and somatostatin analogues: pharmacokinetics and pharmacodynamic effects. Gut 35(3 Suppl):S1-4
Hashimoto H, Uezono Y, Ueta Y (2012) Pathophysiological function of oxytocin secreted by neuropeptides: a mini review. Pathophysiology 19(4):283–298
Hökfelt T, Broberger C, Xu Z-QD, Sergeyev V, Ubink R, Diez MJN (2000) Neuropeptides—an overview. Neuropharmacology 39(8):1337–1356
Hökfelt T, Bartfai T, Bloom F (2003) Neuropeptides: opportunities for drug discovery. Lancet Neurol 2(8):463–472
Holden-Dye L, Walker RJ (2013) The roles of neuropeptides in *Caenorhabditis elegans* including their importance in the regulation of feeding and metabolism. Protein Pept Lett 20(6):636–646
Hosokawa Y, Kawakita R, Yokoya S, Ogata T, Ozono K, Arisaka O, Hasegawa Y, Kusuda S, Masue M, Nishibori H, Sairenchi T, Yorifuji T (2017) Efficacy and safety of octreotide for the treatment of congenital hyperinsulinism: a prospective, open-label clinical trial and an observational study in Japan using a nationwide registry. Endocr J 64(9):867–880
Hui L, Cunningham R, Zhang Z, Cao W, Jia C, Li L (2011) Discovery and characterization of the Crustacean hyperglycemic hormone precursor related peptides (CPRP) and orcokinin neuropeptides in the sinus glands of the blue crab *Callinectes sapidus* using multiple tandem mass spectrometry techniques. J Proteome Res 10(9):4219–4229
Ito T, Honma Y, Hijioka S, Kudo A, Fukutomi A, Nozaki A, Kimura Y, Motoi F, Isayama H, Komoto I, Hisamatsu S, Nakajima A, Shimatsu A (2017) Phase II study of lanreotide autogel in Japanese patients with unresectable or metastatic well-differentiated neuroendocrine tumors. Invest New Drugs 35(4):499–508
Jakobsson JE, Ma H, Lagerström MCJN (2019) Neuropeptide Y in itch regulation. Neuropeptides 78:101976
Jayasena CN, Abbara A, Comninos AN, Nijher GM, Christopoulos G, Narayanaswamy S, Izzi-Engbeaya C, Sridharan M, Mason AJ, Warwick J, Ashby D, Ghatei MA, Bloom SR, Carby A, Trew GH, Dhillo WS (2014a) Kisspeptin-54 triggers egg maturation in women undergoing in vitro fertilization. J Clin Invest 124(8):3667–3677
Jayasena CN, Comninos AN, Narayanaswamy S, Bhalla S, Abbara A, Ganiyu-Dada Z, Busbridge M, Ghatei MA, Bloom SR, Dhillo WS (2014b) Acute and chronic effects of kisspeptin-54 administration on GH, prolactin and TSH secretion in healthy women. Clin Endocrinol (oxf) 81(6):891–898
Jayasena CN, Comninos AN, Stefanopoulou E, Buckley A, Narayanaswamy S, Izzi-Engbeaya C, Abbara A, Ratnasabapathy R, Mogford J, Ng N, Sarang Z, Ghatei MA, Bloom SR, Hunter MS, Dhillo WS (2015) Neurokinin B administration induces hot flushes in women. Sci Rep 5:8466
Jones CE, Otara CB, Younan ND, Viles JH, Elphick MR (2014) Bioactivity and structural properties of chimeric analogs of the starfish SALMFamide neuropeptides S1 and S2. Biochim Biophys Acta 1844(10):1842–1850
Kahsai L, Kapan N, Dircksen H, Winther AM, Nassel DR (2010) Metabolic stress responses in Drosophila are modulated by brain neurosecretory cells that produce multiple neuropeptides. PLoS One 5(7):e11480
Karad SN, Pal M, Crowley RS, Prisinzano TE, Altman RA (2017) Synthesis and Opioid Activity of Tyr(1) -psi[(Z)CF=CH]-Gly(2) and Tyr(1) -psi[(S)/(R)-CF3 CH-NH]-Gly(2) Leu-enkephalin Fluorinated Peptidomimetics. ChemMedChem 12(8):571–576
Kask A, Harro J, von Horsten S, Redrobe JP, Dumont Y, Quirion R (2002) The neurocircuitry and receptor subtypes mediating anxiolytic-like effects of neuropeptide Y. Neurosci Biobehav Rev 26(3):259–283
Kastin AJ, Olson RD, Schally AV, Coy DH (1979) CNS effects of peripherally administered brain peptides. Life Sci 25(5):401–414
Kaur S, Bhararia A, Sharma K, Mittal S, Jain R, Wangoo N, Sharma RK (2016) Thyrotropin-releasing hormone loaded and chitosan engineered polymeric nanoparticles: towards effective delivery of neuropeptides. J Nanosci Nanotechnol 16(5):5324–5332
Kavaliers M, Choleris E (2011) Sociality, pathogen avoidance, and the neuropeptides oxytocin and arginine vasopressin. Psychol Sci 22(11):1367–1374
Kim DK, Cho EB, Moon MJ, Park S, Hwang JI, Do Rego JL, Vaudry H, Seong JY (2012) Molecular coevolution of neuropeptides gonadotropin-releasing hormone and kisspeptin with their cognate G protein-coupled receptors. Front Neurosci 6:3
Knickelbine JJ, Konop CJ, Viola IR, Rogers CB, Messinger LA, Vestling MM, Stretton AOW (2018) Different bioactive neuropeptides are expressed in two sub-classes of GABAergic RME nerve ring motorneurons in ascaris suum. ACS Chem Neurosci. https://doi.org/10.1021/acschemneuro.7b00450
Kokot F, Ficek R (1999) Effects of neuropeptide Y on appetite. Miner Electrolyte Metab 25(4–6):303–305
Konig S, Marco H, Gade G (2017) The hypertrehalosemic neuropeptides of cicadas are structural isomers-evidence by ion mobility mass spectrometry. Anal Bioanal Chem 409(27):6415–6420
Kormos V, Gaszner B (2013) Role of neuropeptides in anxiety, stress, and depression: from animals to humans. Neuropeptides 47(6):401–419
Kovac S, Walker MC (2013) Neuropeptides in epilepsy. Neuropeptides 47(6):467–475
Kumar J, Vollm B, Palaniyappan L (2014) Oxytocin affects the connectivity of the precuneus and the amygdala: a randomized, double-blinded, placebo-controlled neuroimaging trial. Int J Neuropsychopharmacol 18(5):pyu051
Kunz TO, Chen J, Wegener C (2018) Metabolic labeling to quantify drosophila neuropeptides and peptide hormones. Methods Mol Biol 1719:175–185
Li H, Kentish S, Wittert G, Page AJ (2018) "The role of neuropeptide W in energy homeostasis. Acta Physiol (Oxf) 222(1):e12884

Lin EJ (2012) Neuropeptides as therapeutic targets in anxiety disorders. Curr Pharm Des 18(35):5709–5727
Lipkowski AW, Misicka A, Carr DB, Ronsisvalle G, Kosson D, Bonney I (2004) "Neuropeptide mimetics for pain management. Pure Appl Chem 76(5):941–950
Liu Y, Lu D, Zhang Y, Li S, Liu X, Lin H (2010) The evolution of somatostatin in vertebrates. Gene 463(1–2):21–28
Lozić M, Šarenac O, Murphy D, Japundžić-Žigon N (2018) Vasopressin, central autonomic control and blood pressure regulation. Curr Hypertens Rep 20(2):1–7
Ludwig M (2011) Are neuropeptides brain hormones? J Neuroendocrinol 23(4):381–382
Magrill DS (1973) Phytate inhibition of enamel hardening by mineralizing solutions. J Dent Res 52(6):1342
Maldonado-Ruiz R, Fuentes-Mera L, Camacho A (2017) Central modulation of neuroinflammation by neuropeptides and energy-sensing hormones during obesity. Biomed Res Int 2017:7949582
Malpas SC, Ramchandra R, Guild SJ, McBryde F, Barrett CJ (2006) Renal sympathetic nerve activity in the development of hypertension. Curr Hypertens Rep 8(3):242–248
Marciniak P, Szymczak M, Pacholska-Bogalska J, Audsley N, Rosinski G (2013) Identification and localisation of selected myotropic neuropeptides in the ventral nerve cord of tenebrionid beetles. Comp Biochem Physiol A Mol Integr Physiol 166(1):44–51
Marcos-Contreras OA, Martinez de Lizarrondo S, Bardou I, Orset C, Pruvost M, Anfray A, Frigout Y, Hommet Y, Lebouvier L, Montaner J, Vivien D, Gauberti M (2016) Hyperfibrinolysis increases blood-brain barrier permeability by a plasmin- and bradykinin-dependent mechanism. Blood 128(20):2423–2434
Marks NJ, Maule AG (2010) Neuropeptides in helminths: occurrence and distribution. Adv Exp Med Biol 692:49–77
Mascarin A, Valverde IE, Vomstein S, Mindt TL (2015) 1,2,3-Triazole Stabilized Neurotensin-Based Radiopeptidomimetics for Improved Tumor Targeting. Bioconjug Chem 26(10):2143–2152
Masoumi J, Abbasloui M, Parvan R, Mohammadnejad D, Pavon-Djavid G, Barzegari A, Abdolalizadeh J (2018) Apelin, a promising target for Alzheimer disease prevention and treatment. Neuropeptides. https://doi.org/10.1016/j.npep.2018.05.008
Matsuda K, Kang KS, Sakashita A, Yahashi S, Vaudry H (2011) Behavioral effect of neuropeptides related to feeding regulation in fish. Ann N Y Acad Sci 1220:117–126
Mechenthaler I (2008) Galanin and the neuroendocrine axes. Cell Mol Life Sci 65(12):1826–1835
Menon N, Prabhavalkar KS, Bhatt LK (2017) Neuropeptides: a promising target for treating seizures. Neuropeptides 65:63–70
Merighi A, Salio C, Ferrini F, Lossi L (2011) Neuromodulatory function of neuropeptides in the normal CNS. J Chem Neuroanat 42(4):276–287
Mills EG, Izzi-Engbeaya C, Abbara A, Comninos AN, Dhillo WS (2021) Functions of galanin, spexin and kisspeptin in metabolism, mood and behaviour. Nat Rev Endocrinol 17(2):97–113
Misu R, Oishi S, Yamada A, Yamamura T, Matsuda F, Yamamoto K, Noguchi T, Ohno H, Okamura H, Ohkura S, Fujii N (2014) Development of novel neurokinin 3 receptor (NK3R) selective agonists with resistance to proteolytic degradation. J Med Chem 57(20):8646–8651
Moller C, Melaun C, Castillo C, Diaz ME, Renzelman CM, Estrada O, Kuch U, Lokey S, Mari F (2010) Functional hypervariability and gene diversity of cardioactive neuropeptides. J Biol Chem 285(52):40673–40680
Morimoto H, Murai M, Maeda Y, Hagiwara D, Miyake H, Matsuo M, Fujii T (1992) FR 113680: a novel tripeptide substance P antagonist with NK1 receptor selectivity. Br J Pharmacol 106(1):123–126
Mostafa GA, Bjorklund G, Urbina MA, Al-Ayadhi LY (2016) The levels of blood mercury and inflammatory-related neuropeptides in the serum are correlated in children with autism spectrum disorder. Metab Brain Dis 31(3):593–599
Navarro VM (2013) Interactions between kisspeptins and neurokinin B. Adv Exp Med Biol 784:325–347
Newton CL, Anderson RC, Millar RP (2016) Therapeutic neuroendocrine agonist and antagonist analogs of hypothalamic neuropeptides as modulators of the hypothalamic-pituitary-gonadal axis. Endocr Dev 30:106–129
Nixon JP, Kotz CM, Novak CM, Billington CJ, Teske JA (2012) Neuropeptides controlling energy balance: orexins and neuromedins. Handb Exp Pharmacol. https://doi.org/10.1007/978-3-642-24716-3_4
Nyberg F, Hallberg M (2011) Localization of neuropeptides by radioimmunoassay. Methods Mol Biol 789:191–201
Palkhiwala SA, Frishman WH, Warshafsky S (2001) Bradykinin for the treatment of cardiovascular disease. Heart Dis 3(5):333–339
