Received: 19 September 2022 | Revised: 11 November 2022 | Accepted: 30 November 2022

DOI: 10.1111/jne.13224

REVIEW ARTICLE

Journal of Neuroendocrinology WILEY

Toward a consensus nomenclature for ghrelin, its non-acylated form, liver expressed antimicrobial peptide 2 and growth hormone secretagogue receptor

Mario Perelló[1] | Suzanne L. Dickson[2] | Jeffrey M. Zigman[3] | Lorenzo Leggio[4] | on behalf of The Ghrelin Nomenclature Consensus Group

[1]Grupo de Neurofisiología, Instituto Multidisciplinario de Biología Celular (IMBICE), Universidad Nacional La Plata (UNLP), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) y Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CIC-PBA), La Plata, Argentina

[2]Department of Physiology/Endocrine, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

[3]Center for Hypothalamic Research, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA

[4]Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, Translational Addiction Medicine Branch, National Institute on Drug Abuse Intramural Research Program and National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research, National Institutes of Health, Baltimore, MD, USA

Correspondence
Mario Perelló, Laboratory of Neurophysiology, IMBICE, Calle 526 S/N entre 10 y 11, La Plata (1900), Buenos Aires, Argentina.
Email: mperello@imbice.gov.ar

Abstract

The stomach-derived octanoylated peptide ghrelin was discovered in 1999 and recognized as an endogenous agonist of the growth hormone secretagogue receptor (GHSR). Subsequently, ghrelin has been shown to play key roles in controlling not only growth hormone secretion, but also a variety of other physiological functions including, but not limited to, food intake, reward-related behaviors, glucose homeostasis and gastrointestinal tract motility. Importantly, a non-acylated form of ghrelin, desacyl-ghrelin, can also be detected in biological samples. Desacyl-ghrelin, however, does not bind to GHSR at physiological levels, and its physiological role has remained less well-characterized than that of ghrelin. Ghrelin and desacyl-ghrelin are currently referred to in the literature using many different terms, highlighting the need for a consistent nomenclature. The variability of terms used to designate ghrelin can lead not only to confusion, but also to miscommunication, especially for those who are less familiar with the ghrelin literature. Thus, we conducted a survey among experts who have contributed to the ghrelin literature aiming to identify whether a consensus may be reached. Based on the results of this consensus, we propose using the terms "ghrelin" and "desacyl-ghrelin" to refer to the hormone itself and its non-acylated form, respectively. Based on the results of this consensus, we further propose using the terms "GHSR" for the receptor, and "LEAP2" for liver-expressed antimicrobial peptide 2, a recently recognized endogenous GHSR antagonist/inverse agonist.

KEYWORDS
acyl-ghrelin, desacyl ghrelin, ghrelin, unacylated ghrelin

1 | INTRODUCTION

Ghrelin is a 28-residue acylated peptide mainly synthesized in enteroendocrine cells of the stomach.[1] It acts via the growth hormone secretagogue receptor (GHSR), which is mainly expressed in the brain and in the pituitary, as well as in some other organs.[2,3] Plasma ghrelin levels are linked to acute and long-term energy status.[4] Plasma ghrelin levels increase in anticipation of set meals and decrease after eating.[5–9] Also, plasma ghrelin levels are lower in individuals with obesity, whereas they increase in conditions of energy deficit[9] and in some pathologies such as anorexia nervosa[10,11] and cancer-associated cachexia,[12] amongst others. Ghrelin is a pleiotropic hormone that

displays a variety of endocrine, metabolic, autonomic and behavioral actions, as reviewed previously.[4,13,14] The cardinal actions of ghrelin include stimulatory effects on growth hormone (GH) release,[1] food intake,[9,15] gastric motiliy,[16] and reward-related behaviors,[14,17–19] as well as actions to protect against severe hypoglycemia.[20] The biosynthetic pathway that generates ghrelin is well defined.[21] Briefly, the mRNA that encodes ghrelin is translated into a precursor (preproghrelin), which is next cleaved into proghrelin. Proghrelin is mainly acylated at Ser3 by ghrelin-*O*-acyl transferase (GOAT). Acylated-proghrelin is then cleaved into ghrelin, and the C-terminal segment that, after an additional cleavage, results in a 23-residue peptide named obestatin, for which the biological significance is yet uncertain. In plasma, ghrelin is also found as a non-acylated form (i.e., so-called desacyl-ghrelin),[22] which is either co-secreted together with ghrelin or derived from desacylation of ghrelin. No specific receptor has been identified for desacyl-ghrelin, and its putative physiological roles remain less well-characterized than those of ghrelin.

