Title
Editorial: Neuropeptide GPCRs in neuroendocrinology, Volume II.

Permalink
https://escholarship.org/uc/item/2gc5n90m

Authors
Vaudry, Hubert
Schoofs, Liliane
Civelli, Olivier
et al.

Publication Date
2023

DOI
10.3389/fendo.2023.1219530

Peer reviewed

Editorial: Neuropeptide GPCRs in neuroendocrinology, Volume II

Hubert Vaudry[1]*, Liliane Schoofs[2], Olivier Civelli[3] and Masayasu Kojima[4]

[1]Institute of Biomedical Research and Innovation, University of Rouen Normandy, Mont-Saint-Aignan, France, [2]Department of Biology, KU Leuven, Leuven, Belgium, [3]Department of Pharmaceutical Sciences, University of California, Irvine, Irvine, CA, United States, [4]Institute of Life Science, Kurume University, Fukuoka, Japan

KEYWORDS

neuropeptides, G protein-coupled receptors, biologically active peptides, signaling mechanisms, neuroendocrine communication

---

Editorial on the Research Topic
Neuropeptide GPCRs in neuroendocrinology, Volume II

Neuropeptides are the largest and most diverse class of neuromediators in the central and peripheral nervous systems. They play multiple roles in the control of various biological functions including feeding, reproduction, development, growth, learning, nociception, stress coping, thermoregulation, osmoregulation, and a vast array of behaviors. Most neuropeptides exert their activities through G protein-coupled receptors (GPCRs), which represent the largest family of cell membrane receptors. Neuropeptide signaling is phylogenetically conserved throughout the animal kingdom from cnidarians to mammals. Not surprisingly, neuropeptides and their GPCRs are implicated in a number of pathologies such as obesity, infertility, stunting, pain, narcolepsy, diabetes insipidus, gastrointestinal diseases and mood disorders. Therefore, drugs targeting neuropeptide GPCRs have strong potential for the development of novel therapeutic agents.

To celebrate the 10th anniversary of the Nobel Prize awarded to Robert J. Lefkowitz and Brian K. Kobilka for their seminal discoveries of the inner working of GPCRs, this Research Topic is aimed at gathering a bouquet of 27 review papers and original articles, written by prominent scientists in this fast-evolving field, that illustrate the crucial role of neuropeptide GPCRs in neuroendocrinology.

Ghrelin is a 28-amino acid acylated peptide, initially isolated from the rat stomach, that stimulates growth hormone (GH) release from pituitary cells through activation of a GPCR, the GH secretagogue receptor (GHSR) (1). Central and peripheral administration of ghrelin stimulates food intake and increases body weight (2). Hassouna et al. now show that, in adult female, but not in male mice, preproghrelin gene deletion markedly attenuates pulsatile GH secretion. Surprisingly, however, in *Ghrl*$^{-/-}$ mice, food consumption and body weight are unaltered. The lateral parabrachial nucleus (lPBN) includes a population of anorexic neurons (3) and abundantly expresses GHSR mRNA (4). Le May et al. report that selective silencing of GHSR-positive cells of the lPBN inhibits food intake and reduces fat weight, indicating that these GHSR-expressing cells are involved in hyperphagia and weight gain. It has recently been reported that a peptide called liver-expressed antimicrobial peptide 2 (LEAP-2) acts as a natural antagonist of GHSR1a (5). The review by Lu et al. discusses the mechanism of action

of LEAP-2 both as an inverse agonist and antagonist of GHSR1a, and the potential applications of this novel peptide in various pathologies including obesity.

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP) are two related peptides that act via three GPCRs i.e. the PACAP-specific receptor PAC1 and the VIP/PACAP mutual receptors VPAC1 and VPAC2 (6). Consistent with the widespread distribution of these receptors in the central nervous system (CNS) and in peripheral organs, VIP and PACAP exert a large array of biological activities (7). Ago et al. review the evidence linking VIP2 microduplication to schizophrenia and other psychiatric disorders. They propose that excessive VPAC2 signaling disrupts maturation of certain brain structures including the prefrontal cortex. It has been previously reported that PACAP knock-out ($Pacap^{-/-}$) mice exhibit behavioral abnormalities including hyperlocomotor activity and deficit in prepulse inhibition (8) that are reversed by $5\text{-}HT_{2A}$ receptor antagonists (9). Here, Hayata-Takano et al. show that PACAP-PAC1 signaling induces internalization of $5\text{-}HT_{2A}$ receptors in transfected cells and that $Pacap^{-/-}$ mice exhibit an increase of $5HT_{2A}$ levels on cell membranes in the frontal cortex, suggesting that the PAC1 receptor could be a target for the treatment of some psychiatric disorders. VIP/VPAC2 signaling plays a crucial role in the control of the circadian clock in the suprachiasmatic nucleus (SCN) (10). Since thyroid cells possess a circadian clock (11), Georg et al. have investigated the possible impact of VIP/VPAC2 signaling in the expression of thyroid clock genes. The data indicate that the thyroid clock is largely independent from the master SCN clock. The neurotrophic and neuroprotective effects of VIP and PACAP are partly mediated by a glial protein termed activity-dependent neuroprotective protein (ADNP) (12). In an Opinion paper, Gozes and Shazman discuss the possible involvement of ADNP gene mutations at protease cleavage sites in autism and Alzheimer's disease.

Gonadotropin inhibitory hormone (GnIH) is a C-terminally amidated dodecapeptide initially isolated from the quail brain on the basis of its ability to inhibit gonadotropin release (13). The mammalian orthologue of GnIH is generally called RFRP-3. The effects of GnIH and its orthologues are mediated via activation of GPR147, also named GnIH-R (14). The review by Bédécarrats et al. summarizes the multiple actions of the GnIH/GnIH-R signaling system not only on reproductive functions but also on the regulation of energy homeostasis, stress response and thyroid hormone secretion. A sister review by Teo et al. focuses on the involvement of GnIH on biological rhythms, stress response and social behaviors. Taken together, these review articles illustrate the numerous activities of this fascinating peptide.

Melanocortin receptors (MCRs) constitute a family of five GPCRs with multiple physiological functions (15). The activity of MCRs is regulated by two melanocortin receptor accessory proteins, MRAP1 and MRAP2 that form heterodimers with MC2R (16) and possibly with MC3R and MC4R (17). In a hypothesis and theory article, Dores and Chapa describe the phylogenetic evolution of MC2R and its essential accessory player MRAP1. Since MRAPs function as antiparalelled homodimers, Wang et al. have investigated the internal symmetry of the MRAP2 homodimer. Their study reveals the importance of the orientation of the various domains of MRAP2 in the activity of MC4R.

The oxytocin (OT) and vasotocin (VT) genes derive from a common ancestral gene that existed before the emergence of vertebrates (18). The actions of OT and VT are mediated through a series of GPCRs (OTR and VTR) whose genes also arose from a common ancestor (19). Ocampo Daza et al. have conducted synteny analyses to elucidate the phylogenetic history of OTR and VTR in jawed vertebrates. Their data led them to recommend a rational nomenclature for OTR and VTR genes that differs from that recently proposed by Theofanopoulou et al. (20).

Apelin is a 36-amino acid peptide that counteracts the antidiuretic action of vasopressin (21). The apelin receptor APJ and the angiotensin receptor AT1 are two GPCRs which display 31% sequence identify (22). The review by Girault-Sotias et al. analyses the opposite actions of apelin and vasopressin in the control of diuresis and discusses the therapeutic potential of apelin agonists for the treatment of the syndrome of inappropriate antidiuresis.

Motilin (MLN) is a 22-amino acid peptide, isolated half a century ago from the porcine gastro-intestinal tract (23), that acts via activation of a GPCR called MLN-R. In a comparative perspective, Kitazawa and Kaiya review the current knowledge regarding the structure, distribution and biological activities of MLN and MLN-R in various vertebrate species from fish to mammals.

Bombesin (Bn) is a member of a family of bioactive peptides that also includes neuromedin B (NMB) and gastrin-releasing peptide (GRP) (24). These peptides act though three types of GPCRs i.e. the NMB receptor (NMBR), the GRP receptor (GRPR) and the Bn-receptor subtype 3 (BRS-3) now renamed by NC-IUPHAR BB1, BB2 and BB3, respectively (25). Moody et al. recapitulate the evidence that Bn-related peptides and their receptors are frequently overexpressed in a number of tumor cells, suggesting their potential for imaging and/or targeted therapy of neural tumors.

Corticotropin-releasing hormone (CRH) was initially characterized in the hypothalamus based on its ability to stimulate the release of adrenocorticotropin from pituitary corticotrope cells (26). It was later reported that CRH and/or CRH-related peptides are also present in peripheral organs, notably in the skin, immune system and reproductive organs (27). In their mini-review, Kassotaki et al. make a focus on the role of placenta CRH on fetal neurodevelopment and the control of the length of pregnancy.

Neuromedin U (NMU) and neuromedin S (NMS) are two structurally related peptides whose actions are mediated by two mutual GPCRs, i.e. NMUR1 and NMUR2 (28). Malendowicz and Rucinski provide a comprehensive review on the anatomical distribution of NMU, NMS and their receptors, and the biological and pharmacological activities of these peptidergic systems.

Orphanin FQ/nociceptin is a 17-amino acid peptide identified, via a reverse pharmacology approach, as the ligand of a GPCR that displays sequence similarity to opioid receptors (29, 30). This GPCR, now named NOP receptor, mediates pain transmission and is involved in various physiological and behavioral effects notably on locomotor activity (31). In order to develop novel analgesic compounds, Azevedo Neto et al. investigated the differential effects of NOP biased agonists on nociception vs locomotion. In normal mice, none of the NOP agonists tested exhibit functional selectivity on antinociception vs motor impairment.

Nesfatin-1, an 82-amino acid polypeptide derived from the processing of nucleobindin-2, was initially characterized for its anorexigenic activity (32). Since then, nesfatin-1 has been found to exert pleiotropic effects in the CNS and in peripheral organs (33). Here, Rupp et al. provide a comprehensive review of the multiple neuroendocrine systems and signaling pathways recruited by nesfatin-1. They point out the urgent necessity of identifying the nesfatin-1 receptor which, so far, remained elusive.

Pulsatile release of gonadotropin-releasing hormone (GnRH) is essential for normal reproductive functions (34). Uenoyama et al. describe the pivotal role of a set of neurons expressing kisspeptin, neurokinin B and dynorphin (KNDy neurons), located in the arcuate nucleus of the hypothalamus, in the control of episodic and surge secretion of GnRH. They also call attention to species and sex differences in the functioning of this GnRH pulse generator.

Processing of the neurotensin (NTS) precursor can generate a mature form of 13 amino acids and an extended form of 163 amino acids called long form NTS (LF NTS) (35). Elevated levels of LF NTS in plasma predict the incidence of diabetes and cardiovascular disease in the elderly population (36). Wu et al. have thus developed a monoclonal antibody against LF NTS. Their results show that, in mice subjected to high-fat diet, this antibody has the potential to reduce body weight and adipocyte volume.

Prokineticins (PKs) are two secreted polypeptides involved in the control of several neuroendocrine functions including reproduction, feeding behavior and circadian rhythms. The effects of PKs are mediated through activation of two GPCRs designated PKR1 and PKR2 (37). Verdinez and Sebag have identified two N-linked glycosylation positions within the N-terminal domain of PKR2 which are essential for its plasma membrane targeting and Gαs signaling.

The hypothalamo-pituitary-thyroid axis (HPT) plays a pivotal role in the control of energy homeostasis. The activity of the HPT is primarily regulated by the neuropeptide thyrotropin-releasing hormone (TRH) and its cognate GPCR expressed by pituitary thyrotrope cells (38). In their review article, Parra-Mones de Oca et al. focus on sex dimorphism in the control of the HPT activity not only resulting from sex steroids but also from differences in diet, physical activity and differential response to stress.

It is now widely accepted that many neuropeptide GPCRs have an ancient evolutionary origin and that several vertebrate GPCRs have orthologs in protostomian phyla, such as arthropods, nematodes, mollusks and annelids, among others (39). The evolutionary investigation of Li et al. shows the presence of galanin receptor (GALR)-like genes in a cephalopod mollusk and challenges the widely accepted paradigm that allatostatin-A (AST-A)/buccalin receptors are the orthologues of vertebrate GALRs in protostomes. The data further reveal that the three allatostatin peptide-receptor systems have a broad tissue distribution in bivalves and that the allatostatin-C neuropeptide system might be involved in the animal's immune response.

Alexander et al. investigated pigment dispersing neuropeptide hormones (PDH) in the crustacean model *Carcinus maenas*, and found that 4 PDH isoforms preferentially activate two distinct PDH receptors. In addition, the study unveils a previously undescribed neurohaemal area in one of the eyestalk retractor muscles of the crab, likely to be involved in photic adaptation. The anatomical distribution of each of the four PDH neuropeptides and their GPCRs suggests distinct functions as secreted hormones and/or neuromodulators.

In insects, various hormones act upon the Malpighian tubules via a variety of GPCRs linked to second messenger systems that influence ion transporters and aquaporins; thereby regulating fluid secretion. The study of Orchard et al. reviews the current knowledge on the neuroendocrine control of diuresis and provides the reader with new insights from an in-depth transcriptome analysis of the Malpighian tubules of fed and unfed Rhodnius prolixus (kissing bug). Of particular interest is the presence of GPCR transcripts for which the role in Malpighian tubule physiology is currently unknown. As such, this study illustrates that Malpighian tubules are much more than transporting epithelia, hereby paving the way for future GPCR research.

Since about half of the most sold drugs for humans act on GPCRs, neuropeptide GPCRs have been accepted as highly druggable targets and this drug discovery potential is being extended to alternative insect pest and nematode-control strategies (40). Parasitic nematodes cause substantial morbidity and mortality in animals and people and major losses to food production. Atkinson et al. thus made use of elegant *in silico* approaches to develop a nematode drug target prioritization pipeline that highlights the most promising nematode neuropeptide GPCRs as candidate targets for parasitic control.

In summary, 27 articles addressing a variety of facets of neuropeptide GPCRs are enclosed in the present Research Topic. This collection of papers illustrates the multiple functions and therapeutical applications of neuropeptide GPCRs in neuroendocrinology. It also highlights the challenges that remain to be taken up for the next decade. It is our hope that the readers will enjoy reading these papers, and that this Research Topic will become a major set of references for all researchers involved in this rapidly expanding field.

Author contributions

HV and LS wrote the first draft of the manuscript. OC and MK provided revisions that were incorporated by HV. All authors have read and approved the final manuscript.

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* (1999) 402:656–60. doi: 10.1038/45230

2. Tschöp M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. *Nature* (2000) 407:908–13. doi: 10.1038/35038090

3. Wu Q, Boyle MP, Palmiter RD. Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. *Cell* (2009) 137:1225–34. doi: 10.1016/j.cell.2009.04.022

4. Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK. Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J Comp Neurol* (2006) 494:528–48. doi: 10.1002/cne.20823

5. Ge X, Yang H, Bednarek MA, Galon-Tilleman H, Chen P, Chen M, et al. LEAP2 is an endogenous antagonist of the ghrelin receptor. *Cell Metab* (2018) 27:461–9.e6. doi: 10.1016/j.cmet.2017.10.016

6. Harmar AJ, Fahrenkrug J, Gozes I, Laburthe M, May V, Pisegna JR, et al. Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR review 1. *Br J Pharmacol* (2012) 166:4–17. doi: 10.1111/j.1476-5381.2012.01871.x

7. Vaudry D, Falluel-Morel A, Bourgault S, Basille M, Burel D, Wurtz O, et al. Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. *Pharmacol Rev* (2009) 61:283–357. doi: 10.1124/pr.109.001370

8. Hashimoto H, Shintani N, Tanaka K, Mori W, Hirose M, Matsuda T, et al. Altered psychomotor behaviors in mice lacking pituitary adenylate cyclase-activating polypeptide (PACAP). *Proc Natl Acad Sci USA* (2001) 98:13355–60. doi: 10.1073/pnas.231094498

9. Hashimoto R, Hashimoto H, Shintani N, Chiba S, Hattori S, Okada T, et al. Pituitary adenylate cyclase-activating polypeptide is associated with schizophrenia. *Mol Psychiatry* (2007) 12:1026–32. doi: 10.1038/sj.mp.4001982

10. Aton SJ, Colwell CS, Harmar AJ, Waschek J, Herzog ED. Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons. *Nat Neurosci* (2005) 8:476–83. doi: 10.1038/nn1419

11. Fahrenkrug J, Georg B, Hannibal J, Jørgensen HL. Hypophysectomy abolishes rhythms in rat thyroid hormones but not in the thyroid clock. *J Endocrinol* (2017) 233:209–16. doi: 10.1530/JOE-17-0111

12. Gozes I, Divinsky I, Pilzer I, Fridkin M, Brenneman DE, Spier AD. From vasoactive intestinal peptide (VIP) through activity-dependent neuroprotective protein (ADNP) to NAP: a view of neuroprotection and cell division. *J Mol Neurosci* (2003) 20:315–22. doi: 10.1385/JMN:20:3:315

13. Tsutsui K, Saigoh E, Ukena K, Teranishi H, Fujisawa Y, Kikuchi M, et al. A novel avian hypothalamic peptide inhibiting gonadotropin release. *Biochem Biophys Res Commun* (2000) 275:661–7. doi: 10.1006/bbrc.2000.3350

14. Ubuka T, Kim S, Huang Y, Reid J, Jiang J, Osugi T, et al. Gonadotropin-inhibitory hormone neurons interact directly with gonadotropin-releasing hormone-I and -II neurons in European starling brain. *Endocrinology* (2008) 149:268–78. doi: 10.1210/en.2007-0983

15. Cone RD. Studies on the physiological functions of the melanocortin system. *Endocr Rev* (2006) 27:736–49. doi: 10.1210/er.2006-0034

16. Metherell LA, Chapple JP, Cooray S, David A, Becker C, Rüschendorf F, et al. Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2. *Nat Genet* (2005) 37:166–70. doi: 10.1038/ng1501

17. Ji R-L, Tao Y-X. Regulation of melanocortin-3 and -4 receptors by isoforms of melanocortin-2 receptor accessory protein 1 and 2. *Biomolecules* (2022) 12:244. doi: 10.3390/biom12020244

18. Gwee P-C, Tay B-H, Brenner S, Venkatesh B. Characterization of the neurohypophysial hormone gene loci in elephant shark and the Japanese lamprey: origin of the vertebrate neurohypophysial hormone genes. *BMC Evol Biol* (2009) 9:47. doi: 10.1186/1471-2148-9-47

19. Mayasich SA, Clarke BL. Vasotocin and the origins of the vasopressin/oxytocin receptor gene family. *Vitam Horm* (2020) 113:1–27. doi: 10.1016/bs.vh.2019.08.018

20. Theofanopoulou C, Gedman G, Cahill JA, Boeckx C, Jarvis ED. Universal nomenclature for oxytocin-vasotocin ligand and receptor families. *Nature* (2021) 592:747–55. doi: 10.1038/s41586-020-03040-7

21. De Mota N, Reaux-Le Goazigo A, El Messari S, Chartrel N, Roesch D, Dujardin C, et al. Apelin, a potent diuretic neuropeptide counteracting vasopressin actions through inhibition of vasopressin neuron activity and vasopressin release. *Proc Natl Acad Sci USA* (2004) 101:10464–9. doi: 10.1073/pnas.0403518101

22. O'Dowd BF, Heiber M, Chan A, Heng HH, Tsui LC, Kennedy JL, et al. A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. *Gene* (1993) 136:355–60. doi: 10.1016/0378-1119(93)90495-o

23. Brown JC, Cook MA, Dryburgh JR. Motilin, a gastric motor activity stimulating polypeptide: the complete amino acid sequence. *Can J Biochem* (1973) 51:533–7. doi: 10.1139/o73-066

24. Gonzalez N, Moody TW, Igarashi H, Ito T, Jensen RT. Bombesin-related peptides and their receptors: recent advances in their role in physiology and disease states. *Curr Opin Endocrinol Diabetes Obes* (2008) 15:58–64. doi: 10.1097/MED.0b013e3282f3709b

25. Alexander SPH, Christopoulos A, Davenport AP, Kelly E, Mathie A, Peters JA, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. *Br J Pharmacol* (2019) 176(Suppl 1):S21–141. doi: 10.1111/bph.14748

26. Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* (1981) 213:1394–7. doi: 10.1126/science.6267699

27. Kalantaridou S, Makrigiannakis A, Zoumakis E, Chrousos GP. Peripheral corticotropin-releasing hormone is produced in the immune and reproductive systems: actions, potential roles and clinical implications. *Front Biosci* (2007) 12:572–80. doi: 10.2741/2083

28. Al-hosaini K, Bloom SR, Hedrick J, Howard A, Jethwa P, Luckman S, et al. Neuromedin U receptors (version 2019.4) in the IUPHAR/BPS guide to pharmacology database. *GtoPdb CITE* (2019) 2019:1–11. doi: 10.2218/gtopdb/F42/2019.4

29. Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, et al. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. *Nature* (1995) 377:532–5. doi: 10.1038/377532a0

30. Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, et al. Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. *Science* (1995) 270:792–4. doi: 10.1126/science.270.5237.792

31. Reinscheid RK, Civelli O. The history of N/OFQ and the NOP receptor. *Handb Exp Pharmacol* (2019) 254:3–16. doi: 10.1007/164_2018_195

32. Oh-I S, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K, et al. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. *Nature* (2006) 443:709–12. doi: 10.1038/nature05162

33. Leung AK-W, Ramesh N, Vogel C, Unniappan S. Nucleobindins and encoded peptides: from cell signaling to physiology. *Adv Protein Chem Struct Biol* (2019) 116:91–133. doi: 10.1016/bs.apcsb.2019.02.001

34. Goodman RL, Herbison AE, Lehman MN, Navarro VM. Neuroendocrine control of gonadotropin-releasing hormone: pulsatile and surge modes of secretion. *J Neuroendocrinol* (2022) 34:e13094. doi: 10.1111/jne.13094

35. Friry C, Feliciangeli S, Richard F, Kitabgi P, Rovere C. Production of recombinant large proneurotensin/neuromedin N-derived peptides and characterization of their binding and biological activity. *Biochem Biophys Res Commun* (2002) 290:1161–8. doi: 10.1006/bbrc.2001.6308

36. Fawad A, Bergmann A, Struck J, Nilsson PM, Orho-Melander M, Melander O. Proneurotensin predicts cardiovascular disease in an elderly population. *J Clin Endocrinol Metab* (2018) 103:1940–7. doi: 10.1210/jc.2017-02424

37. Negri L, Lattanzi R, Giannini E, Melchiorri P. Bv8/Prokineticin proteins and their receptors. *Life Sci* (2007) 81:1103–16. doi: 10.1016/j.lfs.2007.08.011

38. Ortiga-Carvalho TM, Chiamolera MI, Pazos-Moura CC, Wondisford FE. Hypothalamus-pituitary-thyroid axis. *Compr Physiol* (2016) 6:1387–428. doi: 10.1002/cphy.c150027

39. Grimmelikhuijzen CJP, Hauser F. Mini-review: the evolution of neuropeptide signaling. *Regul Peptides* (2012) 177:S6–9. doi: 10.1016/j.regpep.2012.05.001

40. Birgül Iyison N, Shahraki A, Kahveci K, Düzgün MB, Gün G. Are insect GPCRs ideal next-generation pesticides: opportunities and challenges. *FEBS J* (2021) 288:2727–45. doi: 10.1111/febs.15708