Supplementary Information

Adipokinetic hormones and their G protein-coupled receptors emerged in Lophotrochozoa

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Table **S1.** Primer sets used for cloning of *C. gigas* AKH and the four *C. gigas* AKH receptors.

Figure S1. cDNA and corresponding amino acid sequence of the *C. gigas* AKH preprohormone. The signal sequence (highlighted in grey and underlined) is followed by the AKH sequence (highlighted in yellow). The KR sequence (highlighted in green) is recognized by prohormone convertase that cleaves the protein C-terminally of the R residue. Subsequently the C-terminal KR residues are removed by a carboxypeptidase, after which the G residue (highlighted in blue) is converted into a C-terminal amide group. The C-terminal half of the preprohormone is highlighted in grey and contains two C residues (underlined) that form a cystine bridge. The cloned cDNA sequence was submitted to GenBank with the following accession number: KM205073.

Figure S2. Dose-response curves of the activation of *C. gigas* AKHR1-A by various peptides. **(A)** *C. gigas* AKH (Cg-AKH). **(B)** *Locusta migratoria* ACP (Lom-ACP). **(C)** *Nasonia vitripennis* ACP (Nv-ACP). **(D)** *Tribolium castaneum* ACP (Tc-ACP). The E_{50} values are given in the boxes belonging to each panel. All other details are given in the legends of Fig. 5.

Figure S3. Alignment of the amino acid sequences of *C. gigas* AKH, the three insect ACPs that were tested in Supplementary Fig. S2 online, and *C. gigas* corazonin. Note that the AKHs and ACPs are all 10 amino acid residues long, while corazonin is 11 residues long, which might explain why corazonin does not activate the *C. gigas* AKHR1-A and -B receptors (Fig. 5). AKHs, ACPs, and corazonins have many residues in common, but the ACPs have RD or KG residues at positions 8 and 7 that do not occur at these positions in AKHs.

Figure S4. Amino acid sequences and GenBank accession numbers of the preprohormones of the peptides given in Table 1. The signal peptides are underlined. The biologically active sequences are highlighted in yellow, the dibasic cleavage sites for prohormone convertase are highlighted in green, and the glycine residues, which are converted into C-terminal amide groups are highlighted in blue. Cysteine residues that could form cystine bridges are highlighted in red.

Figure S5. Amino acid sequences and GenBank accession numbers of the receptors used in Fig. 8.

Figure S6. Alignment of the peptides given in Table 1 plus selected AKHs, ACPs, corazonins and GnRHs. It can be seen that the proto-AKHs are more similar to AKHs (and ACPs) than to GnRHs.

Figure S7. Phylogenetic tree of the peptides aligned in Supplementary Fig. S6 online. Again, it can be seen that the proto-AKHs are more related to AKH (and ACP) than to GnRH.

Table S1. Primers used for cloning of *C.gigas* AKH, *C. gigas* AKHR1-A, *C. gigas* AKHR1-B, *C. gigas* AKHR1-C, *C. gigas* AKHR1-D, and *C. gigas* AKHR2 cDNAs. The sense primers for cloning *C. gigas* AKHR1-A and *C. gigas* AKHR1-B contain a *Pst*I restriction site marked with green, while all the antisense primers for cloning the receptors contain a *Sac*II restriction site marked with red. A Kozak consensus sequence marked with blue was included in the 5' end of the sense primers, which began at the first nucleotide of the receptor coding DNA sequence to facilitate the gene expression in CHO cells.

Gene	Sense 5'-3'	Antisense 5'-3'
C. gigas AKH	ATGCTCTGCAAATTCTGTATTCT	CCTCCTAATGTTAAAGATTTTGAGT
C. gigas AKHR1-A	CTGCAGCCACCATGAATTCCGACGCGGAT	CCGCGGTTCAGTGCTTGTCCATCGT
C. gigas AKHR1-B	CTGCAGCCACCATGAATTCCGACGCGGAT	CCGCGGTCTTAATTAGTGTTGCTATAGC
C. gigas AKHR1-C	GCCACCATGGATGAACATCTTTCGACT	CCGCGGTCTTAATTAGTGTTGCTATAGC
C. gigas AKHR1-D	GCCACCATGGATGAACATCTTTCGACT	CCGCGGTTCAGTGCTTGTCCATCGT
C. gigas AKHR2	GCCACCATGAATTTAACATATAGCTAT	CCGCGGCTACTTGAAATTGTCTTGTT