2 | GHRELIN AND ITS NON-ACYLATED FORM

In their search of an endogenous ligand for GHSR, Kojima et al. discovered, in extracts from rat stomach, a 28-residue peptide that is *n*-octanoylated at Ser3.[1] They named the peptide "ghrelin" based on "ghre", a word root in Proto-Indo-European languages for "grow" in reference to its ability to stimulate GH release. The term "ghrelin" also resonates with its GH-releasing activity because it is a conjunction of GH and "rel", from "release". In a further study, this team also purified from rat stomach des-Gln14-ghrelin, which is identical to ghrelin except for the deletion of Gln14, and also activates GHSR.[23] Human and rat/mouse ghrelin only differ in positions 11 and 12, with this being Arg11-Val12 in humans and Lys11-Ala12 in rats and mice. In the human stomach (and plasma), other ghrelin-related molecules were found such as 27- or 28-residue variants, the former lacking Arg28, or variants non-acylated, octanoylated, decanoylated or decenoylated.[24] Ghrelin, des-Gln14-ghrelin and acylated variants of ghrelin of 27 or 28 residues in length display similar bioactivity.[23,24] Importantly, ghrelin itself (i.e., the 28-residue octanoylated peptide) is the major acylated form of the hormone detected in rat and human blood.[25]

The term "desacyl-ghrelin" was first used in the aforementioned study reporting the discovery of ghrelin,[1] when Kojima et al. were challenged to determine the residue sequence of the purified GHSR ligand and made a synthetic peptide, corresponding to rat desacyl-ghrelin.[26] Interestingly, the sequence of m46, a protein obtained from mouse stomach tissue (accession no. AJ243503), was already present in the EMBL/GenBank database and named motilin-related peptide (MTLRP).[27] The research team that discovered ghrelin also showed that both ghrelin and desacyl-ghrelin are detected in plasma by using separation strategies followed by the two radio-immunoassays (RIAs): one that recognizes only the octanoylated N-terminal end of ghrelin (i.e., measures ghrelin) and another that recognizes its C-terminal end (i.e., measures ghrelin plus desacyl-ghrelin).[23] The referred study explicitly named the des-acylated form of ghrelin as "desacyl-ghrelin".

3 | LACK OF AGREEMENT ON NAMES FOR THE PEPTIDE AND ITS NON-ACYLATED FORM

Ghrelin and desacyl-ghrelin are currently referred to using many different terms. This is both confusing and unnecessary. The purpose of this consensus article is to provide recommendations on nomenclature in the ghrelin field, based on commonly used nomenclature. A PubMed search performed in July 2022 for the terms "ghrelin", "acylated ghrelin", "acyl ghrelin" (or "acyl-ghrelin"), "active ghrelin", "octanoyl ghrelin", "*n*-octanoyl ghrelin", and "bioactive ghrelin", retrieved 12,062, 622, 525, 242, 47, 13 and 12 results, respectively. Similarly, a PubMed search for "unacylated ghrelin", "desacyl ghrelin" (or "desacyl-ghrelin"), "desacylated ghrelin", "deacylated ghrelin", "non-acylated ghrelin" "desoctanoyl ghrelin" and "desoctanoylated ghrelin" retrieved 177, 145, 26, 10, 8, 6 and 3 results, respectively. The broad terminology devoted to ghrelin and its desacylated form does not have a consensual scientific explanation. The expressions "active ghrelin" and "bioactive ghrelin" are not only redundant, but also misleading because they imply that desacyl-ghrelin is not bioactive. The expressions "octanoylated ghrelin", "octanoyl ghrelin" and "*n*-octanoyl ghrelin" are redundant because ghrelin is, according to the initial definition, an octanoylated peptide. Although the expressions "acyl ghrelin" and "acylated ghrelin" may seem more comprehensive and inclusive because ghrelin's post-translational modifications can involve different acyl groups, they appear to be unnecessary because octanoylation is the most frequent naturally-occurring acylation of ghrelin.[24] Importantly, synthetic ghrelin is commercialized as the 28-residue peptide octanoylated at Ser3, unless otherwise requested by the customer.