Pandit A, Fay N, Bordes L, Valéry C, Cherif-Cheikh R, Robert B, Artzner F, Paternostre M (2008) Self-assembly of the octapeptide lanreotide and lanreotide-based derivatives: the role of the aromatic residues. J Pept Sci 14(1):66–75
Parker JA, Bloom SR (2012) Hypothalamic neuropeptides and the regulation of appetite. Neuropharmacology 63(1):18–30
Portelli J, Michotte Y, Smolders I (2012) Ghrelin: an emerging new anticonvulsant neuropeptide. Epilepsia 53(4):585–595
Prokai-Tatrai K, Prokai L (2011) Prodrug design for brain delivery of small- and medium-sized neuropeptides. Methods Mol Biol 789:313–336
Qaiser F, Wahab F, Wiqar MA, Hashim R, Leprince J, Vaudry H, Tena-Sempere M, Shahab M (2012) Study of the role of novel RF-amide neuropeptides in affecting growth hormone secretion in a representative non-human primate (*Macaca mulatta*). Endocrine 42(3):658–663
Quillet R, Ayachi S, Bihel F, Elhabazi K, Ilien B, Simonin F (2016) RF-amide neuropeptides and their receptors in mammals: pharmacological properties, drug development and main physiological functions. Pharmacol Ther 160:84–132
Rebillard G, Carlier E, Rebillard M, Pujol R (1977) Enhancement of visual responses on the primary auditory cortex of the cat after an early destruction of cochlear receptors. Brain Res 129(1):162–164
Reglodi D, Renaud J, Tamas A, Tizabi Y, Socias SB, Del-Bel E, Raisman-Vozari R (2017) Novel tactics for neuroprotection in Parkinson's disease: Role of antibiotics, polyphenols and neuropeptides. Prog Neurobiol 155:120–148
Riesco N, Cernuda-Morollon E, Pascual J (2017) Neuropeptides as a Marker for Chronic Headache. Curr Pain Headache Rep 21(4):18
Robertson CR, Flynn SP, White HS, Bulaj G (2011) Anticonvulsant neuropeptides as drug leads for neurological diseases. Nat Prod Rep 28(4):741–762
Rosen T, Seeger TF, McLean S, Desai MC, Guarino KJ, Bryce D, Pratt K, Heym J, Chalabi PM (1993) Synthesis, in vitro binding profile, and autoradiographic analysis of [3H]-cis-3-[(2-methoxybenzyl) amino]-2-phenylpiperidine, a highly potent and selective nonpeptide substance P receptor antagonist radioligand. J Med Chem 36(21):3197–3201
Russo AF (2017) Overview of neuropeptides: awakening the senses? Headache 57(Suppl 2):37–46
Saavedra JM (2005) Brain angiotensin II: new developments, unanswered questions and therapeutic opportunities. Cell Mol Neurobiol 25(3–4):485–512
Saidi M, Beaudry F (2015) Liquid chromatography-electrospray linear ion trap mass spectrometry analysis of targeted neuropeptides in Tac1(-/-) mouse spinal cords reveals significant lower concentration of opioid peptides. Neuropeptides 52:79–87
Saidi M, Beaudry F (2017) Targeted high-resolution quadrupole-Orbitrap mass spectrometry analyses reveal a significant reduction

of tachykinin and opioid neuropeptides level in PC1 and PC2 mutant mouse spinal cords. Neuropeptides 65:37–44
Sanchez-de-la-Torre M, Barcelo A, Pierola J, Esquinas C, de la Pena M, Duran-Cantolla J, Capote F, Masa JF, Marin JM, Vila M, Cao G, Martinez M, de Lecea L, Gozal D, Montserrat JM, Barbe F (2011) Plasma levels of neuropeptides and metabolic hormones, and sleepiness in obstructive sleep apnea. Respir Med 105(12):1954–1960
Schoofs L, De Loof A, Van Hiel MB (2017) Neuropeptides as regulators of behavior in insects. Annu Rev Entomol 62:35–52