1 ATG CTC TGC AAA TTC TGT ATT CTG GCT GTA GTA GCA CTG AGC CTT CTC TCG TTG ACG CTT

M L C K F C I L A V V A L S L L S L T L

61 GGA CAA GTT AGC TTT TCC ACA AAC TGG GGC AGT GGA AAG CGT TCT TCA TCT TCA TTC ATA

G **Q V S F S T N W G S** G K R S S S S F I

121 GCT CCT CAA GCT GAC GAT GCC TGC TGG ACG AAA TCA AAC GCC AAA CTA CTG TAC GAC TTA

A P Q A D D A **C** W T K S N A K L L Y D L

181 ATG CAG GTG ATC CAG AAA CAA GTT GAT CGT CTT GTT GCT TGT CAA AAC AGT AAC GAC GAT

M Q V I Q K Q V D R L V A **C** Q N S N D D

241 TTG CAT CGG ATA TGA CTCAAAATCTTTAACATTAGGAGG

L H R I *

Fig. S1

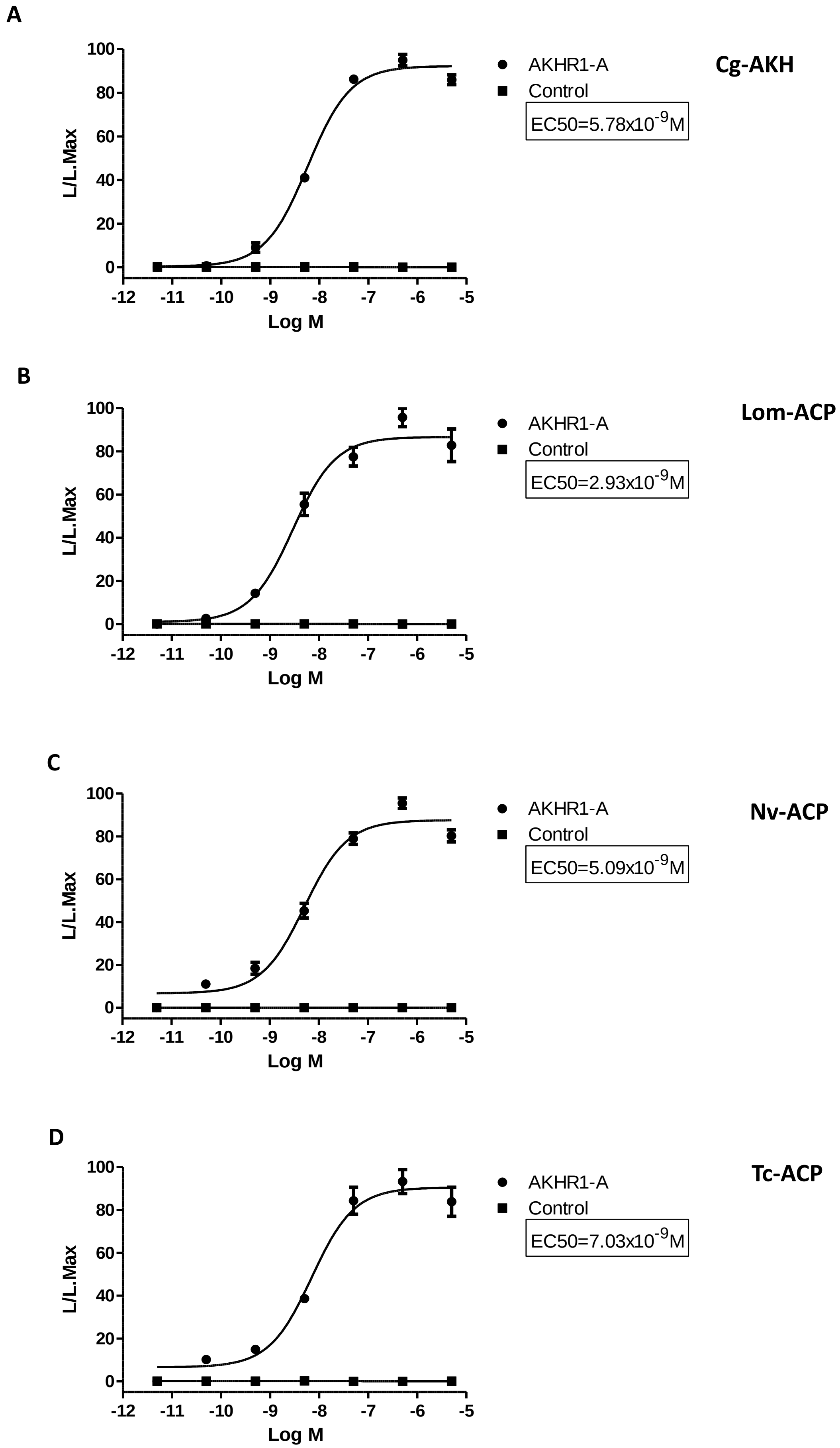
A
Cg-AKH
AKHR1-A
Control
EC50=5.78x10-9M
B
Lom-ACP
AKHR1-A
Control
EC50=2.93x10-9M
C
Nv-ACP
AKHR1-A
Control
EC50=5.09x10-9M
D
Tc-ACP
AKHR1-A
Control
EC50=7.03x10-9M
L/L.Max
0
20
40
60
80
100
Log M
-12
-11
-10
-9
-8
-7
-6
-5

Fig S2

Cgig-AKH	**pQ-V**S**FS**TN**W**GS**amide**
Lmig-ACP	**pQ-V**T**FS**RD**W**SP**amide**
Nvit-ACP	**pQ-V**T**FS**KG**W**GP**amide**
Tcas-ACP	**pQ-V**T**FS**RD**W**NP**amide**
Cgig-CRZ	**pQ**NYH**FS**NG**W**QP**amide**

Fig. S3

Fig. S4

Locusta migratoria AKH-1 (P55319)
MVQRCALVVLLVVAVAAALCSAQLNFTPNWGTGKRDAADFADPYSFLYRLIQAEARKMSGCSN

Globodera rostochiensis AKH (from EST, EE266432.1)
MPSLVFPTLCFFVSAVVLANSQMTFSDGWGKRSAVAPLALLADRHMTEPTKRQQKLKPFANLFVSPDEDTLTMNPEMEACHAGYAQRLIQLHEQMLSLFSTYQQCQTKAATETKKAMRQLR

Hysibius dujardini AKH (from EST, CF075783.1)
MGSAVQSLGLGFLGALLLVQVLFFQVPTANSQLSFSTGWGHGKRSGNVPVNLAPADYRNGKANGDLCSAAYNEMAVARIQELIQEEGLRQLACRKR

Priapulus caudatus AKH (from WGS, AXZU01076239.1)
MHCILILATCLLGLYIHESSAQIFFSKGWRGGKRQEAPLMRHPTDVEEDTNQLVTTALGKESLKLGPSTEPLVDVSLRDAKAWHLTYRTPS

Aplysia californica AKH (XP_012941224.1)
MESSSILLILVVLVIGTSTCLAQIHFSPDWGTGKRAVSTVTEKEIPHCWQIADKEIIDIMLLIQRTAKKLSSCLNTCPEL

Crasssostrea gigas AKH (KM205073)
MLCKFCILAVVAVSLLSLTLGQVSFSTNWGSGKRSSSSFIAPQADDACWTKSNAKLLYDLMQVIQKQVDRLVACQNSNDDLHRIW

Lottia gigantea AKH (from WGS, AMQO01003719.1)
MSLSRNLSVLVCLCCLLSMCLAQIHFSPTWGSGKRSAPVQTYPDSSNTNCYDKLNTKILYQLVKIIKKESEELTACLLQDDDFLRR

Bithynia siamensis goniomphalos AKH (from TSA, GAQQ01002646.1)
MAQTTMTSLLAVLLLLSLVLTPVTSQIHFTPGWGSGKRSGRDDPSSSSSSSASSSSHSSSSIPLPFSSIDSCWAEADFRLFLQLARLVKREAKRFSQCLETENSMAENQENGPDFL

Tritonia diomedea AKH-like (from EST, EV287376.1)
MKIPDMHRTLHCSIPVLVLLMCVCSSLAQIHFSPGWEPGKRSMEEPTRANKMACYDQLDMSLLLDILKIIKRQAEKLSYCTKSCPQL

Hyriopsis cumingii AKH (from EST, GW693635.1)
MQTTCIIAVTLVALWTFTSAQISFSTNWGSGKRSGYQDLQSAACLDDLEINVMKDLAALIKMEANRAAKCIIDAKTRKLTGVYETPDK

Mytilus galloprovincialis AKH (from WGS, APJB010624986.1)
MKSFFLICLLISLIGDSAEQISFSTDWGSGKRSFLESYENICKSKLEQSLIFDIASLVQVNICPSLGKDSLAF

Biomphalaria glabrata proto-AKH (from WGS, APKA01093331.1)
MQNARFVTLLTLMTIGWTLGQIHFTPDWGNNGKRSLTSQFEEESSYSSISCLEQTDLKFLLDIAKL
LTKPEQTQKEPCDLKLMKTKDLEVVYK

Capitella teleta GnRH-2 (from WGS, AMQN01004296.1)
MKHFTLLLVACIVVAYHMNTASAQFSFSLPGKWGNGKRAFSFSLPGRWGAQGKRASGWTGATTDCS
RMESDGMMSVYAAIQEEAIKMLECMGKTSADKQDAS

Capitella teleta GnRH-3 (from WGS, AMQN01001996.1)
MVVLVACSVLAFQLHSAEAQGFSFSLPGKWGGAGKRSGGVPWLKDGLGECGTYDPSLVVELYKIIQ
AEAFRLNECLMKAQREGN

Capitella teleta proto-AKH (from WGS, AMQN01001098.1)
MSCLIRVVIVLFGLSLLVLCCDGQLTQSLGWGSAGSPGKRNFRSYEAAGYNDQLMSSTECRMSAQT
YRVMTDMLEREISRLQRCR

Platynereis dumerilii proto-AKH-1 (from EST, JZ447807.1)
MRAWLVLLVACIVIAYQAHTSDAQFSFSLPGKWGNGKRAALGWGKRGECGDFDPDAIFNVYRAIQA
EALRINECMQQKLEEESKKH

Platynereis dumerilii proto-AKH-2 (from EST, JZ459150.1)
MMRLWVVYLTVCVMMLFAFFPHVCHSQLTQSLGWGSAGSSGKRSVKSPIYYGDDDDYDYDVRQVRK
NRLTLSEALCSQDEKDAISKIKKLIQREVVRQRYCNRKK

Helobdella robusta GnRH (from WGS, AMQM01007250.1)
MNCLALFLACLVLSTVIILPAKSQFSFTPPGKWPFGTGKRDKIISDDDLTSFQEECFKQDPRILSQ
TFLRLQKEANIAKECLKKIYPNARK

Lingula anatina proto-AKH (from WGS, LFEI01000562.1)
MVTKHNMLWISVTVIVMVLQNTNCQWHQTLGWGAAGMVGKRTNPSSIFSQDSQDDSLCDDRRNSEV
MKLIRDLLQVSDRCWSFLCRLSGSCHTRLSCRG

Fig. S5. Amino acid sequences and GenBank accession numbers of the receptors used in Fig. 8.

>Acyrthosiphon_pisum_AKHR (XP_003245941.1)
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NATWYEQCVTYNAFSSKLHELAYLYFGMFMMYWLPLIVILFCYASIIIEIYRRSRESICDNVRRLG
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>Aedes_aegypti_AKHR (XP_001655248)
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LPTEKHEFAYFLVNMILMYVIPLVSTLYCSCAALFEIIRRANTANDKMRRSGIGLLGRARARTLKM
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NNHVTNGMV

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VVHHPTKEKDAIRVSLAALCLFDPFAAQSTFQDNDQ

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NRRKRTAYSRLNLFIMHLCIADLIVTFVMMPLEIVWHVTVAWLAGDVACRLLMFWRAFGFYLSSFI
LVAISLDRYFAIARPLSLADAHSRGRLMLVLAWALSCVASIPQSVIFHIERHPKYPWFSQCVTFGF
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SLCMATPEE


>Crassostrea_gigas_AKHR1-A (KM205066)
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>Crassostrea_gigas_AKHR1-B (KM205067)
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>Crassostrea_gigas_AKHR1-C (KM205068)
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TQSPRTRSFMAATAWVLSAILSAPESVIFHVETHPKYRTFRQCVTFNFFPSHNHELAYNLFNLITL
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>Crassostrea_gigas_AKHR1-D (KM205069)
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TQSPRTRSFMAATAWVLSAILSAPESVIFHVETHPKYRTFRQCVTFNFFPSHNHELAYNLFNLITL
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> Crassostrea_gigas_AKHR2 (KM205070)
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>Daphnia_pulex_AKHR (ACD75498)
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VLVLIGIDRFVAVKYPMKTLNTAKKCNQLISFIWFISFILSTPQVVIFHVAQGPFIEDFSQCVTHG
FYTEVWQEQLYTTLSLIFMFIMPLTILITTYMSTVITIARSERLFKSELANSSSAHKTGDVNRRRL
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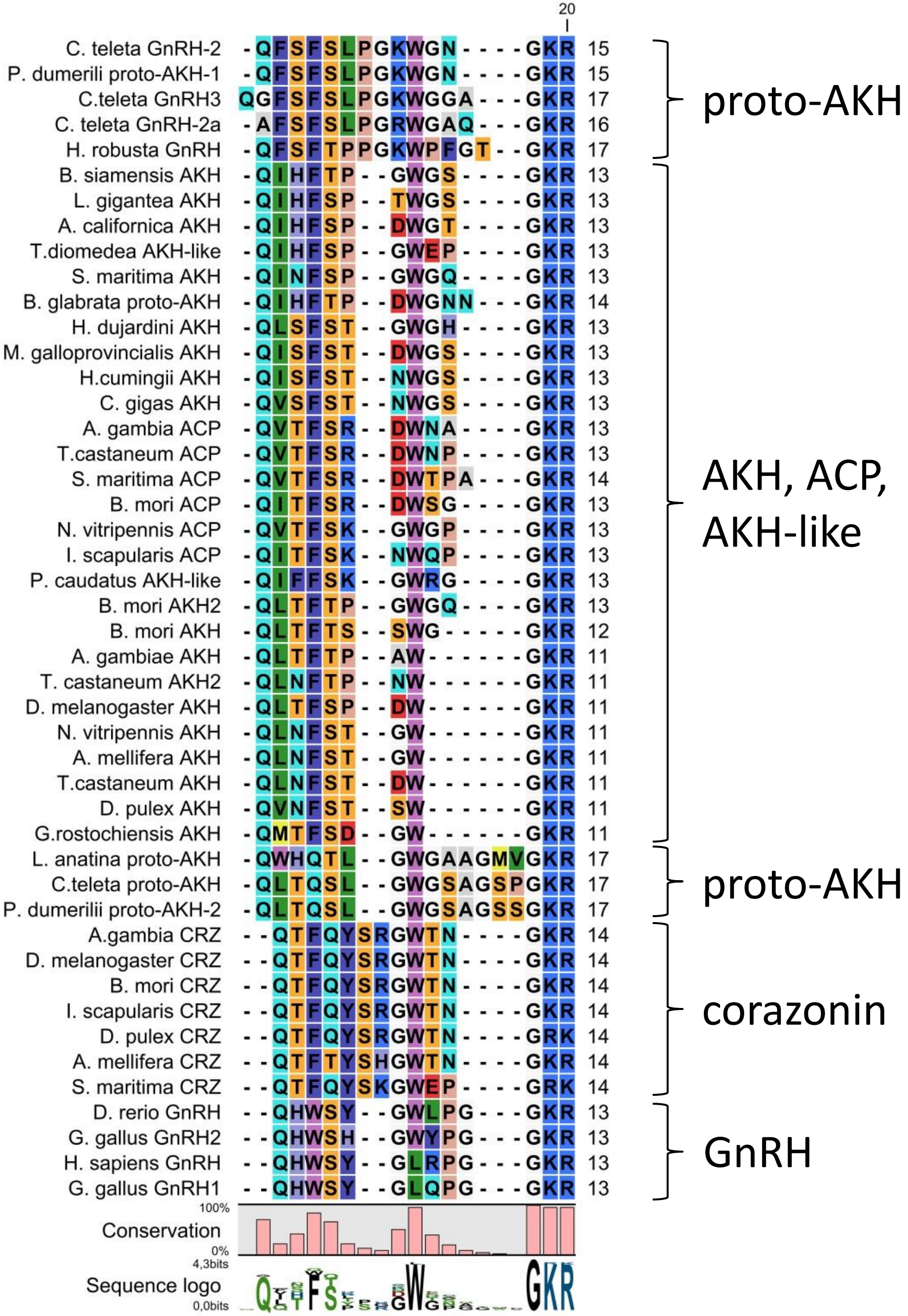