The terminology used to describe the deacylated form of ghrelin is even more complex. The adjectives "desacylated", "deacylated" and "desoctanoylated" seem to refer to an acylated or octanoylated peptide from which the ester bond has been hydrolyzed; this may not necessarily be the case, however, because ghrelin-secreting cells also produce unacylated ghrelin precursor and secrete unacylated ghrelin.[28] In this regard, the expressions "desoctanoyl-ghrelin", "non-acylated ghrelin" and "unacylated ghrelin", as well as "desacyl-ghrelin", seem to be stricter as they unbiasedly describe the lack of the acyl moiety, without assumptions about how that took place. Of note, the prefixes "non" or "un" are general inflectional affixes that create a new word denoting the absence of something, whereas the prefix "de" more accurately describes a molecule characterized by the removal of one or more atoms (of a given element). However, the term deacylated ghrelin has not been as widely used as others.

The expression "total ghrelin" is likely one of the most confusing terms used in the field despite also being extensively used; indeed, a

TABLE 1 Proposed terminology for the peptide ghrelin, its non-acylated form, LEAP2 and GHSR and survey responses

Statement	Proposed terminology[a]	Survey responses[b]			Agreement vs. disagreement (%)[b]
		Agree	Neutral	Disagree	
The proposed terminology for GS-S(*n*-octanoyl)-FLSPEHQRVQQRKESKKPPAKLQPR (amino acid sequence in humans) is ghrelin. The identical term ghrelin should be used for the octanoyl-modified version of the homologous peptide in other species	ghrelin	36	3	1	90.0 vs. 2.5
The proposed terminology for GSSFLSPEHQRVQQRKESKKPPAKLQPR (amino acid sequence in humans) is desacyl-ghrelin. The identical term desacyl-ghrelin should be used for the non-acylated version of the homologous peptide in other species	desacyl-ghrelin	35	3	2	87.5 vs. 5.0
The proposed terminology to describe plasma levels of ghrelin plus desacyl-ghrelin, as determined using a "total ghrelin" assay kit that assesses levels of both, is total ghrelin	total ghrelin	38	1	1	95.0 vs. 2.5
The proposed terminology for MTPFWRGVSLRPIGASCRDDSECITRLCRKRRCSLSVAQE (amino acid sequence in humans) is liver-expressed antimicrobial peptide 2 or its abbreviation, LEAP2	LEAP2	33	6	1	82.5 vs. 2.5
The proposed terminology for the G protein coupled receptor that has both ghrelin and LEAP2 as ligands is the growth hormone secretagogue receptor or its abbreviation, GHSR	GHSR	34	1	5	85.0 vs. 12.5

[a]This is the proposed terminology in the survey.
[b]The data and percentages reflect the responses of the 40 people who filled out the survey and does not include the four authors of the current study.

PubMed search retrieves 492 results. The term "total ghrelin" was first used by Murakami et al.[29] in a publication in which peptide levels were assessed in non-separated plasma using the two aforementioned RIAs. In their study, the RIA using the antibody against the N-terminal end of ghrelin was considered specific for ghrelin, whereas the RIA using the antibody against the C-terminal end of ghrelin was assumed to correspond to ghrelin plus desacyl-ghrelin and used to estimate the "total ghrelin". Thus, the initial use of the term "total ghrelin" was justified because the early available immunoassays did not discriminate ghrelin and its desacylated forms. Because ghrelin (or desacyl-ghrelin) can now be separately quantified using commercially available sandwich immunoassays, the term "total ghrelin" could be dropped. Of note, further studies found that RIAs using antibodies against the C-terminal end of ghrelin also detect other species including fragmented ghrelin species[30,31] and unprocessed proghrelin species.[32]

4 | THE TERMINOLOGY FOR THE RECEPTOR

Despite a 2005 report proposing the designation "ghrelin receptor" as an official International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification nomenclature,[33] uncertainty currently exists regarding the most appropriate nomenclature for GHSR. GHSR was cloned from the pituitary and hypothalamus in 1996 by Howard et al.[2] The term "GHSR" refers to the seminal finding that this receptor acts as a target of some synthetic GH secretagogues.[2] Early sequence analysis showed that the *GHSR* gene could give rise to two types of cDNAs, which were referred to as Ia and Ib. The type Ia cDNA encodes a 366-residue protein with seven transmembrane domains that acts as the receptor for ghrelin. The type Ib cDNA is a result of the presence of a stop codon in the intron 1 of the *GHSR* gene and is predicted to encode a non-signaling truncated 289-residue protein with five transmembrane domains that does not function as a ghrelin receptor.[34] Likely as a consequence of the initial description of two splicing variants of the *GHSR* gene, several different terms are currently used to refer to this receptor in the scientific literature. For example, a PubMed search performed in July 2022 for the terms "GHSR", "GHS-R1a", "GHS-R", "GHSR-1a" and "ghrelin receptor" retrieved 1199, 2917, 568, 135 and 1139 results, respectively. Notably, GHSR is known to display a variety of ligand-independent actions, via either its constitutive activity or interaction with other G protein coupled receptors.[35,36] As mentioned below, GHSR also serves as the receptor for liver-expressed antimicrobial peptide 2 (LEAP2), which is a GHSR antagonist and inverse agonist.[37,38] Thus, the term "ghrelin receptor" appears too narrow. Importantly, the Human Genome Organization Gene Nomenclature Committee has proposed the use of "GHSR" as the symbol for GHSR gene (https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:4267).

5 | THE TERMINOLOGY FOR LEAP2

In 2018, Ge et al.[37] reported that LEAP2 is an endogenous ligand of GHSR.[37] LEAP2, which is mainly produced in liver and jejunum, was an already known peptide isolated in 2003 from human blood ultrafiltrate, and mainly produced in the liver and jejunum.[39] The peptide was termed "LEAP-2" because the same team had previously described another blood-derived antimicrobial peptide from the liver that was termed LEAP-1/hepcidin.[40] The initial studies referred to the peptide as "LEAP-2", although later studies have omitted the hyphen. Strikingly, a PubMed search for the terms "LEAP2" and "LEAP-2" retrieved markedly differing results (132 and 78, respectively).

6 | TOWARD A SURVEY-BASED CONSENSUS NOMENCLATURE

To develop a document toward a consensus nomenclature in the ghrelin field, the main authors of the current article formed a Consensus Committee and conducted a survey-based assessment among experts in the topic. Based on informal conversations with different colleagues, we first agreed on a proposed nomenclature for the peptide ghrelin, its non-acylated form, LEAP2 and GHSR (Table 1). Next, we sent a survey and an accompanying letter (see Supporting information, Appendix S1) to experts in the field (Consensus Group). Experts were found using the keywords "ghrelin" and "ghrelin receptor" in the Expertscape Explorer, which uses PubMed-based algorithms to identify the top 0.1% of scholars writing on a given topic over the past 10 years. Additional experts were also included, based on the citations included in papers published by the scientists identified via Expertscape Explorer. The survey was sent to 56 people on May 18, 2022, and 40 of them agreed to participate. The survey was closed on July 14, 2022. The statements and the responses are outlined in the Table 1. It is to be emphasized that the choice to employ the terms "ghrelin" and "desacyl-ghrelin" reflects not only the original nomenclature as proposed by Kojima et al.,[1] but also that they are among the most commonly used terms. Importantly, all statements reached an agreement > 80%, which suggests that consensus has been achieved, as per previous studies.[41–43]

7 | FINAL REMARKS

Based on the responses to the survey, we propose the use of the terms: "ghrelin" to describe the octanoyl-modified version of the peptide; "desacyl-ghrelin" to describe the non-acylated form of the peptide; "GHSR" to indicate the receptor for ghrelin and LEAP2; and "LEAP2" as the name for the recently recognized endogenous GHSR antagonist/inverse agonist. Data comparing the ratio of ghrelin and its non-acetylated form in tissue or plasma would be encouraged to use the ration of "ghrelin: desacyl-ghrelin". The use term "total ghrelin" should be limited to refer to quantifications based on immunoassays using antibodies against the C-terminal end of ghrelin, for which use, in turn, is discouraged for the reasons discussed above. We acknowledge that the approach taken here may have some limitations (e.g., some experts may have not been identified via our methodology, we could have used a different methodology such as a multiple-choice survey), and so we recognize that these recommendations may not reflect a general consensus. Given the complexity of the molecular process that are involved in the biosynthesis of ghrelin, we also acknowledge that the proposed ghrelin terminology may be oversimplified in studies investigating specific variants of ghrelin, such as peptides with acyl groups, which has been named ghrelin (C8:0), ghrelin (C10:1) and ghrelin (C10:0),[24] or splicing variants of ghrelin or GHSR transcripts. However, we are confident that the proposed terminology will help the scientific community avoid confusions or miscommunications within the ghrelin literature.

AUTHOR CONTRIBUTIONS

Mario Perelló: Conceptualization; funding acquisition; investigation; project administration; supervision; writing – original draft; writing – review and editing. **Suzanne L Dickson:** Conceptualization; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing. **Jeffrey Zigman:** Conceptualization; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing. **Lorenzo Leggio:** Conceptualization; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

MP is supported by Fondo para la Investigación Científica y Tecnológica (FONCyT, PICT2017-3196, PICT2019-3054 and PICT2020-3270) and CONICET (PUE105). SLD is supported by the Swedish Research Council (Vetenskapsrådet, 2019-01051), Hjärnfonden (FO2019-0086), the Novo Nordisk Fonden (NNF17OC0027206 and NNF19OC0056694) and the Swedish state under the agreement between the Swedish Government and the county councils in the ALF agreement (ALFGBG-723681). JMZ is supported by the National Institutes of Health (NIH, R01 DK119341, R01 DK103884, and P01 DK119130). LL is supported by the NIH Intramural Research Program (IRP) funding (ZIA-DA000635) via the National Institute on Drug Abuse (NIDA) IRP and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Division of Intramural Clinical and Biological Research. The views expressed herein are those of the authors and do not reflect the official policy or position of the funding agencies. The authors would like to thank: Dr. Lisa Farinelli (NIDA/NIAAA; NIH) for management support with the project; Mr. Max Dennis (NIDA/NIAAA; NIH) and Mr. Miguel Silbestro (IMBICE) for technical and administrative support with the project; Ms. Diane Cooper (NIH Library) for bibliographic assistance; Dr. Gail Seabold (NIDA) for assistance with manuscript editing; Dr. Pablo N De Francesco (IMBICE) for graphic design assistance.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. The sponsors had no role in the design of the study, the collection, analyses or interpretation of data, writing of the manuscript, or the decision to publish the results.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/jne.13224.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Mario Perelló https://orcid.org/0000-0003-2114-6765
Suzanne L. Dickson https://orcid.org/0000-0002-3822-5294
Jeffrey M. Zigman https://orcid.org/0000-0003-3477-1295
Lorenzo Leggio https://orcid.org/0000-0001-7284-8754

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;402:656-660. doi:10.1038/45230
2. Howard AD, Feighner SD, Cully DF, et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science*. 1996;273:974-977. doi:10.1126/science.273.5277.974
3. Guan XM, Yu H, Palyha OC, et al. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. *Brain Res Mol Brain Res*. 1997;48:23-29. doi:10.1016/s0169-328x(97)00071-5
4. Deschaine SL, Leggio L. From "hunger hormone" to "It's complicated": ghrelin beyond feeding control. *Physiology*. 2022;37:5-15. doi:10.1152/physiol.00024.2021
5. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes*. 2001;50:1714-1719. doi:10.2337/diabetes.50.8.1714
6. Cummings DE, Frayo RS, Marmonier C, Aubert R, Chapelot D. Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time- and food-related cues. *Am J Physiol Endocrinol Metab*. 2004;287:E297-E304. doi:10.1152/ajpendo.00582.2003
7. Drazen DL, Vahl TP, D'Alessio DA, Seeley RJ, Woods SC. Effects of a fixed meal pattern on ghrelin secretion: evidence for a learned response independent of nutrient status. *Endocrinology*. 2006;147:23-30. doi:10.1210/en.2005-0973
8. Verhagen LA, Egecioglu E, Luijendijk MCM, et al. Acute and chronic suppression of the central ghrelin signaling system reveals a role in food anticipatory activity. *Eur Neuropsychopharmacol*. 2011;21:384-392. doi:10.1016/j.euroneuro.2010.06.005
9. Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. *Nature*. 2000;407:908-913. doi:10.1038/35038090
10. Ariyasu H, Takaya K, Tagami T, et al. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. *J Clin Endocrinol Metab*. 2001;86:4753-4758. doi:10.1210/jcem.86.10.7885
11. Otto B, Cuntz U, Fruehauf E, et al. Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. *Eur J Endocrinol*. 2001;145:669-673.
12. Shimizu Y, Nagaya N, Isobe T, et al. Increased plasma ghrelin level in lung cancer cachexia. *Clin Cancer Res*. 2003;9:774-778.
13. Mani BK, Shankar K, Zigman JM. Ghrelin's relationship to blood glucose. *Endocrinology*. 2019;160:1247-1261. doi:10.1210/en.2019-00074
14. Perello M, Dickson SL. Ghrelin signalling on food reward: a salient link between the gut and the mesolimbic system. *J Neuroendocrinol*. 2015;27:424-434. doi:10.1111/jne.12236
15. Wren AM, Small CJ, Ward HL, et al. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology*. 2000;141:4325-4328. doi:10.1210/endo.141.11.7873
16. Masuda Y, Tanaka T, Inomata N, et al. Ghrelin stimulates gastric acid secretion and motility in rats. *Biochem Biophys Res Commun*. 2000;276:905-908. doi:10.1006/bbrc.2000.3568
17. Dickson SL, Egecioglu E, Landgren S, Skibicka KP, Engel JA, Jerlhag E. The role of the central ghrelin system in reward from food and chemical drugs. *Mol Cell Endocrinol*. 2011;340:80-87. doi:10.1016/j.mce.2011.02.017
18. Farokhnia M, Faulkner ML, Piacentino D, Lee MR, Leggio L. Ghrelin: from a gut hormone to a potential therapeutic target for alcohol use disorder. *Physiol Behav*. 2019;204:49-57. doi:10.1016/j.physbeh.2019.02.008
19. Morris LS, Voon V, Leggio L. Stress, motivation, and the gut-brain Axis: a focus on the ghrelin system and alcohol use disorder. *Alcohol Clin Exp Res*. 2018;42:1378-1389. doi:10.1111/acer.13781
20. Goldstein JL, Zhao T, Li RL, Sherbet DP, Liang G, Brown MS. Surviving starvation: essential role of the ghrelin-growth hormone axis. *Cold Spring Harb Symp Quant Biol*. 2011;76:121-127. doi:10.1101/sqb.2011.76.010447
21. Cornejo MP, Mustafá ER, Cassano D, Banères JL, Raingo J, Perello M. The ups and downs of growth hormone secretagogue receptor signaling. *FEBS J*. 2021;288:7213-7229. doi:10.1111/febs.15718
22. Hosoda H, Kojima M, Matsuo H, Kangawa K. Ghrelin and des-acyl ghrelin: two major forms of rat ghrelin peptide in gastrointestinal tissue. *Biochem Biophys Res Commun*. 2000;279:909-913. doi:10.1006/bbrc.2000.4039
23. Hosoda H, Kojima M, Matsuo H, Kangawa K. Purification and characterization of rat des-Gln14-ghrelin, a second endogenous ligand for the growth hormone secretagogue receptor. *J Biol Chem*. 2000;275:21995-22000. doi:10.1074/jbc.M002784200
24. Hosoda H, Kojima M, Mizushima T, Shimizu S, Kangawa K. Structural divergence of human ghrelin. Identification of multiple ghrelin-derived molecules produced by post-translational processing. *J Biol Chem*. 2003;278:64-70. doi:10.1074/jbc.M205366200
25. Kojima M, Kangawa K. Ghrelin: structure and function. *Physiol Rev*. 2005;85:495-522. doi:10.1152/physrev.00012.2004
26. Kojima M. The discovery of ghrelin-a personal memory. *Regul Pept*. 2008;145:2-6. doi:10.1016/j.regpep.2007.09.023
27. Tomasetto C, Karam SM, Ribieras S, et al. Identification and characterization of a novel gastric peptide hormone: the motilin-related peptide. *Gastroenterology*. 2000;119:395-405. doi:10.1053/gast.2000.9371
28. Zhu X, Cao Y, Voogd K, Steiner DF. On the processing of proghrelin to ghrelin. *J Biol Chem*. 2006;281:38867-38870. doi:10.1074/jbc.M607955200
29. Murakami N, Hayashida T, Kuroiwa T, et al. Role for central ghrelin in food intake and secretion profile of stomach ghrelin in rats. *J Endocrinol*. 2002;174:283-288. doi:10.1677/joe.0.1740283
30. Akamizu T, Sakura N, Shigematsu Y, et al. Analysis of plasma ghrelin in patients with medium-chain acyl-CoA dehydrogenase deficiency and glutaric aciduria type II. *Eur J Endocrinol*. 2012;166:235-240. doi:10.1530/EJE-11-0785
31. Liu J, Prudom CE, Nass R, et al. Novel ghrelin assays provide evidence for independent regulation of ghrelin acylation and secretion in healthy young men. *J Clin Endocrinol Metab*. 2008;93:1980-1987. doi:10.1210/jc.2007-2235
32. Burnett LC, LeDuc CA, Sulsona CR, et al. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome. *J Clin Invest*. 2017;127:293-305. doi:10.1172/JCI88648
33. Davenport AP, Bonner TI, Foord SM, et al. International Union of Pharmacology. LVI. Ghrelin receptor nomenclature, distribution, and function. *Pharmacol Rev*. 2005;57:541-546. doi:10.1124/pr.57.4.1

34. Mary S, Fehrentz JA, Damian M, et al. Heterodimerization with its splice variant blocks the ghrelin receptor 1a in a non-signaling conformation: a study with a purified heterodimer assembled into lipid discs. *J Biol Chem*. 2013;288:24656-24665. doi:10.1074/jbc.M113.453423
35. Cornejo MP, Mustafá ER, Barrile F, et al. The intriguing ligand-dependent and ligand-independent actions of the growth hormone Secretagogue receptor on reward-related behaviors. *Neurosci Biobehav Rev*. 2021;120:401-416. doi:10.1016/j.neubiorev.2020.10.017
36. Navarro G, Rea W, Quiroz C, et al. Complexes of ghrelin GHS-R1a, GHS-R1b, and dopamine D1 receptors localized in the ventral tegmental area as Main mediators of the dopaminergic effects of ghrelin. *J Neurosci*. 2022;42:940-953. doi:10.1523/JNEUROSCI.1151-21.2021
37. Ge X, Yang H, Bednarek MA, et al. LEAP2 is an endogenous antagonist of the ghrelin receptor. *Cell Metab*. 2018;27:461-469. doi:10.1016/j.cmet.2017.10.016
38. M'Kadmi C, Cabral A, Barrile F, et al. N-terminal liver-expressed antimicrobial peptide 2 (LEAP2) region exhibits inverse agonist activity toward the ghrelin receptor. *J Med Chem*. 2019;62:965-973. doi:10.1021/acs.jmedchem.8b01644
39. Krause A, Sillard R, Kleemeier B, et al. Isolation and biochemical characterization of LEAP-2, a novel blood peptide expressed in the liver. *Protein Sci*. 2003;12:143-152. doi:10.1110/ps.0213603
40. Krause A, Neitz S, Mägert HJ, et al. LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. *FEBS Lett*. 2000;480:147-150. doi:10.1016/s0014-5793(00)01920-7
41. Rodriguez-Manas L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci*. 2013;68:62-67. doi:10.1093/gerona/gls119
42. Stewart D, Gibson-Smith K, MacLure K, et al. A modified Delphi study to determine the level of consensus across the European Union on the structures, processes and desired outcomes of the management of polypharmacy in older people. *PLoS One*. 2017;12:e0188348. doi:10.1371/journal.pone.0188348
43. Ulschak FL. *Human Resource Development: the Theory and Practice of Need Assessment*. Reston Publishing Company Inc; 1983.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Perelló M, Dickson SL, Zigman JM, Leggio L, on behalf of The Ghrelin Nomenclature Consensus Group. Toward a consensus nomenclature for ghrelin, its non-acylated form, liver expressed antimicrobial peptide 2 and growth hormone secretagogue receptor. *J Neuroendocrinol*. 2022;e13224. doi:10.1111/jne.13224