Singh PK, Maji SK (2012) Amyloid-like fibril formation by tachykinin neuropeptides and its relevance to amyloid beta-protein aggregation and toxicity. Cell Biochem Biophys 64(1):29–44
Sivertsen B, Lang M, Frimurer TM, Holliday ND, Bach A, Els S, Engelstoft MS, Petersen PS, Madsen AN, Schwartz TW, Beck-Sickinger AG, Holst B (2011) Unique interaction pattern for a functionally biased ghrelin receptor agonist. J Biol Chem 286(23):20845–20860
Smith AB 3rd, Charnley AK, Hirschmann R (2011) Pyrrolinone-based peptidomimetics. "Let the enzyme or receptor be the judge." Acc Chem Res 44(3):180–193
Snider RM, Constantine JW, Lowe JA, Longo KP, Lebel WS, Woody HA, Drozda SE, Desai MC, Vinick FJ, Spencer RW (1991) A potent nonpeptide antagonist of the substance P (NK1) receptor. Science 251(4992):435–437
Stemmler EA, Barton EE, Esonu OK, Polasky DA, Onderko LL, Bergeron AB, Christie AE, Dickinson PS (2013) C-terminal methylation of truncated neuropeptides: an enzyme-assisted extraction artifact involving methanol. Peptides 46:108–125
Strand FL (1999) Neuropeptides: regulators of physiological processes. MIT press, Cambridge
Tajti J, Szok D, Majlath Z, Tuka B, Csati A, Vecsei L (2015) Migraine and neuropeptides. Neuropeptides 52:19–30
Thienel M, Fritsche A, Heinrichs M, Peter A, Ewers M, Lehnert H, Born J, Hallschmid M (2016) Oxytocin's inhibitory effect on food intake is stronger in obese than normal-weight men. Int J Obes (lond) 40(11):1707–1714
Tohyama M (1992) An overview of the ontogeny of neurotransmitters and neuromodulators in the central nervous system. In: Tohyama M (ed) Handbook of chemical neuroanatomy. Elsevier, Amsterdam, pp 647–650
Tsutsui K (2016) How to contribute to the progress of neuroendocrinology: New insights from discovering novel neuropeptides and neurosteroids regulating pituitary and brain functions. Gen Comp Endocrinol 227:3–15
Urbanski A, Lubawy J, Marciniak P, Rosinski G (2018) Myotropic activity and immunolocalization of selected neuropeptides of the burying beetle *Nicrophorus vespilloides* (Coleoptera: Silphidae). Insect Sci. https://doi.org/10.1111/1744-7917.12569
Valverde IE, Huxol E, Mindt TL (2014) Radiolabeled antagonistic bombesin peptidomimetics for tumor targeting. J Labelled Comp Radiopharm 57(4):275–278
Van Dam D, Van Dijck A, Janssen L, De Deyn PP (2013) Neuropeptides in Alzheimer's disease: from pathophysiological mechanisms to therapeutic opportunities. Curr Alzheimer Res 10(5):449–468
Van CT, Nennstiel D, Scherkenbeck J (2015) "Macrocyclic analogues of the diuretic insect neuropeptide helicokinin I show strong receptor-binding. Bioorg Med Chem 23(13):3278–3286
Vargas-Martinez F, Uvnas-Moberg K, Petersson M, Olausson HA, Jimenez-Estrada I (2014) Neuropeptides as neuroprotective agents: oxytocin a forefront developmental player in the mammalian brain. Prog Neurobiol 123C:37–78
Veronesi MC, Kubek DJ, Kubek MJ (2011) Intranasal delivery of neuropeptides. Methods Mol Biol 789:303–312
Wang Y, Wang M, Yin S, Jang R, Wang J, Xue Z, Xu T (2015) NeuroPep: a comprehensive resource of neuropeptides. Database (Oxford). https://doi.org/10.1093/database/bav038
Wassmann S, Nickenig G (2006) Pathophysiological regulation of the AT1-receptor and implications for vascular disease. J Hypertens Suppl 24(1):S15-21