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C. teleta GnRH-2a             -AFSFSLPGRWGAQ---GKR 16
H. robusta GnRH               -QFSFTPPGKWPFGT--GKR 17
B. siamensis AKH              -QIHFTP--GWGS----GKR 13
L. gigantea AKH               -QIHFSP--TWGS----GKR 13
A. californica AKH            -QIHFSP--DWGT----GKR 13
T.diomedea AKH-like           -QIHFSP--GWEP----GKR 13
S. maritima AKH               -QINFSP--GWGQ----GKR 13
B. glabrata proto-AKH         -QIHFTP--DWGNN---GKR 14
H. dujardini AKH              -QLSFST--GWGH----GKR 13
M. galloprovincialis AKH      -QISFST--DWGS----GKR 13
H.cumingii AKH                -QISFST--NWGS----GKR 13
C. gigas AKH                  -QVSFST--NWGS----GKR 13
A. gambia ACP                 -QVTFSR--DWNA----GKR 13
T.castaneum ACP               -QVTFSR--DWNP----GKR 13
S. maritima ACP               -QVTFSR--DWTPA---GKR 14
B. mori ACP                   -QITFSR--DWSG----GKR 13
N. vitripennis ACP            -QVTFSK--GWGP----GKR 13
I. scapularis ACP             -QITFSK--NWQP----GKR 13
P. caudatus AKH-like          -QIFFSK--GWRG----GKR 13
B. mori AKH2                  -QLTFTP--GWGQ----GKR 13
B. mori AKH                   -QLTFTS--SWG-----GKR 12
A. gambiae AKH                -QLTFTP--AW------GKR 11
T. castaneum AKH2             -QLNFTP--NW------GKR 11
D. melanogaster AKH           -QLTFSP--DW------GKR 11
N. vitripennis AKH            -QLNFST--GW------GKR 11
A. mellifera AKH              -QLNFST--GW------GKR 11
T.castaneum AKH               -QLNFST--DW------GKR 11
D. pulex AKH                  -QVNFST--SW------GKR 11
G.rostochiensis AKH           -QMTFSD--GW------GKR 11
L. anatina proto-AKH          -QWHQTL--GWGAAGMVGKR 17
C.teleta proto-AKH            -QLTQSL--GWGSAGSPGKR 17
P. dumerilii proto-AKH-2      -QLTQSL--GWGSAGSSGKR 17
A.gambia CRZ                  --QTFQYSRGWTN----GKR 14
D. melanogaster CRZ           --QTFQYSRGWTN----GKR 14
B. mori CRZ                   --QTFQYSRGWTN----GKR 14
I. scapularis CRZ             --QTFQYSRGWTN----GKR 14
D. pulex CRZ                  --QTFQYSRGWTN----GRK 14
A. mellifera CRZ              --QTFTYSHGWTN----GKR 14
S. maritima CRZ               --QTFQYSKGWEP----GRK 14
D. rerio GnRH                 --QHWSY--GWLPG---GKR 13
G. gallus GnRH2               --QHWSH--GWYPG---GKR 13
H. sapiens GnRH               --QHWSY--GLRPG---GKR 13
G. gallus GnRH1               --QHWSY--GLQPG---GKR 13
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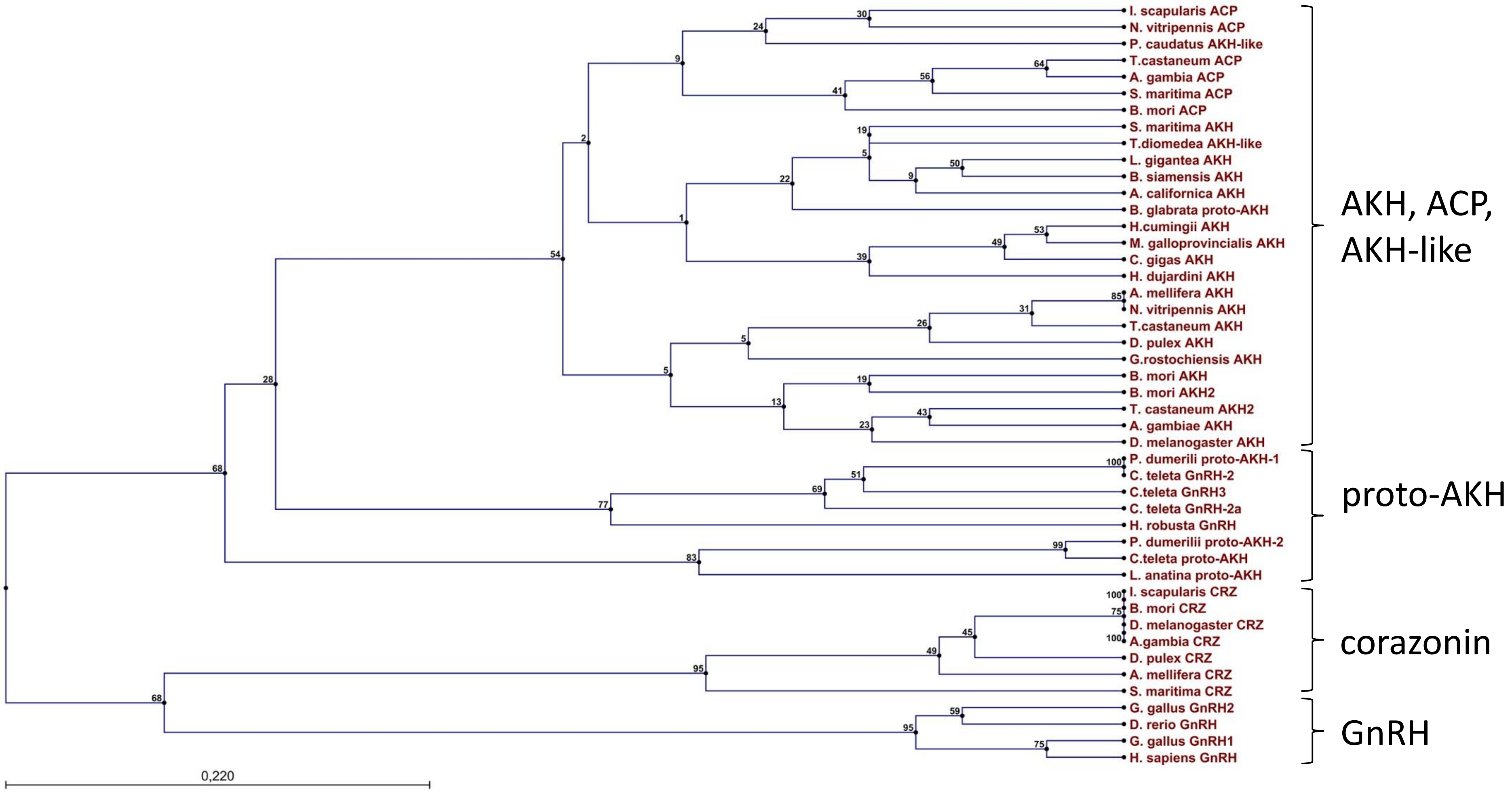
Fig. S6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T.castaneum ACP
A. gambia ACP
S. maritima ACP
B. mori ACP
S. maritima AKH
T.diomedea AKH-like
L. gigantea AKH
B. siamensis AKH
A. californica AKH
B. glabrata proto-AKH
H.cumingii AKH
M. galloprovincialis AKH
C. gigas AKH
H. dujardini AKH
A. mellifera AKH
N. vitripennis AKH
T.castaneum AKH
D. pulex AKH
G.rostochiensis AKH
B. mori AKH
B. mori AKH2
T. castaneum AKH2
A. gambiae AKH
D. melanogaster AKH
P. dumerili proto-AKH-1
C. teleta GnRH-2
C.teleta GnRH3
C. teleta GnRH-2a
H. robusta GnRH
P. dumerilii proto-AKH-2
C.teleta proto-AKH
L. anatina proto-AKH
I. scapularis CRZ
B. mori CRZ
D. melanogaster CRZ
A.gambia CRZ
D. pulex CRZ
A. mellifera CRZ
S. maritima CRZ
G. gallus GnRH2
D. rerio GnRH
G. gallus GnRH1
H. sapiens GnRH
AKH, ACP,
AKH-like
proto-AKH
corazonin
GnRH
30
24
9
64
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41
19
2
5
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9
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1
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100
45
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95
68
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95
75
0,220

Fig. S7