Recent advances in neuropeptide signaling in *Drosophila*, from genes to physiology and behavior

Dick R. Nässel[1] and Meet Zandawala[1, 2]

[1] Department of Zoology, Stockholm University, Stockholm, Sweden

[2] Present address: Department of Neuroscience, Brown University, Providence, RI, USA

Correspondance: dnassel@zoologi.su.se and meet_zandawala@brown.edu

ORCID for D.R.N.: 0000-0002-1147-7766

ORCID for M.Z.: 0000-0001-6498-2208

Abstract

This review focuses on neuropeptides and peptide hormones, the largest and most diverse class of neuroactive substances, known in *Drosophila* and other animals to play roles in almost all aspects of daily life, as well as in developmental processes. We provide an update on novel neuropeptides and receptors identified in the last decade, and highlight progress in analysis of neuropeptide signaling in *Drosophila*. Especially exciting is the huge amount of work published on novel functions of neuropeptides and peptide hormones in *Drosophila*, largely due to the rapid developments of powerful genetic methods, imaging techniques and innovative assays. We critically discuss the roles of peptides in olfaction, taste, foraging, feeding, clock function/sleep, aggression, mating/reproduction, learning and other behaviors, as well as in regulation of development, growth, metabolic and water homeostasis, stress responses, fecundity, and lifespan. We furthermore provide novel information on neuropeptide distribution and organization of peptidergic systems, as well as the phylogenetic relations between *Drosophila* neuropeptides and those of other phyla, including mammals. As will be shown, neuropeptide signaling is phylogenetically ancient, and not only are the structures of the peptides,

precursors and receptors conserved over evolution, but also many functions of neuropeptide signaling in physiology and behavior.

Keywords: insect nervous system, peptide hormone, neuromodulation, endocrinology, G-protein-coupled receptor (GPCR), insulin signaling

Short title: Advances in *Drosophila* neuropeptides

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Abbreviations: CA, corpora allata; CC, corpora cardiaca; CHICO, insulin receptor substrate; CNS, central nervous system; DILP, *Drosophila* insulin-like peptide; dInR, *Drosophila* insulin receptor; DN, dorsal neuron; Ecd, ecdysone; 20E, 20-hydroxyecdysone; EE, enteroendocrine cell; FCs, feminizing cells; FOXO, forkhead transcription factor; Fru, fruitless; GFP, green fluorescent protein; GPCR, G-protein coupled receptor; Grasp, GFP reconstitution across synaptic partners; IDE, insulin-degrading enzyme; IIS, insulin/IGF signaling; IPC, insulin producing cell; JH, juvenile hormone; LN, local neuron; LNC, lateral neurosecretory cell; LN_d, lateral dorsal neuron; LN_v, lateral ventral neuron; MB, mushroom body; MBON, mushroom body output neuron; MNC, median neurosecretory cell; OSN, olfactory sensory neuron; PI, pars intercerebralis; PN, projection neuron; RNAi, RNA interference; RTK, receptor tyrosine kinase; SEZ, subesophageal zone; TOR, target of rapamycin

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1. Introduction

Animal survival and reproduction depend on the ability to display flexible physiology and behavior that enables adaptations to multiple environmental challenges. The nervous and endocrine systems are key organizers of these adjustments and ensure coordination between the external and the internal milieu, as well as optimal nutrient and energy balance and successful reproduction [1-4]. These systems utilize signals with different spatial precision and temporal scales of action [5-11]. Thus, synaptic transmission is usually fast (milliseconds), spatially precise (synaptic junctions) and utilizes small molecule neurotransmitters or electric conduction via gap junctions. At a slower timescale (seconds to hours), signaling is performed by various types of neuromodulators, neurohormones or hormones. These are commonly released at sites distant from *bona fide* synapses or receptor sites. This type of signaling utilizes monoamines, neuropeptides, peptide hormones, steroids, fatty acids and other molecules (as well as nitric oxide). The precision of the slower and more diffuse signaling is determined by the expression of appropriate receptors in target cells, rather than spatial proximity. This review focuses on neuropeptides and peptide hormones, the largest and most diverse class of neuroactive substances, known to play roles in almost all aspects of daily life as well as in developmental processes.

Neuropeptides and peptide hormones are interesting because they can act over a wide range or temporal and spatial scales [7, 8, 10]. In many cases, neuropeptides are considered as neuronal co-transmitters, acting along with small molecule fast transmitters at synaptic sites [7, 9, 12, 13]. However, in invertebrates, neuropeptides are usually thought of as neuromodulators and only a few studies have actually revealed co-transmitter functions [see [9, 10]]. For some neuropeptides, one and the same molecule can play roles both as co-transmitter, neuromodulator and neurohormone. One example of this in *Drosophila* is tachykinin-type peptides (TKs), which are produced by interneurons, neuroendocrine cells of the central nervous system (CNS) and endocrine cells of the intestine [14-17]. Thus, TKs are part of several different neuronal circuits, where they are sometimes co-expressed with GABA or other neuropeptides [16, 18, 19], and also seem to act via endocrine and paracrine signaling [17, 20, 21]. A more general example is cholecystokinin (CCK), which in mammals is produced by gut endocrine cells and brain neurons, and plays multiple roles in stomach acid secretion, gall bladder contractions, pancreatic enzyme secretion, intestinal motility, regulation of satiety and multiple functions as a neuromodulator/co-transmitter in the central and peripheral nervous system (see [22]). Insect sulfakinins (SKs) are orthologs of CCK, which also regulate satiety and food ingestion, aggression, hyperactivity and gut function [see [23-29]]. These are only two examples of multifunctional peptides, and we will highlight further cases where peptidergic signaling orchestrates simple or complex behaviors, and regulates physiological homeostasis and other aspects of the daily life.

Neuropeptides and peptide hormones are crucial in regulation of a rich variety of developmental, physiological and behavioral functions throughout the life cycle of animals. Signaling with neuropeptides is very complex, which is underpinned by the large number of genes encoding peptide precursors (prepropeptides) and receptors in a given species [30-37]. In invertebrates, at least 50 different neuropeptide genes have been identified in each species, and each of these display unique expression patterns in cells and tissues [5, 6, 35, 38-41]. Much of this complexity was unveiled fairly recently by whole genome and transcriptome sequencing of quite a few model and non-model organisms [see e. g. [30, 32, 33, 42-46]]. At first, the massive amount of new information mined from sequence databases was daunting, but with the rapid development of powerful genetic and imaging tools much experimental progress has been made to increase the understanding of the multiple functions of neuropeptides, especially in the worm *Caenorhabditis elegans* [see [39, 47-56]] and the fly *Drosophila melanogaster* (as will be discussed in this review) and more recently, in the marine annelid *Platynereis dumerilii* [57-61]. It is generally accepted that many of the genes encoding neuropeptides and peptide receptors in insects and other invertebrates are ancestrally related to those found in mammals [32, 33, 44, 57, 62], and recent work has suggested that in quite a few cases functions of peptidergic signaling are also partly conserved over evolution [19, 23, 63-66]. Thus, invertebrates with their less complex neuronal and endocrine systems are being explored as models of neuropeptide signaling in a variety of functions [reviewed in [1, 2, 5-7, 9, 10, 30, 31, 43, 46, 67-74]].

Although neuropeptides in *Drosophila* and other invertebrates have been reviewed over the years, developments in the field have been rapid and extensive and it is felt that there is a need for a comprehensive update on what we know about signaling with this ubiquitous and complex group of molecules. In this review, we summarize recent advances in neuropeptide biology and highlight neuropeptide and receptor evolution, the anatomy of peptide signaling systems, as well as the large progress in understanding neuropeptide function in different aspects of the life cycle of *Drosophila*. We also discuss *Drosophila* models of peptidergic signaling where the advantages with a small, short-lived, and less complex organism, combined with genetic tractability are promising. Such studies have employed *Drosophila* to model certain diseases, as well as metabolic regulation, sleep, aggression, reproduction, learning, stress responses, aging and lifespan amongst others. Also, investigations on the role of insulin/IGF-like peptides and associated mechanisms in development, growth, longevity, metabolism, stress responses and reproduction have been numerous in the last 10 years and generated novel insights. Although this review deals primarily with *Drosophila* neuropeptide signaling, it does so in the perspective of findings in other organisms at different levels of organization. For more detailed information and overviews on neuropeptide signaling in insect species other than *Drosophila*, as well as other invertebrates, the reader is referred to some fairly recent reviews [5-7, 10, 32-34, 38, 39, 42-45, 50, 57, 62, 67, 73, 75-95].

Of all the neuropeptides known in *Drosophila,* there are several that have received substantial attention in the last few years, while others have been largely neglected since their discovery. We hope to stimulate interest in investigating these neglected neuropeptides and in providing more complete functional characterization of the better-known peptides, where a lot is still to be learned. Furthermore there is a need to understand the extent to which specific neuropeptides serve multiple disparate functions as local co-transmitters or as part of systems that orchestrate global unified functions. A largely neglected aspect of neuropeptide research in *Drosophila* is the role of these molecules in co-transmission in concert with other neuropeptides or small molecule neurotransmitters |see [9]]. Another gap in our knowledge is the cellular distribution of neuropeptide receptors and a correlation between peptide release sites and target receptors within the CNS. Finally, there is a need to better understand the evolution of peptide signaling systems and to what extent the functional roles of neuropeptides are ancestrally related. Note that Section 5, which provides an update on the biology and functions of all the known *Drosophila* neuropeptides, is presented in a tabular form in Supplementary materials (Supplementary Material Appendix 1).

2. What are neuropeptides and how did they obtain their names?

2. 1. Neuropeptide biosynthesis

Neuropeptides and peptide hormones are produced in neurons and neuroendocrine cells of the CNS, endocrine cells in the intestine or in various peripheral sites, in sensory cells, and in some specific cases in glial cells, muscle cells, embryonic progenitor cells and other cells. These peptides are produced by transcriptional activation of specific genes encoding larger precursor proteins (preprohormones or prepropeptides) from which shorter or longer peptides can be liberated through enzymatic cleavage at specific sites (Fig. 1). In many cases the peptides are further processed posttranslationally to obtain for instance C-terminal amidation or N-terminal pyroglutamate cyclization, formation of disulfide bridges, sulfations, glycosylations or other modifications (Fig. 1). Mature neuropeptides or peptide hormones are stored in large vesicles in the axon terminations, in axon varicosities (boutons), or near release sites in endocrine cells. In *Drosophila,* there are about 50 genes encoding neuropeptide precursors and about the same number of peptide GPCRs [34, 35, 37, 43, 50, 94, 96] (Table 1 and 2). In addition, receptors of tyrosine kinase (RTK) type have been identified for several of the insulin-like peptides (DILPs) [97, 98], prothoracicotropic hormone (PTTH) [99] and ovary ecdysteroidogenic hormone (OEH) [100], and membrane guanylate cyclase (mGC) receptors for eclosion hormone [98, 99, 101] and the NPLP1-derived VQQ peptide [102].

Peptidergic neurons and neuroencrine cells are not homogeneous cell types, although some features are shared. Peptide biosynthesis occurs in the cell body and peptide-containing dense core vesicles are transported to axon terminations or boutons, and in some cases to dendrites where they are stored [8, 103-105] (Fig. 1). Some peptidergic neurons, or neuroendocrine cells, are extra suited to produce, store and release bulk amounts of peptides and these display large cell bodies and expanded axon terminations. In *Drosophila*, these neuroendocrine cells are commonly characterized by expression of the transcription factor Dimmed, which serves to organize the differentiation of cellular components that underlie enlarged capacity for secretory activity [40, 106, 107].

As will be detailed later, *Drosophila* neuropeptides are produced by stereotypic sets of neurons and neuroendocrine cells, and in some cases, in other cell types. Commonly, each peptide is expressed in only a small number of neurons or neurosecretory cells many of which are unique pairs or small groups of identifiable cells. It has been estimated that the *Drosophila* brain consists of about 100,000 neurons [69, 108] and only a small fraction of these are peptidergic. In the larval CNS, the transcription factor Dimmed specifies a large proportion of the peptidergic neurons and is expressed in about 300 neurons [40, 106]. The number of peptidergic neurons is much higher in the adult brain, especially due to the fact that a large portion of the more than 4000 mushroom body Kenyon cells expresses short neuropeptide F (sNPF) [109, 110]. For individual neuropeptide types the number of neurons producing them in the entire CNS range from 2 (eclosion hormone) or 4 (SIFamide), over 20-60 for most neuropeptides, to some exceptional peptides (proctolin and sNPF) that are found in 400 to several thousand neurons [see [35, 40]]. Not all the neuropeptides have been localized in any detail to cells in the brain and ventral nerve cord (VNC) of adult *Drosophila*, but in the larval CNS the majority have been mapped to neurons and neurosecretory cells at least to the level of cell body distribution [see [35, 40, 111]]. Very few studies have attempted mapping of neuropeptide receptor distribution.

2. 2. A note on neuropeptide nomenclature

It is likely that nobody is totally satisfied with the nomenclature used for invertebrate neuropeptides and peptide hormones. Peptides have since the early 20th century been named based on a variety of criteria. Although it became clear in the early 1990s that peptides could have ancestral relationships and be derived from precursors encoded on genes that are evolutionarily related, the naming of neuropeptides continued to be somewhat erratic. Peptides were named after a variety of features such as source of isolation, chemical structure, biological activity, the scientist's imagination and craving to produce a cool name, and combinations of these. Sometimes peptides were grouped together based on sequence similarities (e. g. FMRFamide-related peptides, FaRPs) creating confusion later on when they were found to be derived from several distinct genes and have distinct ancestry, receptors and functions [see [37, 94, 112]]. Only with the whole genome sequencing and annotation of neuropeptide genes it was possible to get an overview of these molecules in multiple organisms and realize that existing peptide names are confusing, at best. Now it appears too late to undo the mistakes and we have to live with the names, in spite of attempts to create a more relevant nomenclature [see [96, 113]].

3. List of neuropeptides, peptide hormones and their receptors in *Drosophila*

Quite a few new neuropeptide genes have been identified the last 10 years. We list the known neuropeptides and peptide hormones in *Drosophila* in Table 1 and 2. Six novel neuropeptide genes were identified the last decade, encoding CNMamide, limostatin, natalisin, orcokinin, RYamide and trissin. Also additional peptide GPCRs matching the novel peptides have been discovered, and a few orphan receptors have been characterized (Table 2). With the aid of gene microarray and RNA sequence data from dissected tissues and different developmental stages we also have very useful databases to examine expression of peptide and GPCR transcripts [FlyAtlas, FlyAtlas2 and MidgutAtlas (http://flyatlas.gla.ac.uk/MidgutAtlas/index.html?page=home)] [114, 115] and modENCODE Tissue Expression Data (modENCODE_mRNA-Seq_tissues) [116]. Recent progress in single-cell transcriptome sequencing has also facilitated the creation of databases that allow mining of gene expression in the brain (http://scope.aertslab.org) and gut (https://www.flyrnai.org/scRNA/) at the cellular level [117-120].

Table 1: Neuropeptides and peptide hormones identified in *Drosophila melanogaster*

Neuropeptide name[1]	Acronym	Sequence[2]
Adipokinetic hormone	AKH	pQLTFSPDWa
Allatostatin A (AstA)	AstA-1	VERYAFGLa
	AstA-2	LPVYNFGLa
	AstA-3	SRPYSFGLa
	AstA-4	TTRPQPFNFGLa
Allatostatin B (AstB; MIP)	MIP-1	AWQSLQSSWa
	MIP-2	AWKSMNVAWa
	MIP-3	RQAQGWNKFRGAWa
	MIP-4	EPTWNNLKGMWa
	MIP-5	DQWQKLHGGWa
Allatostatin C (AstC)	AstC	pQVRYRQCYFNPISCF
Allatostatin CC (AstCC)	AstCC	IQPSGSGGGRAYWRCYFNAVSCF
Bursicon alpha (burs)	burs	141 AAs[3]
Bursicon beta (pburs)	pburs	121 AAs
CAPA-PVK/PK	CAPA-PVK-1	GANMGLYAFPRVa
	CAPA-PVK-2	ASGLVAFPRVa
	CAPA-PK	TGPSASSGLWFGPRLa
	CPPB	GDAELRKWAHLLALQQVLD
CCAP	CCAP	PFCNAFTGCa
CCHamide-1 (CCHa-1)	CCHa-1	SCLEYGHSCWGAHa
CCHamide-2 (CCHa-2)	CCHa-2	GCQAYGHVCYGGHa
CNMamide (CNMa)	CNMa	pQYMSPCHFKICNMa
Corazonin	CRZ	pQTFQYSRGWTNa
Diuretic hormone 31	DH31	TVDFGLARGYSGTQEAKHRMGLAAANFAGGPa
Diuretic hormone 44	DH44	NKPSLSIVNPLDVLRQRLLLEIARRQMKENSRQVELNRAILKNVa
dFMRFamides	dFMRFa-1	SVKQNDFMHFa
	dFMRFa-2	DPKQDFMRFa
	dFMRFa-3	TPAEDFMRFa

	dFMRFa-4	SDNFMRFa
	dFMRFa-5	SPKQDFMRFa
	dFMRFa-6	PDNFMRFa
	dFMRFa-7	SAPQDFVRSa
	dFMRFa-8	MDSNFIRFa
Dromyosuppressin	DMS	TDVDHVFLRFa
Drosulfakinins[4]	DSK-0	NQKTMSFa
	DSK-1	FDD**Y**GHMRFa
	DSK-2	GGDDQFDD**Y**GHMRFa
Ecdysis triggering hormone[5]	ETH-1	DDSSPGFFLKITKNVPRLa
	ETH-2	GENFAIKNLKTIPRIa
Eclosion hormone	EH	53 AAs
Hugin-pyrokinin	hug-PK	SVPFKPRLa
	hug-γ	LRQLQSNGEPAYRVRTPRLa
Ion transport peptide	DrmITP	72 AAs (amidated)
	DrmITPL1	86 AAs
	DrmITPL2	86 AAs
Leucokinin	LK	NSVVLGKKQRFHSWGa
Limostatin	Lst	AIVFRPLFVYKQQEIa
Natalisin	NTL-1	EKLFDGYQFGEDMSKENDPFIPPRa
	NTL-2	HSGSLDLDALMNRYEPFVPNRa
	NTL-3	DKVKDLFKYDDLFYPHRa
	NTL-4	HRNLFQVDDPFFATRa
	NTL-5	LQLRDLYNADDPFVPNRa
Neuropeptide F	NPF	SNSRPPRKNDVNTMADAYKFLQDLDTYYGDRARVRFa
Short NPF (sNPF)	sNPF-1	AQRSPSLRLRFa
	sNPF-1$_{4-11}$	SPSLRLRFa
	sNPF-2	WFGDVNQKPIRSPSLRLRFa[6]
	sNPF-2$_{12-19}$	SPSLRLRFa
	sNPF-3	KPQRLRWa
	sNPF-4	KPMRLRWa
NPLP1	MTYamide	YIGSLARAGGLMTYa
	IPNamide	NVGTLARDFQLPIPNa
	APK	SVAALAAQGLLNAPK
	VQQ	NLGALKSSPVHGVQQ
NPLP2	NEF	TKAQGDFNEF
NPLP3	SHA	VVSVVPGAISHA
	VVIamide	SVHGLGPVVIa
NPLP4	YSY	pQYYYGASPYAYSGGYYDSPYSY
Orcokinin	OK-A	NFDEIDKASASFSILNQLV
	OK-B	GLDSIGGGHLI
Pigment-dispersing factor	PDF	NSELINSLLSLPKNMNDAa
Proctolin		RYLPT
Prothoracicotropic hormone	PTTH	212 AAs
RYamide (RYa)	RYa-1	PVFFVASRYa
	RYa-2	NEHFFLGSRYa
Sex peptide[7]	SP	SWEWPWNRKPTKFPIPSPNPRDKWCRLNLGPAWGGRC
SIFamide	SIFa	AYRKPPFNGSIFa
Tachykinin-related	DTK-1	APTSSFIGMRa
	DTK-2	APLAFVGLRa
	DTK-3	APTGFTGMRa
	DTK-4	APVNSFVGMRa
	DTK-5	APNGFLGMRa
	DTK-6	pQRFADFNSKFVAVRa[8] or QQRFADFNSKFVAVRa
Trissin		IKCDTCGKECASACGTKHFRTCCFNYL

Notes

[1] In some cases the name of the precursor is used (when the peptides derived have multiple names and/or when multiple peptides derived from the same precursor are listed). Synonyms and CG numbers can be found in Table 2. The insulin-like peptides are not included here since their definite structure awaits clarification. Based on [37, 38, 88, 94, 121, 122] and references listed under note 2 below. For more recently identified peptides (after 2010; highlighted in grey) see text for references

(section 5).

[2] Sequences that have been identified from the genome and also confirmed by regular sequencing or mass spectrometry are in black. Sequences that are shown in red have in *Drosophila* only been predicted from genome sequences. Amidation is abbreviated a. Key references to mass spectrometric identification of peptide sequences: [34, 123-127].

[3] Sequences of peptides (proteins) with more than 50 amino acids (AAs) are not given. Instead the reader is referred to original references given in the text (section, 5 and Supplementary Materials Appendix 1; see also [128]).

[4] Y in DSK-1 and DSK-2 is sulfated.

[5] ETH is produced by peritracheal cells (not bona fide neurons), but acts on neurons (see also 7 below)
[6] This was the originally predicted sequence of sNPF-2, but has never been confirmed.

[7] Sex peptide is not a neuropeptide or peptide hormone by strict definition, since it is produced I the male accessory gland, but once transferred to the female with the semen it has peptide hormone-like actions.

[8] This sequence has not been confirmed, but is probably present based on receptor activation studies (Poels *et al*., 2009). Note, however, that DTK-6 is not the ligand of the NKD receptor (TakR86C), as proposed in that paper. Instead NKD is activated by natalisins [129].

Table 2: Neuropeptides and their receptors in *Drosophila melanogaster*[1]

Peptide gene	annotation	peptides	receptor	receptor if not GPCR
Adipokinetic hormone (AKH)	CG1171	AKH	CG11325	
Allatostatin A (AstA)	CG13633	AstA 1-4	CG2872	
			CG10001	
Allatostatin B (AstB/MIP)	CG6456	AstB 1-5	CG30106	
			CG14484	
Allatostatin C (AstC) and AstCC[1]	CG14919	AstC	CG7285	
	CG14920	AstCC	CG13702	
Amnesiac (amn)	CG11937	3 putative	nd	nd
Apis-ITG-like	CG8216		nd	nd
Bursicon alpha (burs)	CG13419	Burs	CG8930	
Bursicon beta (pburs)	CG15284	pBurs	CG8930	
CAPA-PVK/PK	CG15520	CAPA-PVK1-2[2]	CG14575	
		CAPA-PK[2]	CG9918	
CCHamide-1 (CCHa-1)	CG14358	CCHa-1	CG30106	
CCHamide-2 (CCHa-2)	CG14375	CCHa-2	CG14593	
CNMamide (CNMa)	CG13936	CNMa	CG33696	
Corazonin (CRZ)	CG3302	CRZ	CG10698	
Crustacean cardioactive pept. (CCAP)	CG4910	CCAP	CG6111	
Diuretic hormone 31 (DH_{31})	CG13094	DH_{31}	CG32843	
			CG4395	

Diuretic hormone 44 (DH$_{44}$)	CG8348	DH$_{44}$	CG8422 CG12370	
Ecdysis-triggering hormone (ETH)	CG18105	ETH1-2	CG5911	
Eclosion hormone (EH)	CG5400	EH	CG10738	Guanylyl cyclase
FMRFamide	CG2346	dFMRFa1-8	CG2114	
Glycoprotein hormone alpha2 (GPA2)	CG17878	GPA2	CG7665	
Glycoprotein hormone beta5 (GPB5)	CG40041	GPB5	CG7665	
Hugin (*hug*)	CG6371	Hug-PK[3]	CG8795 CG8784	
Ion transport peptide/CHH (ITP)	CG13586	ITP, ITPL1-2	nd	nd
Insulin-like peptides (DILP)	6 genes[4]	DILP1-6	CG18402	Tyrosine kinase
Insulin/relaxin-like peptide	CG13317	DILP7	CG34411[5]	
Insulin/relaxin-like peptide	CG14059	DILP8	CG31096	
Leucokinin (LK/Insect kinin)	CG13480	LK	CG10626	
Limostatin	CG8317	Lst	CG9918	
Myosuppressin /dromysosuppr. (DMS)	CG6440	DMS	CG8985 CG13803	
Natalisin	CG34388	NTL1-5	CG6515	
Neuropeptide F (NPF)	CG10342	NPF	CG1147	
Neuropeptide-like precursor 1 (NPLP1)	CG3441	IPNa, MTYa, APK	CG42636	Guanylyl cyclase[6]
Neuropeptide-like precursor 2 (NPLP2)	CG11051	NEF	nd	nd
Neuropeptide-like precursor 3 (NPLP3)	CG13061	SHA, VVIa	nd	nd
Neuropeptide-like precursor 4 (NPLP4)	CG15361	YSY	nd	nd
Orcokinin	CG13565	OK-A, OK-B	nd	nd
Pigment dispersing factor (PDF)	CG6496	PDF	CG13758	
Proctolin	CG7105	Proctolin	CG6986	
Prothoracicotropic hormone (PTTH)	CG13687	PTTH	CG1389	Tyrosine kinase
RYamide	CG40733	dRYa1-2	CG5811	
Sex peptide (SP) Acp70A	CG8982	SP	CG16752	
Short Neuropeptide F (sNPF)	CG13968	sNPF1-4	CG7395	
SIFamide	CG4681	SIFamide	CG10823	
Sulfakinin/Drosulfakinin (DSK)	CG18090	DSK1-2	CG42301 CG32540	
Tachykinin (TK/DTK)	CG14734	DTK1-6	CG7887	
Trissin	CG14871		CG34381	

[1] AstCC receptor has not been deorphanized in *Drosophila* but AstCC is predicted to activate AstC receptors based on the work in *Tribolium castaneum* [130].

[2] Also termed CAPA-1 and 2, and PK-1

[3] Also designated PK-2

[4] DILP1 = CG13173, DILP2 = CG8167, DILP3 = CG14167, DILP4 = CG6736, DILP5 = CG33273, DILP6 = CG14049

[5] DILP7 is predicted to activate CG34411, which is a relaxin-type GPCR.

[6] This receptor was only proposed for one of the peptides (VQQ) [102].

As will be seen in later sections, much progress has also been made in mapping peptides and GPCRs to neurons and other cells using techniques such as immunocytochemistry, *in situ* hybridization and promoter-Gal4 driver lines. Also, the presence of mature peptides encoded by various precursors has been confirmed biochemically by mass spectrometry [123-127, 131, 132]. However, some predicted peptides are yet to be confirmed biochemically (see Table 1). It is possible that some peptides are not processed the way they were predicted, whereas others are difficult to identify by mass spectrometry.

4. Evolutionary relations of neuropeptides

4. 1. Neuropeptide signaling systems in Bilateria

Establishing evolutionary relationships between vertebrate and invertebrate neuropeptide families have not always been easy or reliable. This is due to the fact that most neuropeptides are too small to perform bioinformatics searches across phyla. Furthermore, some neuropeptides have evolved similar sequences despite having different ancestry. For instance, the large group of FMRFamide-related peptides originates from several neuropeptide precursor genes that have independently evolved the common RFamide C-terminal motif on multiple occasions [37, 94, 112, 133, 134]. Lastly, the lack of genome sequencing from a broad range of phyla resulted in initial phylogenetic analyses with a low resolution. Hence, leucokinins have been referred to as tachykinin-like peptides [see for instance [135, 136]] in spite of these peptides having independent origins [32, 33]. Similarly, allatostatin-A receptors were considered related to a broad group comprising vertebrate somatostatin and opioid receptors [137] but recent analyses have shown that they are related to galanin receptors [32, 33]. These examples should not be taken as criticism of the authors describing the original findings, but merely highlight the difficulties in inferring evolutionary relationships for neuropeptides and GPCRs in the pre-genomics era. However, recent advances in next-generation sequencing have transformed the landscape of neuropeptide research. Two groundbreaking studies have utilized comparative bioinformatics-based approaches to determine the evolution of neuropeptide signaling systems in Bilateria [32, 33]. These clustering and phylogenetic analyses emphasized the GPCR sequences rather than neuropeptide sequences because GPCRs are much larger than their corresponding ligands (hence more phylogenetic signal) and they tend to be more conserved. Moreover, since neuropeptides and their GPCRs have been shown to co-evolve [138], phylogenetic relationships inferred using the GPCR sequences should in theory reflect the evolutionary relationships of their corresponding ligands. Using this approach, [32] and [33] identified a core-set of neuropeptide-receptor signaling pathways that can be traced back to the common ancestor of Bilateria (see Fig. 2) Consequently, five unique associations between protostomian and deuterostomian neuropeptide families were established. This include neuropeptide S (NPS) and crustacean cardioactive peptide (CCAP), orexin and allatotropin, neuropeptide FF/gonadotropin-inhibitory hormone (GnIH) and SIFamide galanin and allatostatin-A (Ast-A), as well as a link between vertebrate endothelin/gastrin-releasing peptide/neuromedin-B peptides and protostomian CCHamide/elevenin/GGNG peptides. Similar *in silico* analyses combined with receptor characterization studies in recent years have now increased the number of this core-set of bilaterian neuropeptides [36, 57, 62, 66, 139]. Thus, the origins of as many as 30 neuropeptide genes/families can now be traced back to Urbilateria as orthologs of several vertebrate neuropeptide signaling systems have been identified in insects and other protostomes (Fig. 2).

4. 2. Functional conservation of neuropeptides

For several of the bilaterian peptides, some of the functions of the signaling systems have also been conserved over evolution. For instance, the orthologs of human insulin and insulin-like growth factor in *Drosophila* are also involved in regulating carbohydrate metabolism and organismal growth, and the signaling pathways downstream of the receptor are conserved from flies to mammals [98, 140, 141] (Table 3). Similarly, the tachykinin substance P modulates pain signaling in the spinal cord of vertebrates and in *Drosophila* TK signaling regulates a specific form of nociception in the VNC [19, 142]. Another example is sulfakinins (DSK) and CCK that regulate satiety and certain gut functions in *Drosophila* and mammals [22-24]. Other examples of functional conservation of neuropeptides in vertebrates and *Drosophila* are listed in Table 3 and will be discussed in later sections.

Table 3: Functional conservation of neuropeptide systems in insects and vertebrates.

Peptide family Vertebrates/insects	**Common functions**	**References**
Galanin/Ast-A	Feeding, sleep, hormone release	[143-145]

Neuromedin U/CAPA Neuromedin U/Hugin-PK	Stress response and ion transport Feeding	[65, 146] [147, 148]
Calcitonin/DH31	Temperature preference	[149]
CRF/DH44	Stress response and feeding	[150-152]
Insulin/DILP1-3, 5	Carbohydrate homeostasis and lifespan	[153-155]
IGF/DILP6	Growth	[156, 157]
Vasopressin/inotocin	Fluid homeostasis	[158, 159]
Relaxin/DILP7	Reproduction	[160]
NPY/NPF	Feeding, metabolism, aggression	[112, 161]
GnIH/SIFamide	Feeding, reproduction	[162]
CCK/DSK	Satiety, gut function	[24]
Substance P/TK	Nociception, gut function, aggression	[19, 21, 163, 164]

In addition to the conserved functions, most signaling systems have also evolved novel functions in various taxa. These novel functions could be species or phylum specific. For instance, various members of the adipokinetic hormone/ gonadotropin-releasing hormone (AKH/GnRH) family have evolved novel functions. Thus, AKH mobilizes lipids from fat stores in insects, red pigment concentrating hormone (RPCH) regulates pigment mobilization in crustaceans, and GnRH stimulates the release of gonadotropins (follicle-stimulating hormone and luteinizing hormone) from the anterior pituitary in vertebrates [see [165-167]]. On the other hand, members of the corazonin family have evolved diverse roles within insects. Hence, the widespread and well conserved peptide corazonin [168] affects various behaviors and physiology, including heart rate in *P. americana* [169] and *Rhodnius prolixus* [170], silk spinning rate in *Bombyx mori* [171], ecdysis initiation in *Manduca sexta* [172], pupariation in *Bactrocera dorsalis* [173], dark-color induction in locusts [174, 175], caste identity in ants [176], sperm transfer in *Drosophila* [177, 178], and regulation of stress responses in various insects, including *Drosophila* [179-183]. In summary, this comparative approach has greatly improved our understanding of the evolution of neuropeptide signaling pathways as well as their functional significance in animals. More importantly, discovering novel neuropeptide/GPCR signaling systems through comparative neuropeptidomics and identifying their functions in invertebrates such as insects, nematodes and annelids can provide clues about the functions of their orthologs in vertebrates including humans.

Finally, it can be added that some insect GPCRs can be activated by more than one ligand (Table 4). In *Drosophila* this has been investigated for PDF, PK-1 and sex peptide receptors (Table 4).

Table 4. Insect GPCRs with more than one ligand

Species	**Receptor**	**Ligands**	**References**
Drosophila	PDF receptor	PDF and DH31	[149, 184, 185]
Drosophila	Sex peptide receptor	Sex peptide and MIPs	[186-188]
Bombyx	Pyrokinin receptor	Pyrokinin and ITP	[189, 190]
Bombyx	Tachykinin receptor	TK and ITPL	[189, 191]
Drosophila	PK-1 receptor	Capa-PK (PK-1) and limostatin	[192]

4. 3. Neuropeptides lost in *Drosophila*

Since the *Drosophila* genome was the second to be sequenced after *C. elegans* [193], it was also the first insect to have its neuropeptidome revealed [37, 94]. As more insect genomes and transcriptomes were sequenced [31, 42, 83, 190, 194] it became apparent that *Drosophila* has one of the smallest insect neuropeptidomes owing to the fact that it has lost several neuropeptide signaling systems which are present in basal insects like the migratory locust *Locusta migratoria* and the termite *Zootermopsis nevadensis* [31]. Neuropeptide systems lost in *Drosophila* include AKH/corazonin related peptide (ACP) [195], agatoxin-like peptide (ALP) [196], allatostatin-CCC [197], allatotropin [37], calcitonin, elevenin, neuroparsin, SMYamide [31], thyrotropin-releasing hormone (TRH) [66], tryptopyrokinin [198], neuroparsins [199] and inotocin (related to vertebrate oxytocin/vasopressin) [159]. The lack of powerful genetic tools in other insect models has hampered investigations into these signaling systems. There are, however, a few studies that have elucidated some of the function of these signaling systems and we highlight some examples here.

Inotocin and allatotropin were among the first insect neuropeptides to be discovered [159, 200, 201]. RNA interference (RNAi) mediated knockdown of inotocin in the red flour beetle *Tribolium castaneum* does not cause mortality or any visible abnormal phenotype [158]. However, it does influence the release of a hormone from the CNS plus corpora cardiaca/corpora allata (CC/CA) that stimulates Malpighian tubule secretion, *in vivo*. Allatotropin was first discovered from *M. sexta* based on its ability to stimulate juvenile hormone (JH) secretion from CA [200]. In these *in vitro* assays, the entire CC/CA complex was used to determine the effect of peptides. Hence, there was some ambiguity over the target site of allatotropin. The characterization and localization of its receptor in *B. mori* revealed that the allatotropin receptor is in fact expressed in the CC, which is also the site for sNPF production [190]. Thus, the effect of allatotropin on JH secretion could be partially mediated by sNPF [202]. In addition to its role in JH secretion, allatotropin influences various other processes including myostimulation [203-207], digestive enzyme secretion [208], feeding [209] and photic entrainment of the circadian clock [210].

The ACP signaling system was discovered relatively recently following the characterization of its receptor in *A. gambiae* and *T. castaneum* [195]. RNAi mediated knockdown of the ACP receptor in *T. castaneum* has no effect on physical appearance, egg number and mortality. Both ACP and its receptor are predominantly expressed in the CNS of *T. castaneum* [195], *R. prolixus* [166] and *A. aegypti* [211], which indicates a neuromodulatory role for this signaling system. In addition, the temporal expression profile data suggest that ACP could be involved in post-ecdysis related processes [166, 211]. Lastly, recent work in the brown planthopper *Nilaparvata lugens* has shown that knockdown of elevenin or its receptor results in cuticle melanization [212]. Hence, it is involved in post-ecdysis related behavior. The functions of ALP, allatostatin-CCC, calcitonin, SMYamide and TRH in insects are still unknown [31, 194, 196, 197].

4. 5. Further vertebrate neuropeptides with potential insect orthologs

It would be safe to assume that some neuropeptide signaling systems remain to be discovered in insects. One such neuropeptide that could be present in *Drosophila* and other insects is nesfatin-1 and nesfatin-1-like peptide, which are encoded on the nucleobindin 2 (NUCB2) and nucleobindin 1 (NUCB1) precursors, respectively [213, 214]. Nesfatin-1 (Nucleobindin-2-Encoded Satiety and FAT-Influencing proteiN-1), was discovered in 2006 as a satiety-inducing factor in the rat hypothalamus [215]. It modulates several other processes including glucose and lipid metabolism, as well as cardiovascular and reproductive functions [216]. On the other hand, nesfatin-1-like peptide derived from NUCB1 was shown to be anorexigenic in goldfish [214]. Interestingly, a NUCB precursor is encoded in the *Drosophila* genome as well as in the transcriptomes of various echinoderms (deuterostomian invertebrates) [62]; however, its peptide products have not yet been experimentally identified. Hence the identity, expression and function of insect nesfatin-1 orthologs remain unknown.

5. Brief overview of *Drosophila* neuropeptides and peptide hormones

In this section, we briefly present data on all the known *Drosophila* neuropeptides and peptide hormones, such as first chemical isolation, gene cloning (or identification by bioinformatics), receptor identification, peptide and receptor distribution and core functions. We provide an extensive summary of data for each neuropeptide known in *Drosophila* in a Tabular form in Supplementary Materials Appendix 1. An emphasis is on updating *Drosophila* findings since 2010 [35]. We also highlight the presence of related peptides (encoded on separate genes) and evolutionary relationships to peptides outside of insects.

Note that there are some ambiguous peptides among the ones listed in that text. Various transcriptomics and peptidomics approaches have led to the discovery of novel potential peptides and peptide-encoding precursors. Purification of peptides based on a particular bioassay has also led to the identification of bioactive peptide fragments. These include anti-diuretic factor, baratin, limostatin, NPLP2, NPLP3, NPLP4, ITG-containing, NVP-containing, IDL-containing peptides and various others [31, 42, 121, 122, 192, 217, 218]. It is still unclear if all of these represent typical neuropeptides in that they are (1) produced in the nervous system, (2) encoded by a larger precursor which contains a signal peptide, (3) mediate their effects by activating a GPCR (or other receptor types) and (4) the mature peptide (not just the precursor) has high sequence similarity with orthologs in other insects. Consequently, several studies have questioned their classification as neuropeptides. Thus, until additional information becomes available supporting their classification as neuropeptides, these peptides are classified as "potential neuropeptides".

For additional details and comprehensive listings of peptide sequences from numerous insect species the reader is referred to the DINeR database (http://www.neurostresspep.eu/diner/insectneuropeptides) [see [96]] and (http://prodata.swmed.edu/FlyXCDB) [see [219]]. By isoforms we mean sequence-related mature peptides encoded on the same precursor, such as for instance allatostatin-A1 - 4; in some cases the precursor contains peptides with unrelated or divergent sequences, or even putative peptides whose functions are not known. Receptors of neuropeptides are GPCRs unless indicated otherwise.

6. Neuropeptides and peptide hormones found in other insects, but not *Drosophila*

6.1. Adipokinetic hormone/Corazonin-related peptide (ACP)

An adipokinetic hormone/corazonin-related peptide (ACP) was isolated from corpora cardiaca extracts of the locust *Locusta migratoria* [220], and was later found in the beetle *Tribolium castaneum* [122], the silkmoth *Bombyx mori* [38], and the mosquitos *Anopheles gambiae* [221] and *Aedes aegypti* [222]. Initially, these peptides were considered as AKHs due to sequence similarities. Now it is clear that, unlike the *bona fide* AKHs, which are produced in corpora cardiaca and mobilize lipids from the fat body, ACPs are produced in neurons of the brain and display no adipokinetic activity [220, 223]. The ACP signaling system is lost in *Drosophila* and the honeybee *Apis mellifera.*

ACP receptors (GPCR) were identified in *A. gambiae* and *T. castaneum* and it was clear that this ligand-receptor complex constitutes a separate signaling system, that is ancestrally related to AKH and corazonin signaling systems [195]. Moreover, phylogenetic analysis of the receptors suggests that AKH and ACP signaling systems are paralogous [139].

The distribution of ACP has been mapped to one pair of large and two pairs of smaller neurons in the brains of *T. castaneum* and *Rhodnius prolixus* [195, 223]. ACP has a broader distribution in mosquitoes where ACP-like immunoreactivity was also detected in neurons in thoracic ganglia [221]. ACP may act as a central neuromodulator, since its receptor is predominantly found in the central nervous system [166, 195]. The specific function of ACP signaling remains unknown, although its temporal expression suggests that it may play a role in development and/or ecdysis [166, 195, 211].

Related peptides: ACP is paralogous to AKH in arthropods, both of which are orthologous of mammalian gonadotropin releasing hormone [224]. ACP is distantly related to corazonin although the two peptides bear sequence similarity.

6. 2. Agatoxin-like peptide (ALP)

Agatoxin-like peptide was recently identified in *Apis mellifera* corpora cardiaca (CC) extract using mass spectrometry [196]. The same study also identified this peptide in the CC extract from the firebrat *Thermobia domestica* and in the brain, CC and stomatogastric nervous system extracts from the cockroach *Periplaneta americana*. This peptide shares sequence similarity with a toxin found in the spider *Agelena orientalis* [225]. ALPs are also found in other insect genomes and they all have 8 conserved cysteine residues. The function of ALPs in insects is not yet known.

6. 3. Allatostatin-CCC (AST-CCC)

This group of peptides was identified in a BLAST search of several arthropod genomes [197]. Among insects, allatostatin-CCC (AST-CCC; Allatostatin triple C) was only identified in the genomes of *Locusta migratoria* and *Athalia rosae*. Other insect genomes (including that of *Drosophila*) only contain genes for AST-C and AST-CC. Like the other two peptides, AST-CCC contains two cysteines that can form a disulfide bridge, but also has a C-terminal amide, which is not found in the other related peptides. The distribution, function and receptor for this peptide are still unknown.

6. 4. Allatotropin (AT)

Allatotropins (AT) stimulate biosynthesis of juvenile hormone (JH) in the corpora allata. The first AT was identified from the moth *Manduca sexta* [200], and an allatotropin gene was cloned in the same species [226]. ATs have been discovered in several insect orders, but AT and its receptor have been lost in *Drosophila* [37]. The ATs have a characteristic TARGFamide C-terminus [227]. Two AT receptors were characterized in *Bombyx mori* [190], followed by identification of receptors in *Aedes aegypti*, *Tribolium castaneum, Schistocerca gregaria* and *M. sexta* [207, 227]. These GPCRs are related to mammalian orexin receptors [32, 33]; however, the insect AT and vertebrate orexin peptides display no similarities and the disulfide bridges of orexins are absent in allatotropins.

AT expression has been mapped in *Schistocerca gregaria, M. sexta, Heliothis veriscens, Leucophaea maderae, Periplaneta americana,* and *Rhodnius prolixus* [203, 206, 228-230]. AT-immunoreactive neurons are spread throughout the CNS, especially in the optic lobes. Also, AT is present in median neurosecretory cells in the brain that send axons to the retrocerebral complex, as well as neurosecretory cells in the abdominal ganglia.

AT stimulates JH biosynthesis in several insect species [227]. Other actions of AT have been found, including myostimulation [203-206], induction of release of digestive enzymes in the midgut [208], entrainment of the circadian clock [210], and regulation of feeding [209, 231]. It has been proposed that in *Drosophila,* the allatotropic role, in the absence of AT, is taken over by DILPs from IPCs [see [232-234]].

6. 5. Calcitonin

A gene that codes for calcitonin was identified in the locust and termite genomes [31]. Earlier, the first protostomian calcitonin gene had been identified in the polychaete annelid, *Platynereis dumerilii* [58]. The insect calcitonin gene gives rise to two transcripts that generate two different peptides calcitonin-A and calcitonin-B. Both of these isoforms have a C-terminal Pro-amide and a disulfide bridge at the Nterminus, which is missing in calcitonin-like diuretic hormone 31 (DH31). Several basal insects possess genes encoding both DH31 and calcitonin, whereas the calcitonin gene has been lost in several insect groups including *D. melanogaster*. Putative receptors for calcitonin-A and calcitonin-B have been predicted [31], but have not yet been functionally characterized. The distribution and function(s) of this peptide remains unknown in insects.

6. 6. Elevenin

In 1984 a cDNA encoding a neuropeptide precursor was isolated from a single neuron, known as neuron L11, in the abdominal ganglion of the slug *Aplysia californica* [235]. The mature peptide generated from this precursor was identified only in 2010 when genes encoding this precursor were found in other mollusks and insects [91]. The name elevinin was derived from the neuron of origin, the L11 neuron. There are two cysteine residues in elevenin, which could result in a disulfide bridge. Thus, the peptide bears structural similarities to CCHamide of insects and GGNG peptides found in annelids and mollusks [33]. An elevenin receptor (GPCR) was identified in the annelid *Platynereis dumerilii* and found to be related to CCHa/EP/neuromedin-B/gastrin-releasing peptide receptors [57]. An elevenin receptor has also been identified in the brown planthopper *Nilaparvata lugens* and shown to regulate cuticle melanization [212].

6. 7. Neuroparsins

Neuroparsin (NP) was originally isolated from the pars intercerebralis-corpora cardiaca complex of the locust *Locusta migratoria,* and thus its name [236, 237]. Neuroparsin B from the locust is a homodimer consisting of two cysteine-rich peptides with 78 residues each, connected by disulfide bridges [236]. Locusts produce several NP variants, probably as a result of alternative splicing and these splice forms are expressed in a tissue-, stage-, and phase-dependent manner [31, 238-240]. NPs and related peptides are known from several insect groups. The sequences of NPs are more divergent in higher insect orders, such as Diptera, and they are absent in *D. melanogaster,* and several related species in the *melanogaster* subgroup of the genus *Drosophila* [199].

A NP-like peptide hormone, the ovary ecdysteroidogenic hormone (OEH), was identified in the mosquito, *Aedes aegypti*, [241]. In the female mosquito OEH stimulates ecdysteroid biosynthesis in ovaries after a protein-rich blood meal. OEH acts on a receptor tyrosine kinase (RTK) to affect egg formation in this mosquito [100]. This OEH receptor is distantly related to insulin receptors, but differs by possessing a Venus flytrap module, present also in amino acid receptors. Close relatives of the OEH receptor are present in several other Diptera, including non-*melanogaster* species of *Drosophila* where NP sequences have also been identified [199].

The distribution of NP in locust and OEH in mosquito has been mapped by immunocytochemistry to cells of the median neurosecretory group in the pars intercerebralis [241-243]. Two to three pairs of OEH expressing neurons were detected in the mosquito brain, whereas a larger number of NP neurons were mapped in the locust. Due to the expression of NP and OEH in neurosecretory cells it is likely that the peptides play hormonal roles.

Locust NP was initially identified as an anti-gonadotrophic factor whose action was opposite to that produced by juvenile hormone (JH), but did not directly affect biosynthesis of JH [237, 244]. In *A. aegypti,* OEH stimulates ecdysteroid biosynthesis in ovaries after a blood meal [241]. NPs also appear to act as hormone binding proteins and they do display sequence similarities to the N-terminal hormone-binding module of IGF binding proteins (IGFBPs) [see [232, 240]]. It was shown that recombinant locust NP interacts with a purified locust insulin-like peptide (ILP) *in vitro* [245]. Other proteins, designated neuroparsin-like peptides (NPLPs) in arthropods, also display similarity to the N-terminal sequence of the IGFBP module in mammals [240]. The *in vivo* function of these IGFBP-like proteins may thus be to control the availability of ILPs, as the IGFBPs do in mammals.

6. 8. SMYamide

Genes encoding this peptide were first identified in the *Locusta* and *Zootermopsis* genomes [31]. These peptides share sequence similarity with SIFamides. The distribution and function of these peptides remain unknown.

6. 9. Vasopressin-like peptides (inotocins)

A vasopressin-like nona-peptide was first identified from the locust *Locusta migratoria* [201] and later in some other insects species such as *Tribolium castaneum* and *Nasonia vitripennis* [159]. However, vasopressin-like peptides have been lost in several insect species, including *Drosophila* [159, 246]. In invertebrates, the vasopressin-like peptides have a well-conserved sequence and are cyclic peptides, due to an internal cysteine bridge [122] and were named inotocins [159]. In *Tribolium* the sequence of inotocin is CLITNCPRGamide [122]. Inotocin receptors have been identified from *Tribolium, Nasonia* and the black garden ant *Lasius niger*, and these display strong sequence similarities to inotocin receptors from the water flee *Daphnia pulex* and the pond snail *Lymnaea stagnalis,* as well as mammalian receptors to oxytocin and vasopressin [158, 159, 247].

In locusts and *Tribolium,* inotocin is distributed in only one pair of neurons with cell bodies in the subesophageal ganglion and processes that arborize extensively in the brain and ventral nerve cord [158, 248, 249]. Vasopressin-like immunoreactivity was also detected in a similar pair of neurons in cockroaches and mantids [250, 251]. In the locust, the inotocin expressing neurons colocalize FLRFamide-immunoreactivity (suggesting presence of myosuppressin) and have inputs from extraocular photoreceptors, but their physiological role was not determined [252]. The inotocin receptor of *Tribolium* is expressed mainly within the CNS, and not in renal tubules [158, 159]. Furthermore inotocin has no direct effect on the *Tribolium* tubules [158]. Thus, since global knockdown of inotocin affects diuresis, although the receptor is confined to the CNS and no processes of the inotocin-producing neurons extend outside the CNS, it was suggested that inotocin regulates neurosecretory cells that produce a diuretic hormone [158]. More recent work has shown that knockdown of inotocin in *Lasius* ants results in increased locomotor activity, self-grooming and influenced expression of genes involved in metabolism [253].

7. Distribution of neuropeptides and their receptors in *Drosophila*

7.1. Peptide and receptor distribution

A first very useful resource to find out where a neuropeptide or its receptor is expressed is to consult the FlyAtlas and FlyAtlas2 databases [http://flyatlas.gla.ac.uk, http://flyatlas.gla.ac.uk/FlyAtlas2/index.html [114, 115]], which provide information about gene transcripts in larval and adult tissues based on gene microarray and RNA-Seq analyses, respectively. In Fig. 3 and 4, we provide a summary of neuropeptide and GPCR gene expression in different tissues of *Drosophila* based on FlyAtlas. In Fig. 5 we show the neuronal distribution of neuropeptides in the larval CNS [based on numerous accounts, including [40, 111]].

The cellular distribution of many neuropeptides has been mapped in more or less detail in *Drosophila* by immunolabeling or Gal4-UAS-driven GFP. For several neuropeptides morphological descriptions are quite detailed, especially in third instar larvae, for others only the cell body locations have been revealed. Here, we supply a set of maps of neuropeptidergic cell bodies in the third instar larva to provide a first idea of the diversity in distribution patterns of different neuropeptides (Fig. 5). Note that this set of maps is not comprehensive; some neuropeptides are missing due to incomplete descriptions. As an example of detailed analysis of peptide distribution, including neuronal processes, we show DH44, leucokinin and leucokinin receptor distribution in Fig. 6.

The introduction of the Gal4-UAS system [254] made it possible to reveal the detailed morphology of sets of neurons by using the promoter of a neuropeptide precursor gene or by using CRISPR/Cas9 edited Gal4-knock-in flies to drive expression of strong fluorescent reporters. Several other strategies have also been developed to examine the expression, and later perturb the function, of genes [255]. Excellent anatomical images describing the expression patterns of these Gal4 lines are available in various databases (Gene Disruption Project Database, http://flypush.imgen.bcm.tmc.edu/pscreen/rmce/ ; FlyLight, http://flweb.janelia.org/cgi-bin/flew.cgi; Flygut, http://flygut.epfl.ch/patterns). These are, however, mostly Z-stacks without detailed annotations or specifics about neuron morphology in relation to CNS structures (neuropils and other neuron types). As will be discussed below, there are several individual publications with more detailed information. Especially by use of refined techniques that enable dissection of peptidergic neuron populations [256-259] our understanding of peptidergic systems has increased immensely. Intersectional techniques that reveal neuron-neuron relations, including GFP reconstitution across synaptic partners (GRASP) [260] and trans-synaptic marking (trans-Tango) [261] have also been recently employed to study peptidergic circuits in flies [162, 262-264].

Unfortunately, there is no comprehensive and systematic analysis of the distribution and morphology of peptidergic neurons available yet. Another shortcoming is the lack of reliable information on expression of receptor protein at the cellular level. Thus, we have very little knowledge about sites of action of neuropeptides. This is accentuated by the fact that neuropeptides are presumed to act also non-synaptically in a paracrine fashion, by so-called volume (or bulk) transmission [see [9, 11, 265, 266]]. Thus, there is the possibility that techniques like trans-Tango and GRASP will not help in identifying all targets of peptidergic neurons. There are, however, a few cases where neurons targeted by specific neuropeptides have been identified by experimental approaches, but in each case only a few neurons at a time. For example in the clock system some of the functional peptidergic "connections" have been established [see e. g. [262, 267, 268] and section 8.1.5.]. Another example: by identifying receptors on the insulin producing cells (IPCs) many of their peptidergic (and other neurotransmitter/ neuromodulator) inputs have been identified [summarized in [232, 269] and section 8. 2. 1]. Thus, in summary, we have to consult individual papers describing the structure and function of specific peptidergic pathways. In Table 5 we list neuropeptides mapped to subregions (neuropils) of the adult brain of *Drosophila* (see also the peptide descriptions in Section 5).

In the adult *Drosophila* brain, many neuropeptides have been mapped in various levels of detail. It is beyond the scope of this review to provide information on all these distribution patterns. In Table 5 we show the distribution of neuropeptides in different neuron types and neuropils of the *Drosophila* brain (based on individual research papers, cited in section 5). The distribution of peptidergic neurosecretory cells is shown in Fig. 7. Most of these larval cell systems have been described in detail and their functional roles worked out to a varying extent as will be described in later sections.

Table 5. Neuropeptides in neurons of the adult *Drosophila* brain and subesophageal ganglion.

Neuropeptide	**Acronym**	**Distribution**[1]							
		Neuropil					Cell bodies		
		AL	MB	OL	CX	UnN	clock	NS	DN
Allatostatin A	AstA	x	-	x	x	x	-	x	-
Allatostatin B/MIP	AstB; MIP	x	-	x	x	x	-	nt	-
Allatostatin C[2]	AstC	-	-	nt	-	x	x[3]	nt	
Capability	CAPA/PK	-	-	-	-	x	-	-	-
CCHamide-1[2]	CCHa1	-	-	x	-	x	x[3]	nt	nt
CNMamide	CNMa	-	-	-	-	-	x[3]	x	-
Corazonin	Crz	x	-	x[4]	-	x	-	x[5]	-
Crustacean cardioactive peptide	CCAP	-	-	-	-	x	-	-	x
Diuretic hormone 44	DH_{44}	-	-	-	-	x	x	x	x
Diuretic hormone 31[2]	DH_{31}	-	-	nt	-	x	x	nt	nt
FMRFamide (extended)	dFMRFa	-	-	x	x	x	-	x	-
Glycoprotein beta 5[3]	GPB5	-	-	-	-	x	-	x	-
Hugin	hug-PK	-	-	-	-	x	x[3]	x	x
Insulin-like peptides (ILPs)	ILP1,2,3,5	-	-	-	-	x	-	x[5]	-
Ion transport peptide	ITP	-	-	-	-	x	x	x[5]	x
IPNamide[2]	IPNa	x	-	x	-	x	x	-	
Leucokinin	LK	-	-	-	-	x	-	-	x
Myosuppressin	DMS	x	-	x	x	x	x[3]	x	
Natalisin	NTL	-	-	-	x	x	-	-	x
Neuropeptide F (long)	NPF	-	-	-	x	x	x	-	x
Orcokinin-A	OK-A	-	-	x	-	x	-	-	-
Pigment-dispersing factor	PDF	-	-	x	-	x	x	-	-
Proctolin	Proct	-	-	x	x	x	-	x[5]	-
Short neuropeptide F	sNPF	x	x	x	x	x	x	x[5]	x
SIFamide[6]	SIFa	x	-	x	x	x	-	-	x

Sulfakinin	DSK	-	-	x	-	x	-	x[5]	x
Tachykinin	DTK	x	-	x	x	x	-	x[5]	x
Trissin[2]	Tris	nt	nt	nt	nt	nt	x[3]	nt	nt

Notes: This Table was updated from Table 5 in [35]

[1] Abbreviations: AL, antennal lobe; *MB*, mushroom body; *OL* optic lobe; *CX*, central complex; *UnN*, neurons branching in neuropils interspersed between the structured ones listed; *clock*, clock neurons; *NS*, neurosecretory cells (MNCs or LNCs in protocerebrum); *DN*, descending neurons. Note that some peptides have been more carefully mapped in the larval brain and the information on adult brain is patchy (see note 2 below). For original references see the text under the headings of the different peptides in section 5. x, detected; nt, not tested; -, not found.

[2] Ast-C, CCHa-1, DH_{31}, IPNa and Tris distributions have not been analyzed in detail in the entire adult brain.

[3] The peptide products of these genes have not been demonstrated in tissues. The data are based on single cell RNAseq analysis or GAL4 driven GFP.

[4] Expression seen mainly in younger flies [270]

[5] These cells may also use peptides to control release of peptide hormones in corpora cardiaca and/or corpora allata.

[6] Four neurons arborize profusely in most brain neuropils

7. 2. Peptide colocalization

It has been found that many peptidergic neurons/neuroendocrine cells in *Drosophila* express more than type of neuropeptide, or even co-express a small molecule (classic) neurotransmitter [summarized in [9]]. This is a widespread phenomenon in vertebrates and e. g. mollusks and crustaceans, where the functional consequences of co-release of neurotransmitters/ neuropeptides has been extensively studied [see [10, 13, 271, 272]]. In CNS circuits, neuropeptides often act as co-transmitters that modulate the response of the classical neurotransmitter at the synapse [10].

Recent reports using single cell transcriptomics have extended our view of the extent of colocalization of peptides with peptides or neurotransmitters in the *Drosophila* brain [117, 118, 273]. It appears to be a quite common phenomenon, but needs to be confirmed by conventional methods where also the morphological identities of the neurons are revealed (now dissociated neurons are identified by gene expression patterns). In *Drosophila* there are some examples of colocalized neuropeptides in the clock system, antennal lobe, neurosecretory cells and neurons of the ventral nerve cord [summarized in [9]]. These are shown in Table 6.

Table 6. Colocalization of neuropeptides with neuropeptides and other neuroactive substances in neurons and endocrine cells of *Drosophila*[1].

Tissue[2]	Cell type[2]	Substances[3]	References
Brain	IPCs (NSCs; PI)	DILP1, 2, 3, 5, DSK	[24, 98, 274]
Brain	MNCs (NSCs; PI)	DH44, DILP2	[275]
Brain	DLP (NSCs; PL)	CRZ, sNPF, proctolin	[183, 276]
Brain	ipc-1 (NSCs; PL)	ITP, sNPF, TK	[17]
Brain	l-LNv (clock neurons)	PDF, NPF, Upd1	[277, 278]
Brain	s-LNv (clock neurons)	PDF, sNPF, glycine[4]	[279, 280]
Brain	5th s-LNv (clock neur.)	ITP, NPF, Ach[4]	[277, 280]
Brain	LNd (clock neurons)	ITP, NPF	[280]
Brain	LNd (clock neurons)	sNPF, Ach[4]	[280]
Brain	DN1a (clock neurons)	DH31, IPNamide, CCHa1, Glutamate[4]	[149, 281-283]
Brain	DN1p (clock neurons)	DH31, Glutamate[4, 5]	[281, 284]
Brain	LN (local neurons; AL)	MIP, Ach[4]	[285]
Brain	LN (local neurons; AL)	AstA, Ach[4]	[285]
Brain	LN (local neurons; AL)	TK, GABA[4]	[16]
Brain	LN (local neurons; AL)	TK, MIP	[285]
Brain	LN (local neurons; AL)	TK, Ast-A	[285]
Brain	LN (local neurons; AL)	MIP, Ast-A	[285]
Brain	OSNs (sensory; AL)	sNPF, Ach[4]	[110, 286]
Brain	OSNs (sensory; AL)[6]	MIP, Ach[4]	[287]
Brain	Kenyon cells (MB)	sNPF, Ach[4]	[109, 288]
Brain	NPF interneurons[7]	NPF, sNPF	[110]
Brain	Small interneurons	sNPF, GABA[4]	[110]
Brain	Small interneurons	sNPF, Ach[4]	[110]
Brain	Small interneurons	sNPF, glutamate[4]	[110]
Brain	ICLI large interneurons	Ast-A, MIP, Natalisin	[131]
SEZ	Hugin neurons (L1)[8]	Hug-PK, Ach[4]	[64]
SEZ	Large SEZ neurons	Capa-PK, Hug-$PK_{2\text{-}15}$	[132]
CC	Corpora cardiaca cells	AKH, Limostatin	[192, 289]
VNC	ABLK (NSCs)	LK, DH44	[150]
VNC	DP1 (interneurons; L3)	DILP7, sNPF, Ach[4]	[110, 290]
VNC	CCAPa (NSCs; L3)	CCAP, Bursicon	[291]
VNC	CCAPp (NSCs; L3)	CCAP, Bursicon, MIP, Ast-CC	[292]
VNC	Motoneurons (RP2; L3)	Proctolin, glutamate[4]	[293]
VNC	CRZ neurons (males)	CRZ, Ach[4]	[178]
Midgut	Endocrine cells	TK, NPF	[294]
Midgut	Endocrine cells, posterior	TK, DH31	[294]
Midgut	Endocrine cells, middle	Ast-C, Orcokinin B	[295]

Midgut	Endocrine cells, L3	MIP, Ach[4]	[296]

Notes
[1] Updated from [9]. In adults, unless otherwise specified (L1 and L3, 1st and 2nd instar larvae)

[2] Abbreviations (some acronyms are established names of neurons, and not explained here):
SEZ, subesophageal zone
CC, corpora cardiaca
VNC, ventral nerve cord
IPCs, insulin producing cells
NSCs, neurosecretory cells
PI, pars intercerebralis
PL, pars lateralis
AL, antennal lobe
OSNs, olfactory sensory neurons (antennae to brain)
MB, mushroom body

[3] Abbreviations of peptides/transmitters as in text. If not otherwise specified determined by immunocytochemistry and/or Gal4 expression; in some cases antisera to biosynthetic enzymes.

[4] Detected by promoter-Gal4 expression or antisera to biosynthetic enzymes

[5] Note that DN1p constitute a cluster of neurons and individual ones have not been investigated; these cells appear heterogeneous in terms of transmitters/modulators.

[6] In female flies

[7] In hugin-PC and hugin-VNC/PH cells

8. Recent advances in roles of neuropeptides and peptide hormones in behavior and physiology of *Drosophila*

Neuropeptides have regulatory roles in various behaviors including locomotion, odor-guided foraging, activity/sleep, feeding, aggression and reproductive behavior, as well as learning and memory. Neuropeptides and peptide hormones are also important in regulation of many aspects of physiology and maintenance of homeostasis in daily life and during the life cycle. In *Drosophila,* progress in this field was slow until rather recently when the availability of powerful molecular and genetic techniques enabled studies of peptide signaling also in the tiny fly. With availability of the Gal4-UAS system and derivative techniques [see [254, 256, 297, 298]] analysis of peptide signaling and its consequences for behavior and physiology has gained traction [see [6, 7, 68, 299]]. There are still difficulties associated with studying neuropeptides such as the diversity in functions of a given neuropeptide, the neuronal colocalization of several neuropeptides, or of neuropeptides and small molecule neurotransmitters, the existence of volume transmission that goes beyond the connectome and the complex signaling downstream of the peptide receptors [reviewed in [9-11, 35, 64]]. Many neuropeptides are functionally pleiotropic and can be released from a huge variety of neuron or cell types in the CNS, periphery, intestine, endocrine cells, glia and so on. Furthermore, the neuropeptide expression and functions may change with the development and aging of the organism. Finally, there is a huge gap in our knowledge of neuropeptide receptor distribution and receptor signaling mechanisms in *Drosophila*, and other insects. Although numerous Gal4 driver lines exist that supposedly represent neuropeptide GPCR expression, very few have been completely verified by immunolabeling with antisera to the receptor protein or other independent techniques. Analysis of GPCR mutants yield data on the overall loss of function, but results may be masked by possible diversity in circuits where receptors act (and by diversity in signaling activated by the receptors). The use of GPCR-RNAi requires screening of huge numbers of neurons (Gal4-lines), unless the receptor distribution is known.

In the following section we summarize known roles of *Drosophila* neuropeptides in regulation of behavior and physiology with an emphasis on recent findings (summarized in Table 7). For more details on these aspects, especially from slightly older work and studies of other insects, the reader is referred to some other reviews [6, 35, 67, 68, 75, 128, 299]

Table 7. Neuropeptides regulating behaviors in *Drosophila*

Behavior	**Neuropeptide**	**Circuit**	**References**
Olfaction	sNPF	OSN-PN Antennal lobe	[300]
	MIP	OSN-PN Antennal lobe	[287]
	TK	LN-OSN-PN Antennal lobe	[16, 301]
	CCHa1	OSNs Antennal lobe	[302]
	DILPs	OSN-PN Antennal lobe	[300]
	NPF	Brain interneurons	[303] [304]
	SIFa	Interneurons	[162]

Taste	sNPF	LNCs-Gr66a[1]	[305, 306]
	Hugin	Hugin neurons (SEZ)	[64, 147]
	TK	Pheromone pahway	[307]
	LK	LK neurons	[308]
	AKH	Gr5a	[309-311]
Food search/ Feeding	NPF	Interneurons	[161, 312-317]
	sNPF	OSNs-PNs, Interneurons MB circuits	[300, 312, 316, 318, 319]
	TK	OSNs-PNs	[301]
	Hugin	SEZ neurons	[147]
	Sex peptide	Via sperm In females	[320-323]
	DSK	IPCs and brain interneurons	[24]
	AKH	CC cells	[289, 309, 324]
	SIFa	Interneurons	[162]
	AstA	Brain neurons or EECs	[143, 145, 316, 325, 326]
	CCHa2	Gut, fat body	[327, 328]
	DH44	MNCs and VNC	[150, 152, 329]
	LK	Brain neurons	[330, 331]
	MIP	Brain neurons	[332]
	ITP	LNCs	[333]
	CRZ	LNCs	[181]
Locomotion (Independent of clock)	DSK	larvae	[334]
	Proctolin	larvae	[335]
	PDF	Outside clock	[336]
	AKH	CC larvae	[337]
	Ast-A	larvae	[325]
	LK	larvae	[338]
Explorative walking	sNPF	Central body	[339]
	TK	Central body	[339]
Clock/Sleep	PDF	clock circuit	[267, 340]
	sNPF	clock and other circuit	[267, 341, 342]
	NPF	clock circuit	[161, 343, 344]
	ITP	clock circuit	[345]
	DH31	clock circuit	[149]
	CCHa1	clock circuit	[283]
	Sex peptide	In females	[346]
	LK	Lateral horn neurons (LHLK)	[347-350]
	DH44	MNCs	[262, 263]
	SIFa	Brain neurons	[262, 348, 351]
	Hugin-PK	SEZ neurons	[263]
	MIP	Brain neurons	[352]
	FMRFa	CNS neurons	[353]
	DILPs	IPCs	[354]

	Bursicon	CNS neurons	[348]
	Ast-A	CNS neurons	[144, 326]
Aggression[2]	NPF	Interneurons	[355]
	Sex peptide	In females	[356]
	DSK	IPCs + others	[25, 357]
	TK	Interneurons	[164]
	DH44	DH44-R1 cells[3]	[358]
	Natalisin	Interneurons	[129]
Learning	sNPF	Mushroom Body	[359]
	Corazonin	Brain neurons[4]	[177]
	NPF	Interneurons	[360-362]
Nociception	sNPF (ILP7)	Interneurons [5]	[290]
	TK	Interneurons [5]	[19]
	Ast-C	Ast-C receptor	[363]
	Leucokinin	Lk receptor	[364]
Ethanol-related behaviors	Corazonin	LNCs	[365, 366]
	DILPs	IPCs	[367]
	NPF	Interneurons	[368]
Mating and copulation	NPF	Interneurons	[305, 368, 369]
	Corazonin	VNC	[177, 178]
	DH44	MNCs	[370]
	PDF	clock circuit	[305, 371]
	Sex peptide	Sperm transfer	[322, 372-374]
	SIFa	Interneurons	[375, 376]
	Natalisin	Interneurons	[129]
	MIP	Interneurons VNC (females)	[377]
Sperm storage	DH44	In females	[370]
Egg laying	DILP7	VNC efferents	[160]

Notes:
[1] The ipc-1 neurons regulate Gr66 bitter taste with sNPF
[2] Males if not indicated
[3] Specific cells in circuit not known
[4] A successful copulation is a reward in male flies and strengthens long-term appetitive memories
[5] Interneurons in VNC of larvae

8. 1. Peptides and regulation of behaviors

8. 1 .1. Aggression

Since male flies defend territories and compete over females they also display higher levels of aggression than females [164, 355, 378-381]. A few neuropeptides have been found to play important roles in regulation of aggression in male *Drosophila*: NPF, TK and DH44 [164, 355, 358]. Also female flies can display aggressive behavior and this aggression increases in mated flies due to sex peptide that is transferred with sperm at copulation [356].

A first study to implicate neuropeptides in modulation of male aggression discovered NPF as a negative regulator [355]. NPF was found to have a male-specific expression in six extra brain neurons compared to female brains [382]. Silencing of the NPF neurons in males leads to an increase in fighting frequencies [355]. These authors also showed that feminizing the NPF neurons with *Tra*^{F} (female splice form of *transformer*) produces more aggressive males. Taken together, this suggests that NPF decreases aggression and the inhibitory action of NPF is presumed to be on a male-specific neuronal circuit required for aggressive behavior [164, 355]. Interestingly, the same neuronal network in males may use NPF to decrease aggression levels and to increase courtship behavior [355, 382]. It is known that males that defend a territory rapidly switch between aggression and courtship depending on whether the invader is male or female [383] and, thus, NPF in these male-specific neurons may provide a switch between opposite social behaviors [355].

Aggression is not only quantitatively different in *Drosophila* males and females, but the actual behavior also differs somewhat between sexes [378, 380]. It has been shown that these differences in behavior are controlled by the gene *fruitless* (*fru*), which due to sex-specific splicing, underlies sex-specific morphologies of a rather large set of neurons [378, 384, 385]. Thus, the male-specific *fru* expressing (FruM^{+}) neurons are necessary and sufficient for male aggression [386]. More specifically, it was shown that a subset of the FruM^{+} neurons that produce TK are responsible for regulating levels of aggression in male flies [164]. Hence, a set of 4 neurons in the brain designated Tk-GAL4^{FruM} neurons control male-male aggression, but have no influence on male-female courtship behavior [164]. The TK receptor TakR99D (DTKR, CG7887) is required for this regulation of aggressive behavior [379]. It was found that the Tk-GAL4^{FruM} neurons also might produce acetylcholine and that this neurotransmitter therefore may play an additional role in the circuit [164].

Another peptide implicated in aggressive behavior is DH44. Knockdown of the DH44 receptor DH44R1 results in male flies that display increased aggressivity if they have been kept singly-housed, but are less aggressive after being kept in a group [358]. This paper provided no details on the DH44 neuron circuit.

As mentioned earlier, *Drosophila* females display aggressive behavior after mating, presumably to defend the territory and to provide for the offspring. A recent study shows that this increased aggressiveness is due to transfer of sex peptide during copulation [356]. It was shown that the presence of a single mated female was sufficient to increase aggression in encounters with other females [356]. Mating and sex peptide transfer produces a long-lasting change in physiology and behavior of the mated fly [322, 373, 387] and therefore it is possible that the increased aggressiveness was a secondary effect of the pregnancy. However, it was found that the elevated aggression required sex peptide transfer, and was not linked to the fly's ability to complete vitellogenesis or initiate egglaying. Surprisingly, flies lacking the sex peptide receptor were also found more aggressive [356]. Additional discussion on the conservation of neural mechanisms regulating aggressive behavior in animals can be found in this recent review [163].

8. 1. 2. Neuropeptides in olfaction and olfaction-guided behavior

Over many years the functional organization of the *Drosophila* olfactory system and olfactory behavior has been extensively investigated [see [7, 388-393]. Still, the roles of neurotransmitters and neuropeptides in olfactory processing and odor-guided behavior have received less attention and the studies so far have mainly concerned small molecule transmitters such as acetylcholine, GABA, glutamate and their receptors in olfaction [389, 394-400].

Using a combination of mass spectrometry and immunocytochemistry several neuropeptides were identified in the *Drosophila* antennal lobe [285]. Neuropeptides and neurotransmitters detected in the antennal lobe are shown in Fig. 8. That study demonstrated seven different neuropeptides in neurons with processes in the antennal lobe: allatostatin A (Ast-A), *Drosophila* myosuppressin (DMS), *Drosophila* tachykinin (DTK), IPNamide, myoinhibitory peptide (MIP; Ast-B), SIFamide and short neuropeptide F (sNPF). Neuropeptides have now been found in all major types of neurons in the antennal lobe: axon terminations of olfactory sensory neurons (OSNs), local neurons (LNs), projection neurons (PNs) and extrinsic (or centrifugal) neurons. Two peptides MIP and sNPF were detected in a subset of the OSNs [110, 285, 287]. sNPF was the first neuropeptide to be clearly identified in sensory neurons of *Drosophila* (and any insect) [110, 285], although tachykinin-related peptide and FMRFamide-like peptide were demonstrated by immunocytochemistry in leg sensory neurons in a locust earlier [401]. The neuropeptides (sNPF and TK) in PNs have only been identified by single cell transcriptomics so far [118]. In fed wild type flies sNPF positive OSN axon terminations are seen in 13 of the 50 glomeruli, suggesting odor-specific functions of the peptide [285]. MIP was only found in female flies in OSNs expressing Ir41a/Ir76b ionotropic receptors that are sensitive to polyamines [287, 402]. Neuropeptides in LNs are TK, Ast-A and MIP, whereas extrinsic neurons produce dromyosuppressin (DMS), IPNamide and SIFamide [16, 285]. It should be noted that the neuropeptides in OSNs, LNs and PNs are all colocalized with small molecule neurotransmitters. Thus, LNs utilize acetylcholine, GABA or glutamate as neurotransmitters and the OSNs and PNs are cholinergic, and neuropeptides of different types are employed as cotransmitters or neuromodulators [see [9, 389, 398]].

A few neuropeptide receptors have also been identified in antennal lobe structures: the sNPF receptor sNPFR1 in OSNs, the DTK receptor DTKR also in OSNs and probably in LNs, the MIP receptor (MIP/sex peptide receptor) in OSNs in female flies and CCHamide1 receptor in OR59b-expressing OSNs [16, 287, 300, 302, 339, 403].

The neuropeptides in OSNs partake in autocrine loops to facilitate food odor signals and strengthening food search in hungry flies (sNPF) or mated female flies (MIP) [287, 300]. The action of sNPF in modulation of food odor detection is based on the following mechanism. Hungry flies display vigorous food search and are mainly attracted to food-related odors. This food odor sensitivity is regulated by systemic insulin (DILP) signaling, acting on an autocrine signaling loop in the OSNs that consists of sNPF and its receptor sNPFR1 [300]. The insulin receptor (dInR) is expressed by OSNs together with sNPF and sNPFR1. A specific glomerulus, DM1, was studied with respect to this mechanism. In hungry flies circulating DILP levels are low and expression of the sNPFR1 is high in Or42b expressing OSNs in DM1 and stimulation with food odor triggers release of sNPF, that acts on the presynaptic autoreceptor and thereby increases release of acetylcholine, the primary transmitter in the synapse with projection neurons (PNs). This potentiates the food odor signal to higher brain centers and results in increased search for food [300]. In fed flies, the circulating DILP levels increase and activates the dInR in OSNs in antennae, which causes an inhibition of transcription of the sNPFR1 and thereby decreased autocrine sNPF signaling resulting in decreased activation of PNs and diminished food search [300].

MIP is another neuropeptide expressed in a subset of OSNs together with the MIP/sex peptide receptor [287]. This is only observed in female flies and specifically in OSNs expressing Ir41a/Ir76b ionotropic receptors known to be sensitive to polyamines [287, 402]. The MIP peptide also acts in an autocrine loop to regulate polyamine attraction in mated flies, and yet sex peptide does not seem to be involved in this specific circuit.

The LNs of the antennal lobe utilize acetylcholine, GABA and glutamate as primary neurotransmitters [389, 398] and some coexpress different neuropeptides: several GABAergic LNs produce TK [16], some cholinergic LNs express MIP or Ast-A, furthermore TK is coexpressed with MIP or Ast-A, and MIP was found together with Ast-A in LNs [285].

It was shown that TK from LNs acts on TK receptors (DTKR, *TkR99D*) in the OSNs to suppress calcium and synaptic transmission, and thus provide presynaptic inhibitory feedback [16]. A later study showed that also the TK receptor expression in OSNs (with Or42b and Or85a receptors) is also regulated DILP signaling after food intake [301]. The coordinated action of sNPF and TK diminishes synaptic outputs from Or42b OSNs (positive valence) and simultaneously increases outputs from Or85a OSNs (negative valence). This action diminishes the overall attraction of food odors. Starvation induces reduced DILP levels, which leads to upregulation of sNPFR and DTKR in their respective OSNs that leads to an increased attraction value of food odors [301]. Whereas it has been shown that sNPF facilitates cholinergic transmission in OSNs, it is not clear whether TK acts to modulate GABA transmission in LNs.

Further discussion of neuropeptides in olfactory processing and odor driven behavior in *Drosophila* and other insects can be found in recent reviews [7, 93, 393].

8. 1. 3. Neuropeptides in mushroom bodies regulating various behaviors

The mushroom bodies (MBs) are paired neuropils of the protocerebrum of the insect brain that are important for olfactory learning and memory [reviewed by [404-409]]. The MBs also play an essential role in controlling locomotor activity [410, 411], food-seeking behavior [316] temperature-preference behavior [412] startle-induced negative geotaxis [413], sleep [414, 415] and feeding [316].

Anatomically, each MBs is composed of about 2000 intrinsic neurons, Kenyon cells, that have dendrites in the calyx and supply axons via the peduncle to three main lobes, the α, β and γ lobes [405]. Chemosensory input neurons synapse with Kenyon cells in the calyx. Numerous MB output neurons (MBONs) have been identified with region-specific dendrite regions in the lobes and outputs in different parts of the brain [288, 407, 416-418].

8. 1. 3. 1. Mushroom bodies and olfactory learning

Most work on neuromodulation in circuits critical for learning and memory associated with mushroom bodies has focused on dopamine and octopamine [see [404, 409, 419-422]. The neurotransmitter of the intrinsic neurons, the Kenyon cells, was identified only recently as acetylcholine [288]. Additionally, sNPF was detected in a majority of the Kenyon cells that supply the lobes, except the α' and β' lobes and a small core in the center of the lobes [109]. Intact signaling with sNPF and its receptor is required in sugar-rewarded olfactory memory [359]. Later, it was shown that sNPF potentiates the response to acetylcholine in MBONs, suggesting that this peptide presynaptically facilitates the response to the fast neurotransmitter [288]. Since it is known that food-associated odor memory formation is enhanced by hunger [360], it would be of interest to determine whether sNPF signaling in the MBs is regulated by the fly's nutritional state and insulin signaling (IIS), similar to the OSNs where sNPF facilitates hunger-driven food seeking by increasing cholinergic transmission of food odors in olfactory circuits [300].

The remaining neuropeptides discussed here are used by neurons extrinsic to the MBs. Neurons producing NPF have been implicated in mushroom body circuits and olfactory learning [360] or in other circuits and forms of learning [362]. In the adult *Drosophila* brain, NPF is expressed in 20-26 neurons [382], and several of these appear to be presynaptic to dopaminergic neurons that innervate the mushroom body lobes [360]. The latter study showed that NPF is expressed in neuronal circuits important for the motivational activation in the output of appetite-related memory in *Drosophila*. Starvation increases the performance in olfactory reward learning and conversely, well-fed flies are poor learners. Stimulation of activity in the NPF neurons mimics food deprivation and promotes appetitive memory performance in fed flies [360]. This form of memory requires expression of the NPF receptor (NPFR) by a set of six dopaminergic neurons that innervate the mushroom body. Inactivation of these dopaminergic neurons increases memory performance in fed flies, whereas stimulating them suppresses memory in hungry flies. Thus, the NPF neurons and the NPFR expressing dopaminergic neurons serve as a motivational switch in the mushroom body circuits and control appetitive memory output [360]. In larvae, it was shown that targeted activation of NPF-producing brain neurons inhibits appetitive olfactory learning by means of a modulation of the signal that mediates the sugar reward during acquisition. This modulation was shown to require engagement of three different NPF expressing neuron types [361].

The insulin receptor substrate CHICO is expressed in the *Drosophila* Kenyon cells of adult flies [423] suggesting that these neurons are targeted by insulin signaling. This study showed that *Chico* mutants display defects in olfactory learning and that memory formation could be restored after *Chico* rescue specifically in mushroom bodies. Similar to a study on MBs and feeding [424], the effects of *Chico* impairment are developmental and influence growth and proliferation. Conditional knockdown of *Chico* or *dInR* in adult Kenyon cells is required to determine acute effects of insulin signaling to the mushroom bodies in learning and feeding.

8. 1. 3. 2. Mushroom bodies and food sensing

A number of neuropeptides have been implicated in regulation of odor-mediated food sensing by acting on dopaminergic neurons, which in turn modulate activity in MBONs that receive inputs from Kenyon cells [316] (Fig. 9). Some neuropeptides act as hunger signals (NPF and sNPF) and others as satiety signals (DILPs and Allatostatin A). Additionally, serotonin, via its receptors 5-HT1B and 5HT-2A, act as a hunger signal in this mushroom body circuit [316]. Thus, in starved flies, the hunger signals (neuropeptides and 5-HT) activate certain subsets of dopaminergic neurons and suppress others, and dopamine acts on the DAMB dopamine receptor on certain MBONs and thereby fine-tunes the Kenyon cell to MBON connectivity and shapes the collective output of the MBONs that are driven by food odors [316].

Another report describes the expression of the insulin receptor (dInR) in a subpopulation of Kenyon cells that also express fruitless [425]. Starvation decreases the sexual receptivity in females and this is insulin dependent. This effect is abolished in flies where the dInR was knocked down in fruitless neurons or MBs, suggesting that insulin-like peptides tune female sexual behavior by altering the pheromone response of these brain neurons [425].

8. 1. 4. Modulation of locomotor activity and explorative walking

Locomotor activity is regulated at multiple levels in the CNS. Local motor circuits in the ventral nerve cord are controlled by higher centers in the brain and subesophageal ganglion [426]. The central complex and mushroom bodies of the brain regulate and coordinate locomotor behavior in specific ways [411, 427, 428]. Thus, the central complex controls velocity of motion, maintenance of activity, symmetry of locomotion and orientation [427], and the mushroom bodies regulate aspects of walking, and suppress long term locomotion [410, 411]. Also, neuroendocrine systems of the brain/corpora cardiaca, like AKH and DILP producing cells, regulate aspects of locomotor activity especially during conditions of low energy stores [289, 311, 429-431]. We deal with aspects of nutrient-dependent regulation of locomotion in more detail in the section 8.2.1. and clock-dependent locomotion in section 8.1.5. Here we summarize the roles of neuropeptides in sexually dimorphic activity patterns, foraging, and short-term actions in locomotor control. Roles of neuropeptides in circadian locomotor activity are discussed separately in the next section.

Drosophila displays sexually dimorphic spontaneous locomotor activity. Locomotor activity in flies occurs in bouts of motion followed by periods of inactivity and the organization of these bouts is sexually dimorphic where female flies stop and start with a higher frequency than males [432]. It was found that the control of this dimorphic behavior resides in two distinct populations of neurons in the pars intercerebralis, the IPCs [431, 433], and ten neurons designated feminizing cells, FCs [430]. Ablation of the IPCs in male flies results in a feminized locomotor profile, suggesting that these neuroendocrine cells may control sex-specific behaviors with DILPs, DSK or other signals. The DILP receptor dInR is expressed in the endocrine cells of the corpora allata (CA) and dInR knockdown in these cells abolishes the sexual dimorphism in locomotor activity [430]. Thus, the CA cells that secrete juvenile hormone (JH), under direct or indirect control of brain-derived DILPs, appear to be important in regulation of the sexually dimorphic locomotor activity [431, 433]. Also other studies have found that the IPCs are involved in regulation of locomotor activity and sleep-wakefulness [434, 435].

The ten FCs in pars intercerebralis also partake in the sexual dimorphic locomotor activity. Genetic feminization of these neurons (but not the IPCs) in male flies eliminates the sexually dimorphic behavior, and the feminization effects can be mimicked by feeding a JH inhibitor to the males [430]. From these studies it is not clear how the signaling from the FCs and the IPCs interact with respect to control of locomotor activity or how JH influences the circuits regulating locomotion.

Starved flies become hyperactive likely representing an increased search for food. Ablation of the corpora cardiaca cells that produce the hormone AKH leads to a loss of this hyperactivity in food deprived flies [289, 429]. During starvation AKH therefore seems to regulate both a mobilization of stored carbohydrate and lipids and trigger locomotion to find new food sources. The action of AKH during starvation-induced hyperactivity requires intact octopamine signaling [311]. A recent study showed that the gut microbiome in *Drosophila* plays a role in modulating fly locomotion and also this requires activation of octopaminergic neurons [436]. Also in cockroaches AKH was proposed to act on octopamine-expressing neurons in the ventral nerve cord to increase locomotor activity [437]. The starvation-induced hyperactivity in *Drosophila* was shown to be suppressed by insulin signaling [311].

Drosulfakinin (DSK) and its receptor CCKLR regulate larval locomotion and DSK signaling is necessary for the stress-induced escape response in larvae [334]. DSK was shown to be a satiety-inducing peptide in *Drosophila* [24] similar to its relative cholecystokinin in mammals [22], but it is not known whether this peptide influences starvation-induced hyperactivity or other locomotion in flies.

In the central complex, different neuron types express peptide products of eight neuropeptide encoding genes: TK, sNPF, MIP, Ast-A, proctolin, SIFamide, NPF, and dFMRFamide [438]. These neuropeptides are distributed in sets of neurons innervating different neuropil regions of the central complex: the fan-shaped body, the ellipsoid body, the nodules or the protocerebral bridge (Fig. 10). All of the eight neuropeptides are found in different layers of the fan-shaped body. GPCRs for sNPF, TK, LK, and proctolin have been detected in the fan-shaped body [330, 331, 439-442]. Of these peptides only TK and sNPF have been investigated for roles in control of explorative walking behavior [339]. By using various enhancer trap-Gal4 lines combined with immunolabeling these authors identified neuron sets that express TK or sNPF. These neurons were specifically targeted by Gal4-UAS mediated RNAi to knock down either of the peptides in the central complex. TK knockdown in certain neurons resulted in flies with increased center zone avoidance, whereas knockdown in other neurons knockdown resulted in flies with increased activity-rest bouts [339]. Diminishing sNPF in specific central complex neurons indicated a role in fine-tuning of locomotor activity levels. TK and sNPF thus seem to be important for spatial orientation, activity levels, and temporal organization of spontaneous walking. These studies suggest a circuit-specific contribution of specific neuropeptides to locomotor control in the central complex [339, 438]. Although only two of eight known neuropeptides have been explored, it is apparent that neuropeptides are likely to play very distinct roles in fine tuning of locomotor walking control and that this control is specific to subsets of central complex neurons. Furthermore, the central complex (especially the ellipsoid body) is important in visually guided behaviors and visual learning, as well as courtship behavior [443-447], and it is a great challenge to explore neuron-specific neuropeptide signaling in all these functions.

8. 1. 5. Neuropeptides regulating circadian activity and sleep

In animals, daily activity and physiology are synchronized with the 24 h cycle of earth's rotation around its axis by means of an endogenous circadian clock. In *Drosophila,* the master clock consists of about 150 brain neurons located in 8 bilateral groups [268, 277, 448] shown in Fig. 11. The first neuropeptide identified in clock neurons was pigment-dispersing factor (PDF), which is expressed in small and large lateral ventral neurons, s-LN$_v$s and l-LN$_v$s [340, 449]. Several other neuropeptides have now been mapped to different clock neurons in *Drosophila* by traditional methods and by single cell transcriptomics: Ast-C, CCH1a, CNMamide, DH31, DH44, DMS, Hugin-PK, ITP, NPF, sNPF, and trissin, [273, 277, 280, 283, 284, 344, 450]. In several of the clock neurons different combinations of these neuropeptides are colocalized.

There are two sets of main pacemaker neurons (morning and evening oscillators) namely the l-LN$_v$s/s-LN$_v$s and LN$_d$s. The l-LN$_v$s receive light inputs both from the compound eyes and the extraretinal photoreceptors of the eyelet, whereas the s-LN$_v$s only have inputs from the latter [277]. These neurons display different combinations of the neuropeptides PDF, NPF, sNPF and ITP and some subsets of neurons also produce acetylcholine, and glycine [277, 279, 280] (Fig. 11). The l-LN$_v$s express PDF and NPF, as well as the cytokine unpaired 1 (Upd1), and the 5th s-LN$_v$ produces ITP, NPF and probably acetylcholine [277, 278, 280]. Recently, single cell transcriptomics identified additional neuropeptide candidates in the LNds: DH44, Ast-C, DMS, Hugin peptides and trissin [273].

The dorsal neurons (DNs) are located in three clusters DN1-3. The two DN1a (anterior) neurons produce glutamate, IPNamide (derived from the NPLP1 precursor), DH31 and CCHa1 [149, 281-283]. In the other DN1 neuron cluster located more posteriorly (DN1p) it is difficult to analyze identified members of the group for neuropeptides. Ast-C was found in a set of DN1 neurons [450]. When isolated from the brain as a group and analyzed by RNA sequencing transcripts of genes coding for DH31, NPF, sNPF, CCHamide1 and CNMamide were found [273]. It is therefore not clear in which specific DN1p neurons the transcripts are expressed or to what extent the neuropeptides are colocalized. Earlier, DH31 was mapped to some DN1p neurons by immunocytochemistry [284].

PDF is the most extensively investigated peptide for roles in the clock network and as an output of LN_vs [see [6, 185, 268, 277, 451, 452]]. NPF and sNPF have also been found to have roles within the clock network, whereas for the other peptides, the main information available suggests roles in network outputs recorded as activity, sleep or other behaviors.

So what is the role of PDF? Both small and large LN_vs signal with PDF to sets of clock neurons that generate evening activity (evening oscillators) and the large LN_vs signal to small ones. All groups of neurons in the clock network, except l-LN_vs, express the PDF receptor (PDFR), and s-LN_vs also seem to utilize the PDFR as an autoreceptor [see [6]]. These autoreceptors inhibit s-LN_v activity and PDF release and thereby are important for setting the phase of daily outputs, including locomotor activity [267]. The PDF signaling to other clock neurons is inhibitory and causes delays in calcium activity in follower neurons, LNd and DN3 (Fig. 12).

NPF and sNPF in clock neurons act in the network to pattern daily rhythms. Release of sNPF from s-LN_vs and LN_ds sculpts the DN1 activity period at night by suppressing DN1 activity at other times [267]. The s-LN_vs receive negative PDF feedback in an autocrine loop, and both sNPF and PDF suppress Ca^{2+} levels in other pacemakers (Fig. 12), thereby providing a neuropeptide-mediated chain of sequential inhibition and delay in the network that ensures phase-setting of neuronal activity (pacemaker entrainment) [267]. It is interesting to note that a single neuron type (s-LN_v) can target different neurons with sNPF and PDF (Fig. 12).

NPF is expressed in 1-3 of the l-LN_vs and in the 5th s-LN_v and peptide function was analyzed in flies after ablating the NPF expressing clock neurons genetically [344]. This eliminates the neurons with both NPF and other colocalized substances and results in flies with prolonged free-running period in constant darkness, an advanced phase of the evening activity peak and reduced amplitude of this peak. It was suggested that this phenotype arose from ablation of the NPF expressing LNds and the 5th s-LN_v [344]. Diminishing NPF by RNAi in clock neurons only had a minor effect and slightly advanced the evening activity phase. Simultaneous knockdown of both PDF and NPF gave a stronger phenotype that resembled the one seen after ablation of the neurons.

The above findings suggest that cotransmission plays a fundamental role in different parts of the clock circuitry and is of key importance for understanding the organization and logic of the regulatory hierarchy in the network.

Some neuropeptides in clock neurons, such as ITP, NPF, sNPF and DH31, appear to play roles other than signaling within the network to modulate rhythmic activity patterns. The expression of ITP in the 5-th s-LN_vs is under clock control and ITP-RNAi targeted to these cells and LNds results in reduced evening activity of the flies and an increase in night activity [345]. Knockdown of both ITP and PDF resulted in hyperactive flies that were arrhythmic in constant darkness, and displayed reduced sleep both during mid-day and night [345].

NPF in clock neurons has been shown to regulate aspects of mating behavior [305, 343, 382] and sleep-wake behavior [161]. By indirect routes, NPF regulates circadian gene expression in the fat body [453]. Also sNPF has been implicated in regulation of sleep. This peptide in s-LN_vs promotes sleep without affecting feeding [342]. DH31 in the clock system was shown to be a wake-promoting neuropeptide acting before dawn [284]. Finally, DH31, and to a lesser extent PDF, acting on DN2 neurons to regulate nighttime temperature preferences in flies [149]. Interestingly, these authors propose that DH31 acts via the promiscuous PDF receptor in DN2 neurons to decrease temperature preference at night onset.

The biological clock in *Drosophila* is also known to time and regulate developmental transitions such as shedding of the old cuticle (ecdysis). The molts depend on timed production of the steroid hormone ecdysone in the prothoracic gland, which is regulated by prothoracicotropic hormone (PTTH) released from two pairs of LNCs [454]. Timing of the final molt, the adult emergence from the puparium, is regulated by the s-LN_vs signaling with sNPF, but not PDF, to the PTTH neurons [455]. The sNPF released from s-LN_vs thereby serves to coordinate the central clock with the local one in the prothoracic gland [455]. Interestingly, the LNvs and PTTH neurons have also been shown to regulate light-avoidance behavior in larvae [456, 457].

There are examples of neuropeptides/proteins released from clock neurons that seem to act on circuits outside the *bona fide* clock network and regulate behavior other than locomotor activity or sleep. One example is the leptin-like cytokine Upd1 (Unpaired 1) that is produced by LNv clock neurons [278]. These authors showed that the Upd1 receptor Domeless (Dome) is expressed in several NPF neurons in the brain, known to be orexogenic. Disruption of Upd1 signaling leads to increased food attraction and food ingestion, as well as an increase in weight of flies [278]. Thus, clock neuron-derived Upd1 suppresses activity in NPF neurons and thereby diminishes food intake. It was not shown whether the Dome receptor expressing NPF neurons are among the clock neurons, or if the Upd1 effect is on NPF neurons outside the clock circuit.

What about clock output pathways? A recent study delineated connections between clock neurons and output neurons that regulate locomotor activity, without affecting feeding rhythms [263]. This pathway comprises connections from s-LN_v neurons to DN1s, that signal to DH44 neurons (MNCs) in the pars intercerebralis, which in turn connect to Hugin neurons in the subesophageal ganglion that via descending axons regulate glutamatergic premotor neurons in the ventral nerve cord [262, 263]. In this pathway, it is suggested (but not clearly shown) that s-LN_vs signal with PDF to the DN1 neurons, which in turn use an unknown substance to activate the DH44-producing MNCs. It was established that the signal between the MNCs and Hugin neurons is DH44, presumably acting on its receptor DH44-R1 and Hugin neurons communicate with glutamatergic neurons in motor circuits possibly with the peptide hug-PK [263] or colocalized acetylcholine [see [64]]. There are possibly additional or alternative signals from s-LN_vs (sNPF or glycine) and the DN1s produce several candidate peptides. Also, the insulin producing cells (IPCs) in the brain are modulated by DN1s which gives rise to rhythmic action potential firing in IPCs [458]. Furthermore, this study suggests that IPCs, despite having cell autonomous nutritional inputs that also affect the firing rhythm, are under additional regulation by clock neurons. Thus, IPC signaling that affects feeding and metabolism is under rhythmic clock control [458].

Finally, there is a link between the central clock of the brain and the peripheral clock in the fat body in *Drosophila*. Many gene transcripts cycle in the fat body, but some cytochrome P450 transcripts cycle independently of the fat body clock and are instead dependent on NPF expressing brain clock neurons, probably LN_ds [453]. However, it was not shown how the signal from the NPF clock neurons reaches the fat body. Probably this signaling occurs by means of interactions between NPF neurons and neurosecretory cells such as IPCs or other MNCs that in turn regulate the fat body hormonally. Also, it is not clear whether NPF is the only required signal from these clock neurons since NPF knockdown was less effective than silencing the NPF neurons [453]. As mentioned above the NPF expressing LN_vs also produce ITP or PDF and the LN_ds express additional neuropeptides.

Sleep in *Drosophila* is under homeostatic regulation and controlled by several neuronal and neuroendocrine systems [459-463]. Thus, in addition to clock neurons, circuits of the central complex and mushroom bodies, as well as neurosecretory cells and neurons of the pars intercerebralis (PI) use different neurotransmitters and neuropeptides/peptide hormones to regulate sleep-wake. These include GABAergic and dopaminergic neurons extrinsic to the mushroom bodies and central complex [460, 461, 463], OA neurons upstream of IPCs [435], the four widely arborizing SIFamide neurons and 14 IPCs of PI and Ast-A producing neurons innervating sleep-promoting neurons (dFB; Ast-A receptor 1 expressing; see Fig. 10) of the dorsal fan-shaped body of the central complex [144, 462, 464]. Other neuropeptides regulating sleep are wake-promoting DH31, DH44, DILPs and NPF in various neurons [461, 463], as well as PDF in l-LNvs [465] and sleep promoting SIFamide, epidermal growth factor (EGF) [464], Ast-A [144, 326], and sNPF [342]. Starvation is known to suppress sleep and a set of LK producing brain neurons is required for this suppression [347, 350]. Taken together these reports suggest a complex regulation of sleep-wake and an association between homeostatic regulation and the circadian clock system.

8. 1. 6. Neuropeptides regulating mating behavior and reproduction

The mating behavior in flies is sexually dimorphic and the generation of the circuits underlying this dimorphism is primarily governed by two transcription factors of *Drosophila* sex-determination hierarchy, *fruitless (fru)* and *doublesex (dsx)* [466, 467]. Sex-specific splicing of these genes determines whether a male-specific or female-specific circuitry is generated. Thus, male-specific proteins Fru^M and Dsx^M coordinate to specify male-specific circuitry [467-474]. The female-specific circuitry, however, is largely governed by the female-specific Dsx^F [472]. It is likely that neuropeptides and neuropeptide receptors that are expressed in these neuronal circuits regulate some aspect of mating behavior [376, 377, 475-477]. *Drosophila* mating and post-mating behaviors, and reproduction have been a subject of intense investigation and this topic has been reviewed in detail recently [3, 7, 467, 478-485]. Here, we highlight some novel roles for neuropeptides in modulating various behaviors and physiology associated with mating which ensures reproductive success. We divide these behaviors/physiology into four categories: courtship, mating, post-mating response and reproductive physiology.

8. 1. 6. 1. Courtship

Drosophila males display a highly ritualized courtship behavior that comprises of several discrete steps: orientation, tapping, singing, licking, attempted copulation and copulation [467, 486]. This stereotyped mating behavior does exhibit plasticity via modulatory peptides (Fig. 13). For instance, the recently discovered neuropeptide Natalisin has been shown to reduce the courtship initiation latency [129]. Various other neuropeptides also modulate the overall courtship behavior. Thus, signaling by NPF, MIP and *hector* (DH31 receptor) results in increased courtship [377, 382, 476]. Genetic ablation of NPF neurons results in decreased male courtship activity [382] because these neurons are also important for detecting the female sex pheromone whose production is regulated by IIS [369, 487]. Females with increased IIS are more attractive to males and those with reduced IIS are less attractive [487]. DTK signaling, on the other hand, inhibits courtship by relaying the signal of an anti-aphrodisiac pheromone from the gustatory neurons on the foreleg to central brain neurons [307]. This repellant pheromone is left behind on the female by a male to prevent approaches by other males. Thus, sex-specific DTK signaling is important in increasing the reproductive success of the first male. Another neuropeptide which modulates courtship is SIFamide whose receptor is expressed in fruitless neurons [376]. Disruption of SIFamide signaling results in males exhibiting remarkable promiscuity in their courtship attempts [375, 376]. Hence, male flies with disrupted SIFamide signaling also court other males, while female flies become more receptive as the time to copulation is drastically reduced.

8. 1. 6. 2. Mating

Once the male has succeeded in his courting attempts, mating begins. Males prolong their mating duration in the presence of competing males to ensure increased reproductive success since *Drosophila* females are polyandrous [305]. This rival-induced prolonged mating is regulated by the clock neurons. Specifically, the presence of NPFR and PDF in four small LNv neurons, and PDFR and NPF in two LNd neurons is required for this behavior (Fig. 13) [305]. Moreover, *Drosophila* males also exhibit rhythms in their courtship activity in the presence of a female. Thus, males display long periods of courtship with a rest phase at dusk. This pattern, like various other circadian rhythms, is regulated by the clock neurons expressing PDF and is disrupted in the absence of PDF [488]. The males also increase the copulation duration when the transfer of sperm and seminal fluid is hindered by blocking the activity of four male-specific corazonin neurons in the abdominal ganglion [178]. Corazonin mediates its effects on sperm and seminal fluid transfer by activating serotonin neurons that innervate the accessory glands. Finally, disruption of Natalisin signaling also results in reduced copulation [129].

It is evident that neuropeptides modulate mating behavior, but mating in itself can also influence the activity/release of neuropeptides. For instance, there is an inverse link between mating and ethanol consumption that is mediated by brain NPF neurons [368]. NPF expression in males is upregulated following mating and downregulated upon sexual deprivation. Moreover, sexually deprived males consume more alcohol while mated males and males in which NPF neurons are activated display decreased alcohol preference. Thus, increased NPF signaling following mating results in decreased alcohol preference [368]. Recently, it was shown that mating, and sex peptide in particular, induces the release of NPF from gut endocrine cells. This gut-derived NPF induces germline stem cell proliferation by activating its receptor on the ovaries [489]. Hence, mating influences the release of NPF from both the brain and the gut.

8. 1. 6. 3. Post-mating response

In many insect species including *Drosophila*, mating triggers a drastic behavioral and physiological switch in female processes related to fertility/reproduction. These changes are mediated by accessory gland proteins (Acps) that are produced in the male accessory glands and are transferred along with the sperm to the female during mating. Several Acps have been identified in *Drosophila* but a 36 amino acid peptide called the sex peptide has been studied the most [479, 490]. Sex peptide induces egg-laying and results in increased feeding to support oogenesis (Fig. 13) [491]. It also causes the females to become more aggressive and less receptive towards courtship attempts by other males [356]. These effects of sex peptide are mediated by the sex peptide receptor (SPR), which is expressed in the female reproductive tract and the CNS, although only the expression in dsx neurons is necessary and sufficient for mediating the post-mating behaviors [188, 492]. *Drosophila* SPR is also activated by MIPs, which are not present in the seminal fluid [186, 187]. Interestingly, female-specific MIP interneurons in the abdominal ganglion also regulate the flies' decision to remate [377]. Surprisingly, activation of these neurons makes mated females receptive to remating, whereas silencing these neurons causes the females to be less receptive. Hence, sex peptide and MIP modulate female remating in opposite directions despite activating the same receptor.

Males utilize sex peptide to avoid sperm competition by altering the female behavior. However, the males also deposit a mating plug in the female uterus, which increases their reproductive success by blocking insemination by other males and allowing for increased sperm storage [322, 479]. *Drosophila* females store only 10-20% of the sperm in their seminal receptacle and spermathecae from the total sperm deposited in the uterus. The rest of the sperm is ejected along with the mating plug about 1-6 hours after mating. DH44, expressed in six median neurosecretory cells, and its receptor DH44R1 expressed in dsx neurons in the abdominal ganglion, increase the latency to sperm ejection thereby allowing for more efficient sperm storage [370].

8. 1. 6. 4. Reproductive physiology

Following mating, *Drosophila* females exhibit increased egglaying. Normally, females prefer to lay their eggs in a medium that is not high in sucrose. However, silencing the DILP7 neurons in the VNC, which project to the female reproductive tract, abolished the ovipositor motor programs and rendered the fly sterile [160, 493]. Overexpression of DILP7, on the other hand, cause the female flies to lay eggs on non-favorable sucrose medium [160]. The role of other insulins in reproductive physiology via their influence on JH production will be addressed below in section *8. 2. 1. 3.* Recent work has shown that ETH is present in adult Inka cells (peritracheal cells) and it also promotes JH production and associated reproductive physiology via activation of ETH receptor in the corpora allata [494]. The release of ETH is dependent on 20E just like it is during the larval ecdysis (see next section) [292, 495, 496].

8. 1. 7. Neuropeptides regulating ecdysis and post-ecdysis behaviors

Insects and other members of the Ecdysozoa clade grow by shedding their cuticle through an innate ecdysis motor behavior [497]. The ecdysis behavioral sequence is composed of pre-ecdysis, ecdysis and post-ecdysis behaviors, which are controlled by peptides from the epitracheal Inka cells (ETH) and CNS (various peptides and hormones) (Fig. 14). These peptides and hormones act in a cascade to regulate stereotyped motor behaviors. Models depicting this cascade of events in various insects have been well described and reviewed elsewhere [498-501]. Here, we highlight some major recent discoveries that have expanded on this model.

Different insect species have slight variations in the neuropeptides regulating these behaviors; however, ETH, 20E, eclosion hormone (EH) and CCAP are considered to be the main players regulating the ecdysis behavior in most insects [292, 498, 502-505]. In *Drosophila,* other neuropeptides that are part of this behavioral cascade include dFMRFamides, LK, MIPs (Ast-B) and bursicon [291, 292, 495, 506, 507]. The endocrine cascade that regulates ecdysis is initiated by 20E-dependent ETH secretion from the Inka cells [292, 500, 508]. ETH subsequently induces the release of EH from brain neurons, which through a positive feedback loop, stimulates further ETH release via activation of a membrane guanylate cyclase receptor [101]. ETH then acts on various sets of peptidergic CNS neurons expressing the ETH receptor (ETH receptor isoforms A and B; see below for more details) to gate and coordinate the timing of various ecdysis behavior stages. Recent studies have tried to address how all the neuropeptides downstream of ETH are able to contribute to different behaviors involved at specific times during the ecdysis cascade [509, 510]. Localization of the receptors for peptides involved in the ecdysis cascade has elucidated the hierarchical organization of this behavioral neural network. Thus, ETH receptors initiate the molting process by activating bursicon and CCAP neurons. Neurons expressing the bursicon receptor then generate motor rhythms within the CNS and finally the downstream CCAP receptor-expressing neurons respond to these rhythms and generate abdominal movements associated with ecdysis [510].

Although it was shown that brain-derived EH stimulates the release of ETH from Inka cells, other roles of EH during this behavior were unknown. Work using *EH* null mutants has shown that EH is also required within the larval CNS for ETH to trigger the pre-ecdysis behavior [511]. Thus, EH mutants fail to release both ETH and CCAP, but the effect on CCAP release is not rescued by systemic ETH injections.

Following the pre-ecdysis behavior, CCAP was thought to initiate the ecdysis behavior and bursicon believed to regulate the post-ecdysis behavior processes such as wing expansion, and cuticle tanning and hardening [292, 506, 512]. However, the exact roles of CCAP and bursicon in ecdysis and post-ecdysis are not so clear. Interestingly, null mutants for CCAP exhibit no apparent defects in ecdysis and post-ecdysis, whereas *pburs* mutants show severe ecdysis defects [513].

Moreover, flies that are mutant for both CCAP and bursicon show stronger defects compared to flies mutant for either peptide alone. Thus, both bursicon and CCAP affect similar aspects of the ecdysis behavior. Bursicon is not only responsible for cuticle tanning and hardening following adult eclosion, it also tans the puparium, suggesting that its role in tanning is conserved throughout development [514].

The increased EH and ETH in the circulation was known to cause air-filling of the trachea [515]. It is now evident that this effect is regulated by ETH through its actions on LK neurons. ETH stimulates the release of LK from abdominal LK neurons (ABLKs), and LK in turn acts on its receptor in tracheal epithelial cells to stimulate tracheal air-filling via intracellular calcium mobilization [515].

All insects studied express two alternate splice forms of the ETH receptor (ETHR-A and ETHR-B) [516]. The role of ETHR-A in *Manduca* and *Drosophila* ecdysis behavior has been well established [292, 502] but the role of ETHR-B was unknown. In both these species, ETHR-A and ETHR-B are largely expressed in non-overlapping populations of neurons. Recent work in *Drosophila* has shown that ETHR-A and ETHR-B expressing neurons play different developmental roles in ecdysis [517]. Hence, ETHR-B neurons are essential during pupal and adult, but not larval, ecdysis, whereas ETHR-A neurons are required for ecdysis at all developmental stages.

Several questions still remain to be answered. What is the actual first trigger that causes the release of ETH from Inka cells to start the entire cascade of events? Although 20E has shown to be involved [292], it is not known if a neuropeptide is also involved. In moths, corazonin has shown to be this trigger [172]; however, this is not the case in *Drosophila*. A targeted RNA sequencing of isolated Inka cells could reveal the receptors expressed in these cells and thus facilitate the identification of this initial trigger. Interestingly, FlyAtlas expression data of the receptors (Fig. 4) suggests that the CAPA-PK receptor is expressed in the trachea. However, it is not known whether the expression is localized to Inka cells or other cell types. Perhaps CAPA-PK is the ecdysis-initiating factor in *Drosophila* since it accelerates pupariation in the grey flesh fly, *Neobellieria bullata* [518]. Another important question worth addressing is the identity of the different motor neurons downstream of the peptides in the ecdysis circuit that are responsible for the various actions such as abdominal contractions and head thrusts, which result in effective shedding of the cuticle. Lastly, are there other neuropeptides that are part of the ecdysis circuit that remain to be discovered? Detailed mapping of ETHR-A expression in *Drosophila* showed that the receptor is expressed in several larval peptidergic neurons including corazonin, myosuppressin, DH31 and NPF, suggesting that these neuropeptides could also be part of the *Drosophila* ecdysis circuit [517]. In addition, PDF neurons in the tritocerebrum, which appear around the time of ecdysis and have neurites overlapping with CCAP and eclosion hormone neurons, could also be involved [519]. Recent work in the blood-sucking bug *Rhodnius* has shown that orcokinin-A knockdown results in ecdysis defects [520]. Moreover, knockdown of ITP in another hemipteran, *Nilaparvata lugens*, resulted in melanized insects and failed wing expansion [521]. In fact, ITP knockdown in *Drosophila* also results in developmental lethality [333] suggesting that it may be another player in the ecdysis cascade.

Some typical ecdysis-associated peptides like ETH and bursicon have now been shown to persist in adults long after ecdysis, where they regulate other processes. ETH in adult *Drosophila* functions as an allatotropin by promoting juvenile hormone production and reproduction [494, 496]. ETH also impairs courtship short-term memory via its action on JH production [522]. Recent work has shown that bursicon (burs alpha), but not burs beta is expressed in the midgut enteroendocrine cells of *Drosophila* [264, 523]. Interestingly, burs alpha released from these cells activates its receptor, DLGR2, in the gut visceral muscles (VM) to regulate intestinal stem cell quiescence through VM-derived EGF-like growth factor Vein [523]. In addition, midgut endocrine cells expressing burs alpha are also nutrient-sensitive. Consequently, burs alpha is released into the hemolymph following sucrose consumption, after which it activates DLGR2 in the CNS to alter systemic metabolic homeostasis through downregulation of AKH signaling [264].

8. 2. Neuropeptides and peptide hormones regulating physiology

Although it is hard to completely detach physiology from behavior, this section focuses on neuropeptides and peptide hormones that have been shown to have major roles in regulation of physiology, metabolism and stress responses. Some of these also have major effects on the life cycle and lifespan. These peptides are produced by neuroendocrine cells in the brain and ventral nerve cord, as well as in endocrines of the intestine and at peripheral sites. The most prominent of these peptide groups are the functional homologs of glucagon and insulin/IGF, which in flies are represented by AKH and the 8 DILPs [see [1, 68]]. But there are also numerous diuretic and antidiuretic hormones to be considered both in water and ion regulation and in stress responses; some of these also affect activity and metabolism. Finally, several regulatory neuropeptides have secondary effects on metabolism and homeostasis. Peptides regulating the lifecycle and physiology in *Drosophila* are shown in Table 8.

Table 8. Neuropeptides/peptide hormones regulating lifecycle and physiology in *Drosophila*

Physiology	Peptide	Cells/tissue	References
Development	DILPs[1]	IPCs, fat body	[524]
	PTTH	LNCs	[99, 454]
	EH	NSCs	[525]
Ecdysis	EH ETH Bursicon CCAP FMRFa LK MIP	Inka cells Neurons NSCs	[291, 292, 495, 515, 525]
Stem cell activation and homeostasis	DILP6	Glial cells	[526, 527]
	DILP3	Gut muscle	[528]
	Bursicon	EECs	[264]
Growth	DILPs[1]	IPCs	[98, 155, 529]
	DILP6	Fat body	[156, 530]
	DILP8	Imaginal discs	[531, 532]
	sNPF	Neurons	[318]
	PTTH	LNCs-protho-racic gland	[531, 532]
Lifespan	AKH	CC	[533]
	DILPs[1]	IPCs	[153, 234, 534]
	DILP1	IPCs	[535]
Metabolism	AKH	CC	[289, 324]
	DILPs[1]	IPCs	[153, 536]

	CRZ	LNCs	[181, 183]
	sNPF	Various neurons	[183, 537]
	SIFa	Interneurons	[162]
	TK	EECs	[21]
Metabolism and gut immune reaction	sNPF	Acts on sNPF-R1 in enterocytes	[538]
	Ast-C	Sensory neuron to fat body	[363]
Diapause	DILPs[1]	IPCs	[539-541]
	AKH	CC	[540]
Diuresis/water and ion homesostasis	DH31	NSCs, EECs	[542]
	DH44	NSCs	[151, 543, 544]
	Capa	NSCs	[65, 146, 545]
	LK	NSCs	[150, 546-548]
	ITP	NSCs	[333]
	NPLP1	NSCs	[102]
	PDF	ENs (hindgut)	[549]
	NPF	EECs	[550]
	sNPF	NSCs	[550]
Intestinal function Note that most of these peptides have not been tested on target tissue. Thus, data are based on presence in EECs, innervation of gut or GPCR distribution	AstA	EECs	[326, 551]
	AstB	EECs	[552]
	AstC	EECs	[553]
	CCHa1, 2	EECs	[295]
	DH31	EECs	[294, 296, 554]
	NPF	EECs	[555]
	Orcokinin	EECs	[295]
	TK	EECs Lipid metabolism	[15, 21]
	DILP7	ENs (hindgut)	[547]
	ITP	ENs (hindgut)	[333, 556]
	PDF	ENs (hindgut)	[557, 558]
	Proctolin	ENs (hindgut)	[559, 560]
	DH44	NSCs	[294]
	GPA2/GPB5	NSCs (hindgut)	[561]
	LK	NSCs (hindgut)	[331, 562]
Stress responses	AKH	CC	[289, 429]
	Corazonin	NSCs	[181-183]
	DILPs[1]	IPCs	[153]
	TK	Neurons/NSCs	[17]

	Capa	NSCs	[65, 146, 545]
	NPF		[563]
Reproduction	DILPs[1]	IPCs	[564]
	ETH	Inka cells (adult)	[494, 496]
	DILP7	Neurons	[160]
Myomodulation	Proctolin	Heart rate	[565]
	FMRFa	Body wall muscle	[566]
	Hugin-PK	Heart rate	[567]

Notes:
Acronyms: CC, corpora cardiaca; EECs, enteroendocrine cells; ENs efferent neurons to gut; IPCs, insulin-producing cells; LNCs, lateral neurosecretory cells; NSCs, neurosecretory cells; Peptide acronyms as in Table 1 and text.
[1] DILPs unspecified, determined by interference with IPCs or dInR (or downstream)

8. 2. 1. Insulin-IGF signaling (IIS): multiple roles in growth, physiology, reproduction, and lifespan

Over the last 15 years there has been a huge effort to understand the intricate regulatory roles of peptides related to insulin, relaxin and insulin-like growth factor (IGF) in *Drosophila*. The insulin-like peptides (DILPs) in *Drosophila* play roles in development, growth, metabolism, reproduction, stress responses and lifespan and this topic has been quite extensively reviewed in recent years, so only a brief summary is provided here. For reviews on *Drosophila* insulin-IGF-signaling (IIS) and general aspects of invertebrate IIS see [1, 2, 68, 232, 269, 524, 529, 534, 568-576], and for reviews on IIS in other insects see [564, 577-581].

In *Drosophila,* there are eight DILPs (DILP1-8), five of which are insulin-like (DILP1-5), two (DILP7 and 8) are relaxin-like and one (DILP6) is structurally and functionally related to mammalian IGFs [94, 98, 141, 156, 530-532]. These DILPs are each encoded by a separate gene. The classification of DILPs as insulin-like relies on similarities in the amino acid sequence of the mature peptides to those of vertebrate insulins; especially in the number and positions of cysteine residues that are well conserved across several phyla. Another conserved feature is the organization of the precursor protein (pre-proinsulin) with B, C and A-chains which can be processed into dimeric peptides with an A and a B-chain linked by disulphide bridges. In contrast, the mature insulin-like growth factors (IGFs) possess a short C-peptide that is retained and therefore the extended peptide is a single chain with internal cysteine bridges. It is presumed that the DILP1-3 and 5 as well as DILP6 act on a tyrosine kinase type receptor, dInR [98, 141, 234, 582]. This receptor was actually identified several years before the DILP ligands had been discovered [97]. It has been shown that DILP8 acts on a relaxin receptor-like GPCR designated Lgr3 [583-585] and DILP7 probably acts on another relaxin receptor-like GPCR, Lgr4 [see [30, 31, 586]. There is some evidence that DILP7 can activate the dInR as well [587]. The signaling downstream the insulin receptor is also well conserved across phyla and has been extensively explored in *Drosophila* and *C. elegans* [140, 570, 577, 588, 589].

The DILPs are produced in specific temporal and spatial patterns. DILP1, 2, 3 and 5 are primarily produced by the 14 IPCs of the brain [98, 154, 590] (Fig. 15). DILP1 can normally be found only during the pupal stage and first few days of adult life, whereas the others are produced throughout larval-adult stages [274]. Recently it was found that in adult flies DILP2 is produced in six additional neurosecretory cells adjacent to the IPCs, the DH44-producing MNCs [275]. DILP6 is produced by the adipocytes of the fat body, and is especially abundant during pupal development [156, 530]. DILP7 is produced by a set of segmental neurons in abdominal ganglia (Fig.15); some of these are interneurons while other neurons innervate the hindgut [98, 160, 493, 547]. DILP8 has mainly been studied in larval development and is produced by imaginal discs after induction by injury or tumor development [531, 532]. DILP4 expression has not been studied in any detail, but may be confined to embryonic stages [98]. In addition to these cellular distributions, DILP3 has been found in midgut muscle fibers [294], DILP5 in Malpighian tubules [591], and *dilp8* transcript is expressed in ovaries [FlyAtlas; [114]].

8. 2. 1. 1. Control of production and release of DILPs in IPCs

In adult flies, the regulation of IPC activity is largely nutrient dependent. The IPCs are cell autonomously glucose sensing and express proteins required for nutrient dependent DILP release [592, 593]. In larvae, AKH cells of the corpora cardiaca are glucose sensing and autonomously regulate hormone release, which in turn can affect DILP release [594]. Nutrient sensing cells are also present in the intestine and fat body [see [595, 596]; summarized in [232]] (Fig. 16). Thus, fat body cells can upon increases in amino acids or carbohydrates release factors like Upd2, FIT, adiponectin, DILP6, and CCHamide2 in adults, and TNF Eiger, adiponectin, stunted, DILP6 and CCHamide2 in larvae (Fig. 16). These factors are presumably acting on cognate receptors in the IPCs.

Several studies have investigated factors that regulate production and release of DILPs, especially from brain IPCs [summarized in [1, 2, 232, 269, 524, 568, 569]]. The neuromodulators and peptide/protein hormones (and their receptors) known to regulate IPCs are shown in Figures 15A, C, 16 and 17. As can be seen in these figures, the types of factors differ somewhat from larvae to adults. It is likely that some of these differences are simply due to the fact the two developmental stages have been analyzed separately and no systematic screen has been performed in both stages. The analysis, in most cases, is based on identifying expression of receptors on the IPCs, then interfering with receptor expression and testing for phenotypes associated with DILP function. Thus, in larvae commonly development and growth was assayed together with expression of DILP/*dilp* protein and mRNA. The larval IPC regulation is by the peptides AKH [597], CCHamide2 [327, 328], DILP6 [598] and proteins TNF Eiger [599], adiponectin [600] and stunted [601] acting on their receptors (AKHR, CCHa2R, dInR, Grindelwald, AdipoR, and Methusaleh). The sources of these factors are: AKH is from the corpora cardiaca, CCHamide2 from the intestine and the others from the fat body. Furthermore, there is a reciprocal regulation of DILP2 and Ecdysone (Ecd) production, where IPC-derived DILPs act on prothoracic glands to regulate Ecd production, and 20-OH Ecd (20E) (after conversion of Ecd in fat body) acts on IPCs to increase production of DILP2 [602] (Fig. 18).

In adults, the following factors were identified as IPC regulators (receptors in brackets): GABA (GABA-B) [603, 604], serotonin (5-HT1a) [357, 605, 606], octopamine (OAMB) [357, 435], dopamine (DopR1) [607], AKH [597], Ast-A (DAR2) [145], DILP6 (dInR) [598], CCHamide2 (CCHa2R) [327, 328], leucokinin (LKR) [331, 350], tachykinin (DTKR/TakR99d) [608], Limostatin (PK1-R; CG9918) [192], Unpaired 2 (Domeless;CG14226) [604], Adiponectin (dAdipoR) [600], and FIT (female-specific independent of transformer; receptor not identified) [609] (Fig. 17).

Of these GABA, serotonin, octopamine, dopamine, Ast-A, leucokinin and tachykinin are produced by brain neurons, AKH and Limostatin are derived from corpora cardiaca, CCHamide2 and perhaps Ast-A are released from the intestine and finally adiponectin, DILP6, FIT, and Upd2 are derived from the fat body (Fig. 15C, 17).

After release of DILPs into the circulation several factors are known to diminish the hormonal activity. These are secreted decoy of insulin receptor (SDR) as well as the ecdysone-inducible gene Imaginal morphogenesis protein-Late 2 (Imp-L2) and acid-labile subunit (ALS) [see [232, 524, 610-612] and Fig. 18]. Also insulin degrading enzyme (IDE) and other peptidases such as nephrilysins degrade DILPs and thus reduce their activity [613, 614].

8. 2. 1. 2. Insulin signaling in development and growth

Organismal growth in *Drosophila* occurs predominantly in the larval stage and relies on IIS and nutrient-dependent TOR signaling [98, 524, 529, 572, 615, 616]. Some additional growth of adult tissues can occur in the pupal stage by DILP6-dependent reallocation of nutrient stores derived from the larva [156, 530]. The larval growth seems to be regulated by several DILPs and since there is substantial redundancy between these peptides, and thus *dilp1-5* or *dilp2,3,5* triple mutants are required to obtain a strong growth phenotype [141, 617]. Single mutations of *dilp1, dilp2* and *dilp6* only result in slightly smaller flies [141, 156, 530]. In over-expression experiments especially DILP2, which is highly expressed during the larva stage, results in increased growth [98, 155, 618]. The complex regulation of larval growth is shown in Fig. 18. In addition to IPC-derived DILPs, there are several secreted factors involved in growth regulation. The IPCs are regulated by CNS-derived modulators, as well as nutrient-dependent factors released from the intestine and fat body. As mentioned in the previous section, the activity of released DILPs is controlled in the circulation by SDR, Imp-L2 and ALS [see [232, 524] and Fig. 18].

Ecd/20E secreted from the ring gland is required for growth and developmental timing and its production is under the control of PTTH. Upon damage of an imaginal disc DILP8 is secreted from this tissue and via interneurons inhibits PTTH release from brain neurosecretory cells innervating the prothoracic gland, thereby resulting in diminished Ecd/20E production [531, 532] (Fig. 18). This delays metamorphosis and slows down growth of imaginal discs, enabling the damaged disc to regenerate and ensures symmetric growth of adult tissues. The action of DILP8 is via the GPCR Lgr3, which is expressed in neurons contacting the PTTH neurons in the brain [583-585].

During the early larval stage, neuroblasts that give rise to adult neurons are dormant and require nutrient-dependent growth induction for activation and subsequent divisions. DILP6 is produced by subperineuronal glial cells in a nutrient-dependent fashion and is required in the neuroblast niche for neuroblast reactivation [526, 527]. The activation of the DILP6 producing glial cells depends on an unidentified factor released from the fat body after activation via the slimfast amino acid sensor [527].

8. 2. 1. 3. Insulin signaling in adult physiology and reproduction

In the adult fly and other insects, IIS is required for the maintenance of nutritional and metabolic homeostasis and for maturation of the ovaries [1, 68, 534, 564, 570, 573, 575, 577, 581]. Insulin signaling is also very important for the lifespan of *Drosophila* [153, 568, 571, 576] and plays a critical role in adult reproductive diapause (or dormancy) [539-541, 578, 619, 620]. Associated with these phenomena, IIS also affects stress responses in flies [153]. The detailed mechanisms for IIS, dInR activation and downstream signaling pathways in different cell types are highly complex and will not be dealt with in this review. Instead, the reader is referred to the reviews listed above. In brief, the dInR binds DILPs and interacts with the receptor substrate Chico. After autophosphorylation of the receptor intracellular signaling is mediated by phosphoinositide-3-kinase (PI3K), protein kinase B (Akt1), and the fork head transcription factor FOXO is antagonized by the protein phosphatase PTEN [534, 575, 615, 621]. Next, we will focus on the interactions of DILPs with JH and Ecd signaling.

The role of IPCs and IIS in metabolism and ovary maturation as well as interactions between neuroendocrine systems and different tissues are shown in Figure 19. The IPCs release DILPs that act on different targets to maintain metabolic homeostasis, and in females to ensure that oocytes mature in the ovaries. The brain IPCs are glucose sensing [592, 593] and receive modulatory inputs from AKH producing cells [597], other nutrient sensors in fat body [595, 604] and probably from the intestine [596] and nutrient sensing brain neurons [350, 622, 623]. *Drosophila* females mutated in the dInR are infertile, non-vitellogenic and display impaired JH production [233]. In *Drosophila,* IPCs regulate production of JH in corpora allata [233, 234, 431, 433, 624] and JH controls biosynthesis of vitellogenin in the fat body, stimulates oocyte maturation and blocks 20E production in the ovaries. Ovaries and vitellogenin production are also under direct DILP control [625-627].

The regulation of nutrient mobilization and storage in the fat body is under antagonistic control by DILPs and AKH [299, 594, 597, 628], although these hormones are also known to act together for fine-tuning homeostasis [145]. Feedback from the fat body to brain IPCs is mediated by DILP6 and several other factors discussed in section 8. 2. 1. In addition to AKH, the brain-derived peptide corazonin also acts on the fat body to maintain metabolic homeostasis [181].

It has been demonstrated by electron microscopical connectomics analysis that the larval IPCs and other MNCs receive multiple inputs from other neurons, including hugin cells of the SEZ [64]. This neuronal communication is likely to be two-way: an interesting link between the IPCs and other brain neuroendocrine cells was suggested by Bader and colleagues [629]. These authors demonstrated that a small set of neurons in the *Drosophila* brain, including the IPCs and the hugin-expressing neurons in the SEZ, express Imp-L2. It is clear from their images that the ITP-producing ipc-1 neurons also express Imp-L2 and this was confirmed later in adult flies [333]. These Imp-L2 expressing neurons take up DILP2, but only the IPCs produce the peptide [629]. The DILP2 uptake mechanism requires Imp-L2, since only IPCs are labeled with anti-DILP2 in *Imp-L2* mutants. The authors also show that activation of IIS leads to Akt1 (protein kinase B) phosphorylation in the hugin and ipc-1 neurons. Thus, it appears that this set of Imp-L2 neurons is a specific target of DILP2 activation [629]. The functional role of the DILP2 signaling to ITP-producing neurons in adults has not been investigated, but it could be speculated that post-feeding release of DILP2 may activate the ITP neurons and thereby release another signal to suppress feeding [333].

Another function of DILPs that does not only involve the IPCs is in activation of midgut stem cell division [528, 630, 631]. Intake of high-nutrient food stimulates stem cell division in the midgut of recently eclosed *Drosophila*, which results in growth of the intestine. Enteroendocrine cells (EECs) of the midgut are important in mediating the link between nutrition and stem cell activation. It was shown that EECs producing tachykinin stimulate production of DILP3 in gut muscle cells and thereby trigger stem cell division [630].

8. 2. 1. 4. Insulin signaling in lifespan and diapause

Some of the earliest studies of insulin signaling in *Drosophila* showed that mutation of the dInR or its substrate Chico extended adult lifespan of the flies [234, 582, 632], similar to earlier reports in *C. elegans* [633]. It has been shown that mutation of *dilp2* is sufficient to extend lifespan, but the extension is increased in triple *dilp2,3,5* mutants [141]. Increased expression of *dilp6* in the fat body promotes longevity probably due to the ensuing decrease in *dilp2* in the brain [598]. Also some other gene manipulations that decrease *dilp2* expression increase lifespan: overexpression of FOXO in the fat body and JNK in the IPCs [634-636]. In contrast, it was recently shown that *dilp1* promotes longevity [535]. The *dilp1* mutant flies have normal lifespan, and so do *dilp1-dilp2* double mutants, suggesting that loss of *dilp1* rescues the lifespan extension of *dilp2* mutants. This study also found that dilp1 is downstream of dilp2 in regulation of AKH [535], another known positive regulator of longevity [533]. It was suggested that DILP2 indirectly regulates AKH by repressing expression of DILP1 (that normally upregulates AKH) and also that DILP1 normally represses JH, which results in prolongevity effects [535].

In response to adverse environmental conditions, such as low temperature and shorter days, many insects enter diapause, either as embryos, larvae, pupae or adults depending on the species [637-639]. *Drosophila melanogaster* can enter a shallow adult diapause when exposed to low temperature and short days [539, 541, 619, 640-643]. This reproductive diapause is characterized by arrested ovary maturation, lowered metabolism, decreased food intake, altered hormonal signaling and drastically extended lifespan [539, 540, 640].

Insulin signaling is downregulated during *Drosophila* diapause, as monitored by expression levels of DILP target genes [540]. Moreover, *dilp5, dilp2,3* and *dilp2,3,5* mutant flies are more prone to enter and maintain diapause [539, 541]. Also *chico* mutants and flies with over-expression of Imp-L2 display enhanced diapause with diminished dependence on low temperature [541]. These authors conclude that *dilp2, 3* and *5* are antagonists of diapause induction. Lowered DILP release leads to diminished IIS in the corpora allata and thereby decreased production of JH leading to arrested maturation (arrested vitellogenesis) of ovaries, also due to diminished 20E production [233, 431, 433, 619, 624]. Thus, it is likely that reproductive diapause is induced by diminished DILP release from IPCs and subsequent lowering of JH and 20E signaling [619, 640].

8. 2. 2. Excretion (water and ion homeostasis)

In insects, water and ion homeostasis are primarily regulated by the actions of the Malpighian (renal) tubules and the posterior intestine, which comprises a hindgut and rectal pad [81, 644]. Insect Malpighian (or renal) tubules are analogous to the human kidney [645-648]. As such, they filter the hemolymph by secreting excess ions, metabolites and water, and producing “primary urine” in the process. This urine then enters the gut, and following a selective reabsorption of essential ions and water, the excess waste is excreted via contractions of the hindgut. The activities of both the Malpighian tubules and hindgut are regulated by neuropeptides [81, 644, 648-651].

In *Drosophila* and most other insects, four classical families of diuretic peptides have been identified and characterized. These include, DH44 (CRF-related diuretic hormone), DH31 (calcitonin-like diuretic hormone), LK and Capa peptides (CAPA-PVK1 and 2) [652-658]. The expression of these peptides has also been mapped in the *Drosophila* CNS and gut (Fig. 20). Since Malpighian tubules are not innervated, diuretic peptides expressed in neurosecretory and/or enteroendocrine cells are released into the hemolymph from which they activate specific cells in the tubules. In adult *Drosophila*, LK is produced by eleven pairs of abdominal neurosecretory cells (ABLKs) [562, 659]. The anterior four out of these eleven pairs coexpress DH44 [150]. DH44, in addition, is expressed in three pairs of median neurosecretory cells in the brain [543], which in adults co-express DILP2 [275]. Capa peptides are solely expressed in three pairs of neurosecretory cells in the abdominal ganglia A2-A4 [132, 653]. These neurons, designated VA neurons, have varicose axon terminations in the dorsal neuronal sheath and proximal section of the abdominal nerve, which represent potential sites of peptide release [653, 660]. Finally, DH31 expression has not been comprehensively localized in the CNS, but it is expressed in several pairs of neurosecretory cells in the abdominal ganglia and in midgut enteroendocrine cells [294, 661, 662].

The receptors for all these peptides have been identified and their expression localized in *Drosophila* (Fig. 20). Both DH44 and DH31 have two receptors in *Drosophila*, of which only one for each peptide is expressed in the renal tubules [476, 544, 663, 664]. *Drosophila* tubules comprise of two types of epithelial cells, the more abundant principal cells and the sparser, star-shaped stellate cells [665]. Receptors for Capa, DH31 and DH44 are all expressed in principal cells, whereas only the LK receptor is expressed in stellate cells [65, 663, 666]. A great deal of effort has gone into characterizing the effects of these four diuretic hormones on Malpighian tubule function *in vitro*. Thus, the two DHs and Capa peptides stimulate fluid transport by acting on the principal cells. DH31 and DH44 do so via cAMP to activate V-ATPase, and the Capa peptides via intracellular calcium, nitric oxide and cGMP signaling [542, 543, 654]. LK, on the other hand, stimulates fluid secretion by acting on stellate cells to increase a calcium activated chloride conductance [546, 667, 668]. In addition to these classical diuretic hormones, there are further hormones that stimulate *Drosophila* tubules. The NPLP1 precursor derived VQQ peptide (NLGALKSSPVHGVQQ) activates fluid transport through an increase in cGMP content of principal cells [102]. Interestingly, the *Drosophila* stellate cells also express a tyramine receptor, which is in fact activated by tyramine produced by the principal cells [669]. This tyramine signaling also results in elevated calcium levels in stellate cells. Thus, both the tyramine and LK signaling act in parallel to promote secretion by stellate cells [670].

As mentioned above, initial efforts mainly focused on characterizing the functions of these neuropeptides *in vitro*. Only recently have experiments been performed that unravel the roles of these diuretic hormones *in vivo* and thus starting to provide data to address the old question as to why multiple diuretic hormones are present in *Drosophila* and other insects. Capa peptide signaling has been implicated in ion transport underlying desiccation and cold tolerance [65, 146, 545, 671]. LK produced in the abdominal ganglion neurosecretory cells (ABLKs) regulates water balance, as flies with disrupted LK signaling have a bloated abdomen [547, 548]. A similar phenotype is also observed in pupae undergoing ecdysis in which LK neuron activity is suppressed [517]. In addition, DH44 is colocalized with LK in the ABLKs (Fig. 6 and 20) and targeted knockdown of each of these peptides impacts resistance to various stresses such as starvation, desiccation, ionic stress and chill coma recovery [150]. In spite of both DH44 and LK being coexpressed in ABLKs, and possibly co-released, only LK has an effect on overall water balance, and only DH44 affects food intake [150]. Hence various diuretic hormones influence the overall physiology of flies in different ways and under diverse conditions.

As seen above, a lot is known about the actions of diuretic hormones, but what about the anti-diuretic hormones? It has been known for long that ITP is an anti-diuretic hormone in locusts, but its role in water and ion homeostasis in *Drosophila* has only been revealed recently. ITP signaling is vital in water conservation by promoting thirst and reducing excretion [333]. Consequently, this affects the flies' ability to survive desiccation and osmotic stresses. ITP produced by lateral neurosecretory cells in the brain and/or abdominal neurons innervating the hindgut [556] could be responsible for this phenotype. Since the identity of the *Drosophila* ITP receptor is still unknown, the precise mechanisms by which ITP mediates its effects remain to be established. Capa peptides (periviscerokinins) are other potential candidates as anti-diuretic hormones. *Rhodnius* Capa peptides unequivocally inhibit Malpighian tubule secretion by activation of its receptor and a subsequent increase in intra cellular cGMP [658, 672, 673]. Recent work in dipterans suggests that this might be a broader phenomenon across insects than previously presumed. Hence, both in *Aedes aegypti* and *Drosophila,* Capa peptides at low doses (femtomolar range) are able to inhibit Malpighian tubule secretion [545, 674, 675]. But at higher doses (micromolar range), the same peptides stimulate secretion. The molecular mechanisms underlying this hormesis (biphasic dose-response) are still unknown. Other peptides that could influence the activity of Malpighian tubules include Ast-A, Ast-B, sNPF and NPF whose receptors are expressed in the tubules (Fig. 4) [676]. The allatostatins are typically associated with inhibitory roles, and all, except sNPF, are expressed in midgut endocrine cells (see section 8. 3.), so it would not be surprising if they regulate secretion following local release from the gut. Interestingly, the NPF and sNPF receptors are more enriched in male tubules and consequently, both NPF and sNPF inhibit basal fluid secretion by male but not female tubules [676]. Finally, the anti-diuretic role of GPA2/GPB5 in *Aedes aegypti* [677], coupled with the high expression of its receptor in *Drosophila* tubules and hindgut (Fig. 4), suggests that this neurohormone could also be anti-diuretic in *Drosophila* [see also [561]].

The peptidergic control of Malpighian tubules has received substantial attention, but we know very little about the hindgut neuromodulation. Several peptides have been shown to impact hindgut contractility. LK signaling stimulates fecal output in adult *Drosophila* through a combined effect on tubule secretion and activation of its receptor on hindgut muscles [331, 547]. Unlike adults, *Drosophila* larvae exhibit rhythmic defecation which is controlled by two sets of glutamatergic motor neurons in the abdominal ganglia, one of which express PDF [558]. These neurons innervate the hindgut and their activation leads to not only the contractions of the hindgut but also the anal sphincter. Thus, PDF regulates anal sphincter contractions non-synaptically. Interestingly, these abdominal PDF neurons have also been shown to hormonally stimulate contractions in the basal portion of the renal tubules (ureter), which perhaps facilitates the transfer of the primary urine from the tubules into the gut [549].

Nothing is known about the neuropeptide regulation of ion and water reabsorption at the *Drosophila* hindgut. Recently, RYamide neurons in the abdominal ganglia were shown to innervate the rectal papillae, a well-known site for water reabsorption [678, 679]. Since the RYamide receptor is also expressed in the hindgut and rectal papillae, it is possible that RYamide signaling regulates water homeostasis.

8. 2. 3. Neuropeptides regulating hunger, satiety and thirst

Peptides and peptide hormones regulating olfaction, taste, foraging, feeding, metabolism and excretion have been discussed in earlier sections (8. 1. 2., 8. 1. 3. 2. and 8. 2. 1. 3.). Here, we briefly discuss the complex physiology of hunger and thirst, and initiation/termination of food seeking and food ingestion. When a fly is hungry or thirsty, as determined by its internal state of desiccation (high osmolality) or low nutrients, respectively, foraging is triggered. The state of hunger is governed by nutrient sensors in the fat body as well as in neuroendocrine cells in the brain and intestine as described in section 8. 2. 1. 1., and osmolality detected by cat ion channels (see below). In Fig. 21 we show a scheme of the behaviors involved in the process of food seeking, food consumption and cessation to feed [for further details see reviews by [680, 681]]. In the fly, thirst and hunger is regulated in opposite direction by two sets of neurons, ISNs (interoceptive SEZ neurons) and ITP-producing neurons (ITP; ipc-1) [310, 333]. These sets of neurons act antagonistically on drinking and food ingestion (thirst and hunger). ITP increases thirst, but depresses hunger [333], and ISNs do the opposite [310]. The ISNs are activated by low osmolality, sensed by the Nanchung cat ion channels (Nan), or AKH released due to low carbohydrate levels and acting on their receptors AKHR [310]. The input signals to the ITP neurons are not known, but they respond to desiccation (high osmolality) and integrate water homeostasis, excretion and feeding [333]. In a hungry fly circulating AKH levels are high and specific DILPs low [see e. g. [1, 7, 68, 680, 681]], and this state sets levels of activity in peptidergic neurons that influence strength of food search (locomotion) as well as meal initiation and ingestion (Fig. 22,23).

As described in section 8. 1. 2., the sNPF-R1, and TK receptor (DTKR) expressed in olfactory sensory neurons (OSNs) can alter the sensitivity of specific odorant channels (Or42b and Or85a) in the hungry fly (low insulin signaling) and thereby increase food odor valence and food search [300, 301, 393] (Fig. 22, 23). Taste receptors are also modulated by neuropeptides; NPF (and dopamine) enhances response of sweet receptors (Gr5a), whereas sNPF and dopamine decreases sensitivity of bitter receptors (Gr66a) [306, 311, 393] (Fig. 23). Hunger induces an increase in locomotor activity in flies [289, 311, 429], which has been associated with intensified food search (Fig. 23). Increased DILP signaling inhibits this activity [311]. Expression of AKHR and dInR coincides on sets of octopaminergic neurons, that in hungry flies activate motor neurons that drive exploratory locomotion [311] (Fig.23).

At the level of meal initiation dopamine and NPF are stimulatory and Hugin, DSK, DILPs and Ast-A are inhibitory [24, 143, 147, 161, 326, 360, 680] (Fig. 22). Interestingly, in larvae, Hugin inhibits feeding and stimulates locomotion [64, 682] (Fig. 24). Although not always clearly distinguished from meal initiation in experiments, food ingestion is stimulated by sNPF and AKH and inhibited by Ast-A, LK, MIP, and at least indirectly by DILPs [143, 318, 326, 332, 628, 680, 683] (Fig. 22).

Upon feeding, satiety signals such as DILPs and DSK are released and the meal is terminated [24, 680, 681]. It is not known how DSK acts to decrease feeding, but the increased levels of circulating DILPs act on neurons of the olfactory and gustatory system to decrease sensitivity to food stimuli [7, 301, 306]. There are also neuropeptides acting in a more integrating fashion to regulate levels of hunger and feeding. One example is SIFamide produced by four neurons in the *Drosophila* brain [162]. These widely arborizing neurons integrate hunger and satiety signals generated by neurons producing MIP (inhibit SIFa neurons) and hugin-PK (stimulate SIFa neurons) and thereby orchestrate appetitive behavior [162]. The SIFa neurons stimulate appetite by sensitizing specific olfactory and gustatory receptors and at the same time they inhibit reproductive behavior [162, 375, 376]. Another integrating system is constituted by the circuits of the mushroom bodies (MB) that process food odors (Fig. 9). As discussed in section 8. 1. 3. 2., peptidergic signals act on dopaminergic neurons (of PPL1- and PAM-types), which in turn activate or inhibit specific MB output neurons (MBONs) that activate food seeking [316]. In general, NPF and sNPF are stimulatory, and Ast-A and DILPs are inhibitory on stimulatory MBONs, whereas serotonin, NPF and sNPF inhibit inhibitory MBONs [316]. Finally, in larvae, the diverse set of Hugin-neurons in the SEZ are known to integrate gustatory inputs, neuroendocrine cells of the brain, feeding behavior and locomotion [64, 684, 685] (Fig. 24). The hugin cells are present also in the adult brain [686], but it is not known whether they regulate feeding at this stage.

8. 3. Gut peptides and the brain-gut axis

The brain-gut axis represents a bidirectional communication between the CNS and gastrointestinal tract. The digestive tract of animals contains enteroendocrine cells (EECs), which sense the internal intestinal environment and secrete neurohormones to modulate diverse physiological processes including gut motility, appetite and nutrient homeostasis [648]. In mammals, incretin peptides like glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are expressed in the EECs, regulate hormone secretion, gut motility, appetite and lipid metabolism [687]. In particular, GLP-1 increases insulin and inhibits glucagon secretion [688, 689], whereas GIP increases secretion of both insulin and glucagon, thus regulating glucose homeostasis [687]. In addition, EEC-derived ghrelin suppresses insulin secretion [690, 691], whereas cholecystokinin (CCK) stimulates the release of insulin and other hormones [692, 693]. Moreover, the release of CCK from EECs is stimulated following ingestion of lipid and protein, as well as by gastrin-releasing peptide [694]. Hence, the activity/release of mammalian gut peptides is dependent on the diet and other peptides, and they are primarily responsible for regulating the secretion of insulin and other factors, including hypothalamic peptides that control appetite and feeding.

The *Drosophila* intestine has become an attractive model in studies of metabolism, stem cell activation, epithelial immune defense and inter-organ communication due to functional similarities with the mammalian system [2, 299, 648, 695-698]. This recent focus has shed new light on the fact that the *Drosophila* intestine, especially the midgut, is a rich source of bioactive peptides (Fig. 25). In adult *Drosophila,* the EECs are located in various regions of the midgut and express the transcription factor *Prospero* [698]. These cells are a source of ten peptide and protein hormones, most of which have mammalian orthologs (Table 9). These include Ast-A, Ast-B (MIP), Ast-C, bursicon alpha, CCHamide1, CCHamide2, DH31, NPF, orcokinin B, and tachykinin [294, 295, 523]. The tachykinins can also be seen in EECs of the anterior hindgut. In addition, DILP3 is produced by muscle cells in regions of the midgut [294]. A summary of the peptide distribution is shown in Fig. 26. Some of the peptides are colocalized in subpopulations of the EECs [699]. For instance, Ast-C and orcokinin B are colocalized in the anterior midgut, and Ast-A and Ast-C are colocalized in the posterior midgut. Furthermore TK and NPF are colocalized in the anterior and middle midgut, and DH31 and TK in the posterior [294, 699]. Many of these peptides have also been identified in endocrines of the larval gut of *Drosophila* [662]. In addition to the peptides produced by cells in the midgut, there are sets of efferent peptidergic neurons whose axons target different parts of the intestine; however, we focus first on the gut-derived peptides.

Table 9. Neuropeptides expressed in *Drosophila* midgut enteroendocrine cells and their mammalian orthologs.

***Drosophila* neuropeptide**	**Acronym**	**Mammalian ortholog**	**Expression in larval gut**	**Expression in adult gut**
Allatostatin A	AstA	Galanin	P	P
Allatostatin B	AstB/MIP	None	A, M, P	M, P
Allatostatin C	AstC	Somatostatin	M, P	A, M, P
Bursicon alpha	burs	None	?	P
CCHamide-1	CCHa-1	Neuromedin B	A, P	P
CCHamide-2	CCHa-2	Neuromedin B	A, P	A, P
Diuretic hormone 31	DH31	Calcitonin	A, M, P	P
Neuropeptide F	NPF	Neuropeptide Y	M	A, M
Orcokinin-B	OK-B	None	M	A, M
Short neuropeptide F	sNPF	Prolactin-releasing peptide	A	-
Tachykinin	TK	Substance P	P	A, M, P

Note: Data based on immunohistochemical localization studies. A = anterior midgut, M = middle midgut and P = posterior midgut.

Despite the high prevalence of EEC-derived peptides, very little is known about the functional role of neuropeptides/peptide hormones in the insect intestine. Studies examining the roles of *Drosophila* gut peptides are scarce largely owing to the fact that it has been difficult to study the *in vivo* effects of gut-derived peptides in isolation from the CNS-derived peptides. DH31 from EECs has been shown to influence midgut peristalsis [296] and recent work has shown that these contractions facilitate the expulsion of opportunistic bacteria [554]. Gut-derived TK was shown to influence lipid homeostasis by controlling lipid production in enterocytes [21]. Both, the DH31 and TK producing EECs are nutrient-sensing and are activated by the presence of dietary proteins and amino acids [596]. Similarly, bursicon alpha neurons are able to sense and consequently be activated by dietary sucrose [264]. Bursicon α is then released into the hemolymph, acts on Lgr2 receptors on brain neurons that in turn downregulate AKH signaling and thereby affect metabolic homeostasis (see Fig. 17). In addition, bursicon alpha also acts locally to control stem cell quiescence in the gut [523]. CCHamide2 has been proposed to target insulin-producing cells in the brain and regulate food intake [327, 328]. Activation of Ast-A expressing brain neurons (PLP) and EECs results in reduced feeding and increased sleep [326]; however, this study was not able to parse out specific functions of the two Ast-A cell-types. Some of the peptides from the gut endocrine cells might act on the Malpighian tubules to regulate secretion. For instance, NPF has been shown to influence the activity of male Malpighian tubules [676]. Since brain NPF is only expressed in interneurons, the source of this hormonal NPF appears to be EECs. Similarly, Ast-A, DH31 and TKs derived from EECs could also influence the activity of the tubules. Lastly, gut muscle-derived DILP3 activates midgut stem cell division to promote nutrient-dependent gut growth [528].

Based on the *in vitro* assays performed in other insects, we can also speculate on functions for some of the peptides expressed in EECs. Receptors for the gut peptides are expressed throughout the gut and in various cell types (Fig. 26 and Supplementary Table 1). However, in most cases, the receptors are typically enriched in EECs. Receptors for Ast-A, Ast-B and DH31 are expressed in the midgut visceral muscles of adult *Drosophila*. Thus it is not surprising that Ast-A has been shown to inhibit and DH31 to stimulate larval midgut contractions [560]. These peptides have also been shown to modulate gut contractions in *Rhodnius, Chironomus riparius, Locusta migratoria* and *Lacanobia oleracea* [700-707]. It is also possible that some of the peptides regulate activity in gut epithelial cells that produce digestive enzymes [28, 208, 708, 709] or cells involved in nutrient or ion absorption [700, 701, 710].

Due to the recent interest in gut function and inter-organ communication, we predict that studies on gut-derived peptides will be extremely vital and become more frequent in the future. Several questions still remain to be answered to understand the function and regulation of enteroendocrine peptide signaling, a field whose surface has barely been scratched. What type of nutrients and factors alter the activity of EECs? Which CNS-controlled behaviors and hormonal systems are modulated by these gut peptides? How does the signaling by EECs influence the overall health and survival of flies? What are the roles of the gut microbiota? Answers to these questions will allow us to understand the hormonal links between diet and the endocrine regulation of feeding.

In addition, to the peptides produced by cells in the midgut, there are sets of efferent peptidergic neurons whose axons target different parts of the intestine as well as neurosecretory cells that may target the gut with peptide hormones. These are derived from neurosecretory cells in the MNC and LNC, hypercerebral ganglion, thoracic and abdominal neuromeres of the VNC, and efferent neurons in posterior neuromeres of the abdominal ganglion. Peptides produced by afferents to foregut and midgut structures (including proventriculus, crop duct and crop) are Ast-A, corazonin, DILP2, 3 and 5, DSK, DH44, DMS and sNPF and ITP [17, 110, 154, 551, 711, 712]. Peptides in afferents to the hindgut are Ast-A, CCAP, DILP7, ITP, PDF and proctolin [493, 551, 556, 557, 559, 713]. Additionally, there are neurohemal release sites supplied by axon terminations of peptidergic neurons with cell bodies in thoracic or abdominal neuromeres. Peptides released from these areas (CAPA, dFMRFamide, GAP2/GPB5, LK) could reach also the intestine and renal tubules [561, 562, 660, 714]. Figure 27 summarizes the peptidergic neurons with cell bodies outside the intestine that could target this tissue and renal tubules.

Also, a number of neuropeptide receptors (GPCRs) have been identified, primarily by identification of their transcripts: Ast-A-R1, Ast-A-R2, Ast-B-R (MIP-R), Ast-C-R1, Ast-C-R2, CCHamide1-R, CCHamide2-R, DH31-R, DH44-R2, DTKR (Takr99D), GPA2/GPB5-R, LK-R, NPF-R, NPLP1-R, and PDF-R (Fig. 26) [295, 715]. The proctolin receptor (CG6986) was detected in the hindgut by immunocytochemistry [440]. Finally, DILP7 was shown to be involved in regulation of tracheal growth around the intestine [587].

In summary, the intestine is under substantial control by neurons of the CNS, both efferents and neurosecretory cells, as well as possible paracrine regulation by EECs. On the other hand, the intestine is likely to signal to other tissues by hormonal release of peptides from EECs, suggesting a two-way communication between the CNS and the gut. Considering the emerging complexity of gut function, including the role of its microbiota, it is not surprising that inter-organ signaling is complex.

9. