ORIGINAL ARTICLE

Hmrbase2: a comprehensive database of hormones and their receptors

Dashleen Kaur[1] · Akanksha Arora[1] · Sumeet Patiyal[1] · Gajendra Pal Singh Raghava[1]

Abstract

Purpose Hormones play a critical role in regulating various physiological processes and any hormonal imbalances can lead to major endocrine disorders. Thus, studying hormones is essential for both the therapeutics and the diagnostics of hormonal diseases. To facilitate this need, we have developed Hmrbase2, a comprehensive platform that provides extensive information on hormones.

Methods Hmrbase2 is a web-based database which is an update of a previously published database, Hmrbase (http://crdd.osdd.net/raghava/hmrbase/). We collected a large amount of information on peptide and non-peptide hormones and hormone receptors, this information being sourced from Hmrbase, HMDB, UniProt, HORDB, ENDONET, PubChem, and the medical literature.

Results Hmrbase2 contains a total of 12,056 entries, which is more than twice the number of entries contained in the previous version Hmrbase. These include 7406, 753, and 3897 entries for peptide hormones, non-peptide hormones, and hormone receptors, respectively, from 803 organisms compared to the 562 organisms in the previous version. The database also hosts 5662 hormone receptor pairs. The source organism, function, and subcellular location are provided for peptide hormones and receptors and properties such as melting point and water solubility is provided for non-peptide hormones. Besides browsing and keyword search, an advanced search option has also been supplied. Additionally, a similarity search module has been incorporated enabling users to run similarity searches against peptide hormone sequences using BLAST and Smith-Waterman.

Conclusions To make the database accessible to various users, we designed a user-friendly, responsive website that can be easily used on smartphones, tablets, and desktop computers. The updated database version, Hmrbase2, offers improved data content compared to the previous version. Hmrbase2 is freely available at https://webs.iiitd.edu.in/raghava/hmrbase2.

Keywords Hormones · Peptide hormones · Non-peptide hormones · Steroid hormones · Knowledgebase · Hormone receptors

Introduction

Hormones are the key chemical players in coordination of activities between the cells and thus are important for maintenance and regulation of homeostasis [1, 2]. These chemical messengers are secreted from specialized cells and undergo targeted signaling. The ability of the target cells to respond to specific hormones is possible due to their receptors. The latter hormone-receptor complexes cause the derivation of intracellular consequences, which culminate in major molecular events leading to diverse cellular responses [3, 4]. These responses are essential for the regulation of physiological functions, including growth, development, metabolism,

✉ Gajendra Pal Singh Raghava
raghava@iiitd.ac.in

Dashleen Kaur
dashleenk@iiitd.ac.in

Akanksha Arora
akankshaar@iiitd.ac.in

Sumeet Patiyal
sumeetp@iiitd.ac.in

[1] Department of Computational Biology, Indraprastha Institute of Information Technology, Okhla Phase 3, New Delhi 110020, India

and reproduction. A pictorial representation of hormonal responses is presented in Fig. 1.

Hormones can be encoded by the genome (peptide-hormones), or they can be derived from other molecules (non-peptide hormones). Non-peptide hormones include steroid and amino acid molecules [5]. They are usually produced in large quantities in plants and animals and are received by the cells via extracellular or intracellular receptors. A plethora of receptors are involved, including G protein-coupled receptors, ion channels, and nuclear receptors [6]. A wide range of animal species are known to suffer from various endocrine disorders. Thus, a comprehensive knowledge of hormones and their corresponding receptors will aid in diagnostics and the therapeutic interventions of endocrine disorders in both humans and animals.

In recent years, numerous databases have been available related to receptors including GPCRDB (https://gpcrdb.org/), BitterDB (https://bitterdb.agri.huji.ac.il/dbbitter.php), and NR-DBIND (http://nr-dbind.drugdesign.fr/), and a few related to ligands and their receptors such as PRRDB 2.0 (https://webs.iiitd.edu.in/raghava/prrdb2/) and EndoNet (http://endonet.bioinf.med.uni-goettingen.de/) [7–11]. PRRDB 2.0 is the database of immunological molecules. EndoNet is an information resource concerning intercellular regulatory communication. Therefore, no resource existed after the development of hmrbase which could provide comprehensive information on hormones and their receptors. The objective of this study is to provide users with a unified platform that offers complete information on hormones and their receptors to accelerate the development of new diagnostics and therapeutics for endocrine disorders that affect a large proportion of the human population.

Hmrbase, a comprehensive database of hormones and their receptors, released its initial version in 2009 [12]. Hmrbase contributed to the creation of new tools such as SATPdb and Feptide [13, 14]. Given that since 2009, additional hormones and their receptors have been researched and identified, expanding our knowledge within the field of endocrinology, the information regarding hormones and their receptors needs to be thoroughly updated. Hmrbase2 is a revised and comprehensive repository on hormones and their receptors. The new version contains in-depth details about hormones and receptors, including their localization and elaborate functions with information on their occurrence, roles, and sequences. Additionally, the updated version contains information about the domains and pharmaceutical use of hormones which were missing in the first version.
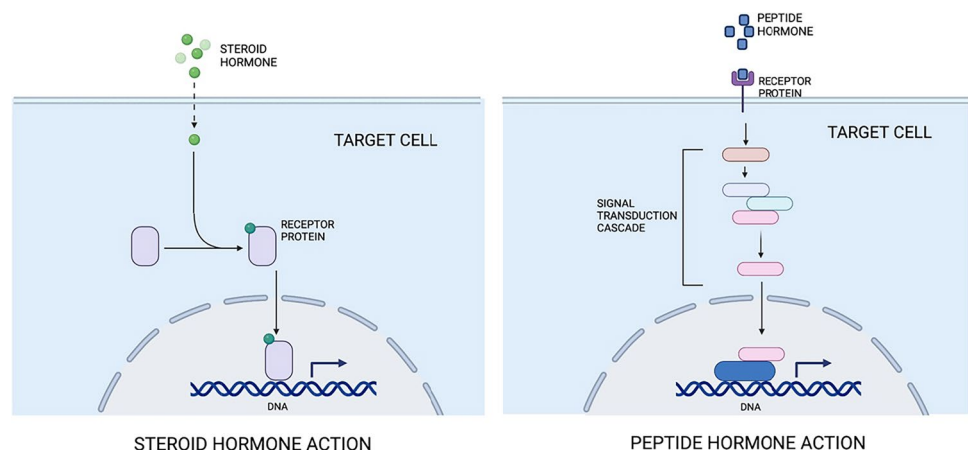
The entries of hormones and their receptors are also linked to a variety of other databases, including UniProt, PubChem, and PDB. Hmrbase2 is also equipped with a sequence similarity search tool to help users map the query peptide sequences with hormonal peptide sequences. Thus, Hmrbase2 provides both comprehensive and easy-to-use information related to hormones and their receptors.

Methods

Data collection

The Hmrbase database, which was first created in 2009, has been updated to include new data on hormones (pharmaceutical use) and receptors that have been explored over the last 13 years from many more organisms. This update reflects the growing interest in hormones across various species of organisms. There is plentiful information on peptide and non-peptide hormones and their receptors that can be found in various sources, including the medical literature, databases, and online resources. To gather information about them, searches were conducted on web resources and databases using keywords related to hormones, including "hormone" and "phytohormone," and hormone-receptors, including "hormone-receptors" from the period between May 2009 and November 2022. Information on peptide hormones and the hormone receptors was obtained from websites such as

Fig. 1 General representation of peptide and non-peptide hormone response

UniProt (https://www.uniprot.org/), HorDB (http://hordb.cpu-bioinfor.org/), Endonet (http://endonet.sybig.de/), and PubMed (https://pubmed.ncbi.nlm.nih.gov/) [11, 15, 16]. To obtain information on non-peptide hormones, HMDB (https://hmdb.ca/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/) were also used along with Endonet and PubMed [17, 18]. Information was collected from various sources and was organized in tabulated form in the Hmrbase2 database. Redundant information was then eliminated.

Database architecture and web interface

Linux-Apache-MySQL-PHP is the standard platform on which Hmrbase2 was created (LAMP). This database was created using Apache (version 2.4.7) as an HTTP server and MySQL (version 5.7.31). To produce responsive front ends that work with smartphones, tablets, and desktops, HTML (version 5), CSS (version 3), PHP (version 7.3.21), and Javascript (version 1.8) were used, and MySQL was used to build the back end. A standard interface was created using PHP programming language. The working architecture of Hmrbase2 is explained in Fig. 2.

Data content

This database contains data about hormones and hormone receptors, including their sources, cellular, physical, and functional characteristics, and sequences. The fields used to represent this information are particular to each type of hormone and receptor and include the following: peptide

hormones containing the organism and taxonomy of the source organism, subcellular location, post-translational modification, function, sequence, receptor, and Uniprot ID; non-peptide hormones having synonym, description, formula, IUPAC, SMILES, corresponding receptor, PDB ID, PubChem ID, KEGG ID, and HMDB ID; and receptors with organism and taxonomy of the source organism, subcellular location, post-translational modification, function, hormone, and Uniprot ID.

Web interface

Hmrbase2 web server, which is openly available, has been built to help the community. It provides information about the hormones and their receptors on one platform. There are three significant modules included in the web server for an effortless search facility, namely "Browse," "Search," and "Similarity."

Browse

The Hmrbase2 website has an uncomplicated and fast browsing option that makes it easier to obtain data from the database. Data can be explored based on fields specific for peptide hormones, non-peptide hormones, and hormone receptors. This allows users to search through different categories of data even if they are unsure what they are looking for.
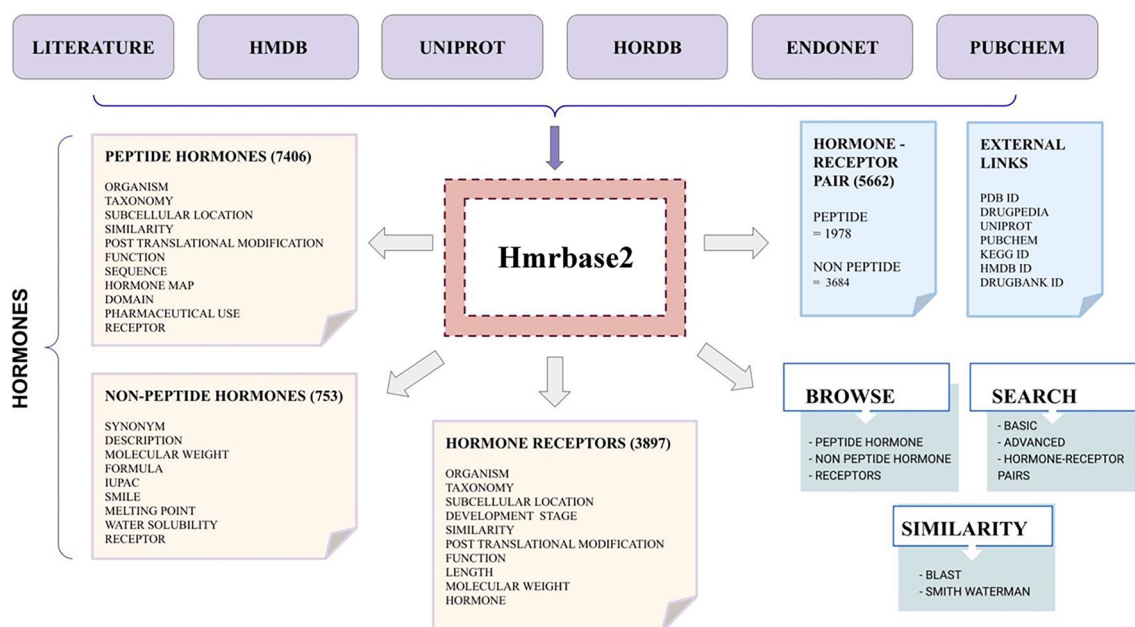

Fig. 2 Architecture of Hmrbase2

Search

There are two different search pages for basic and advanced searches. Besides that, the search page for hormone-receptor pairs has also been incorporated separately for peptide hormone-receptor pairs and non-peptide hormone-receptor pairs.

(i) Basic Search: Separate basic search pages are provided for peptide hormones, non-peptide hormones, and receptors. The architecture of all pages is identical except for the data field options. The searching here can be performed on an individual field or on all fields simultaneously, using a specific keyword to extract data from the database. The search option is available for all the data fields available in the database. Users can define which search results are to be displayed.

(ii) Advanced search: In advanced search, separate pages are provided for peptide hormones, non-peptide hormones, and receptors. With additional boolean operators (such as AND, OR, and NOT), advanced search allows users to submit many queries at once and receive results accordingly. Users can download the displayed entries in comma-separated format.

Similarity

To enable similarity-based search, the Basic Local Alignment Search Tool (BLAST) and Smith-Waterman algorithms have been implemented [19–21]. The user submits the FASTA format peptide sequence with default or specified settings to the BLAST module, and the server runs the BLAST search against the data stored in the database. Similarly, the Smith-Waterman algorithm searches for peptides based on similarity.

Results

Data analysis

The Hmrbase2, the latest version of the Hmrbase database, contains a total of 12,056 entries, including 7406 entries for peptide hormones, 753 for non-peptide hormones, and 3897 for hormone receptors. A comprehensive update on hormones and their receptors has been added. In addition to the 1955 hormones from the first edition of Hmrbase, we have included 6203 more hormones, bringing the total number of hormones to 8158. Similarly, Hmrbase2 includes 901 total hormone receptors researched in the last 13 years, as well as 2996 receptors from the previous database, for a total of 3897 receptors.

The database contains hormones and receptors from 803 organisms across the animal and plant kingdom. Most of the hormones represent human hormones. The distribution of source organisms for both peptide hormones and receptors is depicted in Fig. 3, the proportion of peptide and non-peptide hormones present in this database is shown in Fig. 4, and statistics of peptide and non-peptide hormone of resources used in hmrbase2 are presented in Fig. 5. The amino acid sequences of mature peptide hormones and SMILES of non-peptide hormones are provided in the database. The entries in the database are linked with databases to acquire more information if needed. PDB IDs and PubChem IDs are provided to obtain structural information. Uniprot ID is provided for the peptide hormones and the receptors to gain information about them. Hmrbase2 also hosts 5662 hormone receptor pairs, 1978 for peptide hormones, and 3684 for non-peptide hormones.

Comparison with the previous version

Hmrbase was developed in 2009 and comprised three different modules, as follows: one of the peptide hormones containing 1585 entries provides such information as their respective receptor's name, sequence, sequence length, source organism, and function; another module is of non-peptide hormones containing 370 entries, providing information including name, function, IUPAC, SMILES, and their receptor [12]; and, finally, there is also a module for receptors, containing information on 2996 receptors with their names, functions, length, and post-translational modifications. In the updated version, we have included more hormones and their receptors; thus, the final data consist of 12,056 entries. We have attempted to provide information on the pharmaceutical use of peptide hormones in addition to their name, type, source, and origin. The updated version also hosts 5662 hormone receptor pairs compared to the 4121 in the previous version. Comparative statistics are shown in Table 1. To add more, the data have been linked to PubChem, UniProt, and PDB to provide users with maximum information.

Comparison with the other available databases

There are a limited number of databases that provide information about hormones and their receptors. The updated version of Hmrbase, Hmrbase2, is the only available database that provides comprehensive information on peptide hormones, non-peptide hormones, and their receptors. HORDB is a database of peptide hormones maintained by Dr. Zheng's team and contains only peptide hormones [16]. Endonet focuses on the intracellular network of molecules [11]. The complete comparison of Hmrbase2 with the existing resources is shown in Table 2. We also integrated the data of Endone into our database to provide users with information about all the hormones and their receptors,

Fig. 3 Distribution of source
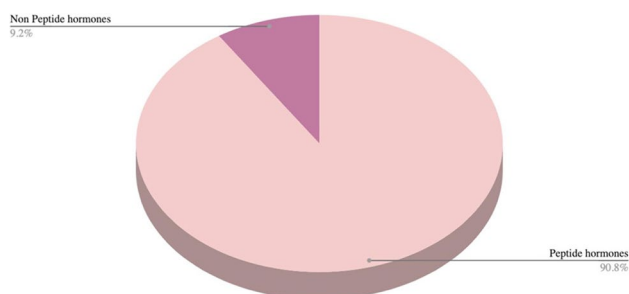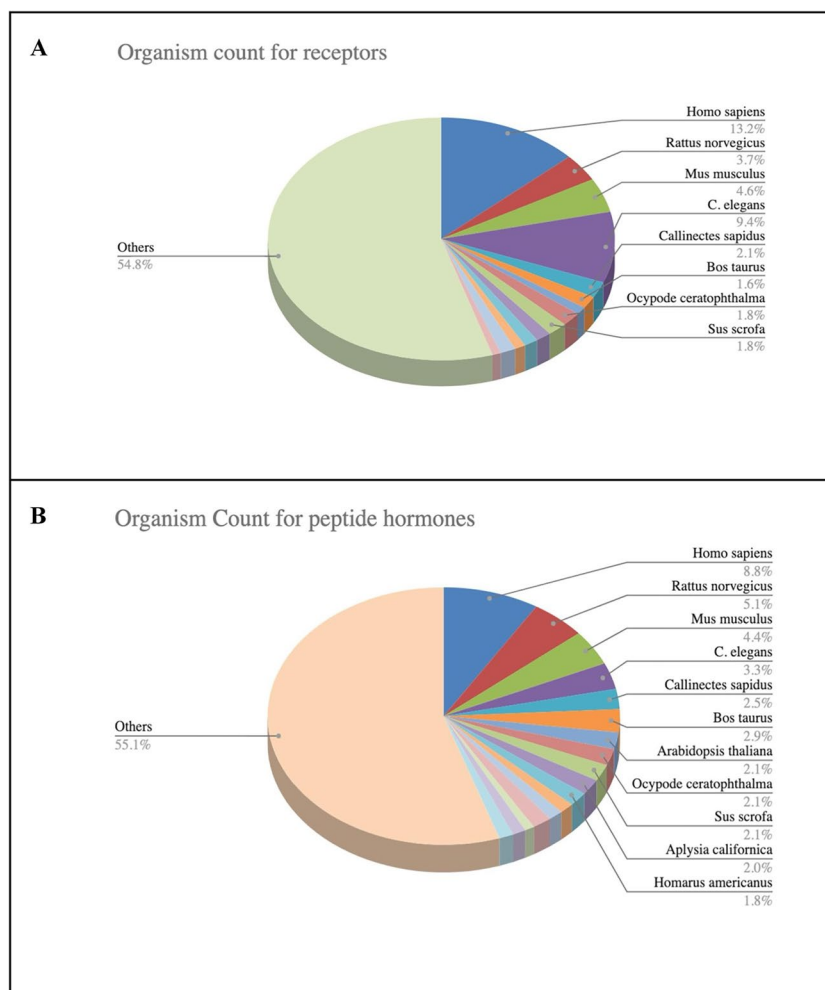of peptide hormones (**A**) and
hormone receptors (**B**)

A Organism count for receptors

Homo sapiens
13.2%
Rattus norvegicus
3.7%
Mus musculus
4.6%
C. elegans
9.4%
Callinectes sapidus
2.1%
Bos taurus
1.6%
Ocypode ceratophthalma
1.8%
Sus scrofa
1.8%
Others
54.8%

B Organism Count for peptide hormones

Homo sapiens
8.8%
Rattus norvegicus
5.1%
Mus musculus
4.4%
C. elegans
3.3%
Callinectes sapidus
2.5%
Bos taurus
2.9%
Arabidopsis thaliana
2.1%
Ocypode ceratophthalma
2.1%
Sus scrofa
2.1%
Aplysia californica
2.0%
Homarus americanus
1.8%
Others
55.1%

Non Peptide hormones
9.2%

Peptide hormones
90.8%

Fig. 4 Proportion of peptide hormones and non-peptide hormones

and we have additionally added the peptide hormones from
HorDB. The aim of Hmrbase2 is to make a comprehensive
all-inclusive collection of all hormones and their receptors
for the assistance of the scientific community working in
this field.

Discussion

The updated version of Hmrbase, Hmrbase2, provides an
in-depth knowledge source on hormones and their recep-
tors. Bidirectional explanations of ligand-receptor interac-
tions have been provided. Users have the option of begin-
ning their search with the hormone entry(ies) and ending it
with the appropriate receptor(s), and vice versa. The data-
base will meet the needs of both theoretical and practising
endocrinologists. The Hmrbase2 data structure is very user-
friendly and straightforward. The mature hormone sequence
is mapped onto its precursor protein sequence to characterize
its functional modes. Additionally, experimental scientists
can use this knowledge to analyze the binding affinity of
hormones to their respective receptors or to develop better
ligands for a given receptor.

Hmrbase2 represents a significant improvement over
its predecessor, Hmrbase, as it offers more extensive and
detailed information. For example, if someone searches for
adiponectin, they can now find information on its pharma-
ceutical use in treating diabetes type 2 and insulin resistance,

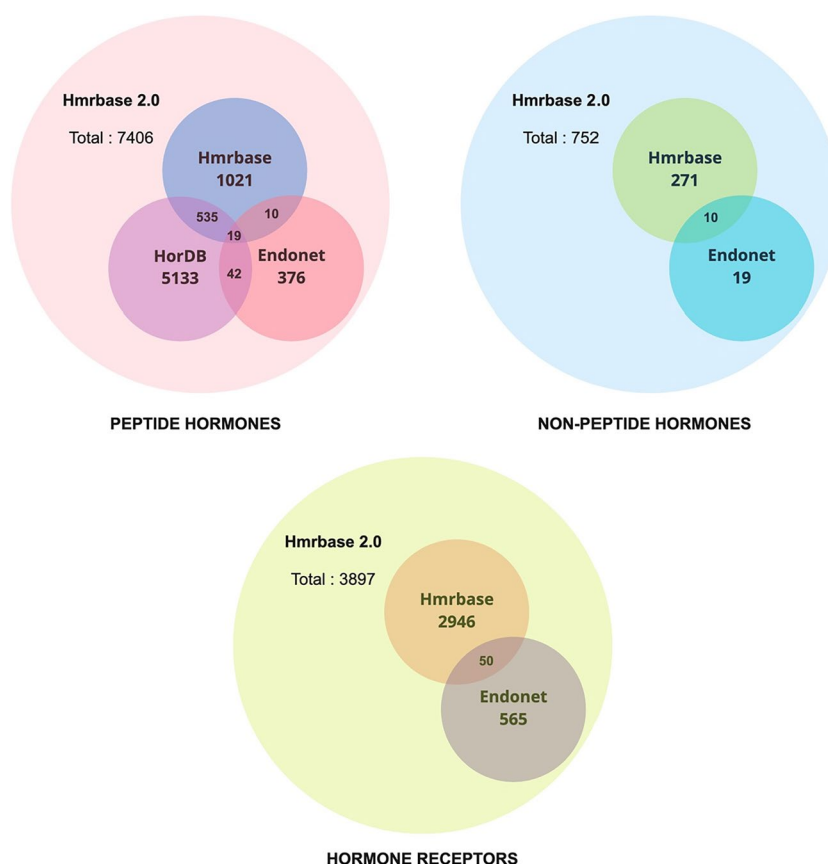**Fig. 5** Information taken from various resources in Hmrbase2

PEPTIDE HORMONES

NON-PEPTIDE HORMONES

HORMONE RECEPTORS

Table 1 Comparison of data in two versions of the Hmrbase database

Category	Peptide hormone		Non-peptide hormone		Total	
	Hmrbase	Hmrbase2	Hmrbase	Hmrbase2	Hmrbase	Hmrbase2
Hormone	1585	7406	370	752	1955	8158
Receptors	828	1597	2168	2300	2996	3897
Hormone-receptor pairs	569	1978	3552	3684	4121	5662

Table 2 Comparison of Hmrbase2 with the existing resources

Database	Peptide hormones	Non-peptide hormones	Hormone receptors	Last updated
Hmrbase2	**7406**	**752**	**3897**	**November 2022**
Hmrbase	1585	370	2996	2009
Endonet	447	29	615	2014
HorDB	5729	–	–	April 2022

The bold entries in the table indicate the statistics of Hmrbase2

which was not available in the previous version. Furthermore, Hmrbase2 has expanded its dataset to include over 12,000 entries, encompassing information on the sequence, length, function, and pharmaceutical use of hormones, as well as the names, functions, length, and post-translational modifications of receptors. An "Advanced Search" feature has also been added to provide customized search results, such as finding all non-peptide hormones within a specific molecular weight range. One unique aspect of Hmrbase2 is its bidirectional explanations of ligand-receptor interactions, allowing users to start their search with either the hormone or the receptor entry and end with the appropriate counterpart. This user-friendly and intuitive data structure makes it easy for both theoretical and practising endocrinologists to efficiently access and analyze information.

The utility of database

Hmrbase2 can be used to obtain complete information about any hormone and its receptors on one platform. For example, if a user is interested in glucagon, a peptide hormone, they

simply need to type glucagon in the search bar given on the basic search page and select the required fields that the user wishes to retrieve. The search results page and the other fields chosen will be displayed upon clicking the search button. Each entry is identified by a distinct ID that links to the hormone or receptor card for that entry, which provides detailed information about it.

Limitation and update

We have made an effort to supply comprehensive information on hormones and their receptors; however, some hormone and receptor sequences are not present in any chemical database or in the literature. In addition, even though the data are routinely filtered and carefully examined to reduce mistakes, claiming complete accuracy would be unfair owing to potential human-made errors. The first version of this database was published 13 years ago, but we will make an effort to revise the database regularly, ideally every 3 years.

Conclusions

In brief, Hmrbase2 provides extensive coverage of both peptide and non-peptide hormones as well as their receptors, which we anticipate will be highly beneficial to researchers in this field. The challenge going forward will be to keep these resources up to date given that the database is manually curated and extracting information from public resources is a time-consuming process. Ideally, there should be a system or software developed to update the database automatically or semi-automatically. Additionally, it should be noted that the information contained in this repository is already existing knowledge obtained from experimental techniques. To further assist the scientific community, in silico methods could be developed to design peptides/proteins with specific hormonal activities.

Declarations

References

1. Hua Z, Li D, Xiang G, Xu F, Jie G, Fu Z, Jie Z, Da P, Li D (2011) PD-1 polymorphisms are associated with sporadic breast cancer in Chinese Han population of Northeast China. Breast Cancer Res Treat. https://doi.org/10.1007/s10549-011-1440-3

2. Zhang D, Wei Y, Huang Q, Chen Y, Zeng K, Yang W, Chen J, Chen J (2022) Important hormones regulating lipid metabolism. Molecules 27. https://doi.org/10.3390/molecules27207052

3. Yen PM (2015) Classical nuclear hormone receptor activity as a mediator of complex biological responses: a look at health and disease. Best Pract Res Clin Endocrinol Metab 29:517–528. https://doi.org/10.1016/j.beem.2015.07.005

4. Bland R (2000) Steroid hormone receptor expression and action in bone. Clin Sci (Lond) 98:217–240

5. Leblebicioglu B, Connors J, Mariotti A (2013) Principles of endocrinology. Periodontol 2000(61):54–68. https://doi.org/10.1111/j.1600-0757.2011.00440.x

6. Alexander SPH, Christopoulos A, Davenport AP, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Sharman JL, Southan C, Davies JA, CGTP Collaborators (2019) The concise guide to pharmacologY 2019/20: G protein-coupled receptors. Br J Pharmacol 176(Suppl):S21–S141. https://doi.org/10.1111/bph.14748

7. Kooistra AJ, Mordalski S, Pándy-Szekeres G, Esguerra M, Mamyrbekov A, Munk C, Keserű GM, Gloriam DE (2021) GPCRdb in 2021: integrating GPCR sequence, structure and function. Nucleic Acids Res 49:D335–D343. https://doi.org/10.1093/nar/gkaa1080

8. Dagan-Wiener A, Di Pizio A, Nissim I, Bahia MS, Dubovski N, Margulis E, Niv MY (2019) BitterDB: taste ligands and receptors database in 2019. Nucleic Acids Res 47:D1179–D1185. https://doi.org/10.1093/nar/gky974

9. Réau M, Lagarde N, Zagury J-F, Montes M (2019) Nuclear receptors database including negative data (NR-DBIND): a database dedicated to nuclear receptors binding data including negative data and pharmacological profile. J Med Chem 62:2894–2904. https://doi.org/10.1021/acs.jmedchem.8b01105

10. Kaur D, Patiyal S, Sharma N, Usmani SS, GPS R (2019) PRRDB 2.0: a comprehensive database of pattern-recognition receptors and their ligands. Database (Oxford) 2019. https://doi.org/10.1093/database/baz076

11. Dönitz J, Wingender E (2014) EndoNet: an information resource about the intercellular signaling network. BMC Syst Biol 8:49. https://doi.org/10.1186/1752-0509-8-49

12. Rashid M, Singla D, Sharma A, Kumar M, Raghava GPS (2009) Hmrbase: a database of hormones and their receptors. BMC Genom 10:307. https://doi.org/10.1186/1471-2164-10-307

13. Singh S, Chaudhary K, Dhanda SK, Bhalla S, Usmani SS, Gautam A, Tuknait A, Agrawal P, Mathur D, Raghava GPS (2016) SATPdb: a database of structurally annotated therapeutic peptides. Nucleic Acids Res 44:D1119–D1126. https://doi.org/10.1093/nar/gkv1114

14. Panyayai T, Ngamphiw C, Tongsima S, Mhuantong W, Limsripraphan W, Choowongkomon K, Sawatdichaikul O (2019) FeptideDB: a web application for new bioactive peptides from food protein. Heliyon 5:e02076. https://doi.org/10.1016/j.heliyon.2019.e02076

15. UniProt Consortium (2021) UniProt: the universal protein knowledgebase in 2021. Nucleic Acids Res 49:D480–D489. https://doi.org/10.1093/nar/gkaa1100

16. Zhu N, Dong F, Shi G, Lao X, Zheng H (2022) HORDB a comprehensive database of peptide hormones. Sci data 9:187. https://doi.org/10.1038/s41597-022-01287-5

17. Wishart DS, Feunang YD, Marcu A, Guo AC, Liang K, Vázquez-Fresno R, Sajed T, Johnson D, Li C, Karu N, Sayeeda Z, Lo E, Assempour N, Berjanskii M, Singhal S, Arndt D, Liang Y, Badran H, Grant J et al (2018) HMDB 4.0: the human metabolome database for 2018. Nucleic Acids Res 46:D608–D617. https://doi.org/10.1093/nar/gkx1089

18. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, Han L, He J, He S, Shoemaker BA, Wang J, Yu B, Zhang J, Bryant SH (2016) PubChem substance and compound databases. Nucleic Acids Res 44:D1202–D1213. https://doi.org/10.1093/nar/gkv951

19. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ (1990) Basic local alignment search tool. J Mol Biol 215:403–410. https://doi.org/10.1016/S0022-2836(05)80360-2

20. Smith TF, Waterman MS (1981) Identification of common molecular subsequences. J Mol Biol 147:195–197. https://doi.org/10.1016/0022-2836(81)90087-5

21. Arora A, Kaur D, Patiyal S, Kaur D, Tomer R, Raghava GPS (2023) SalivaDB-a comprehensive database for salivary biomarkers in humans. Database (Oxford) 2023. https://doi.org/10.1093/database/baad002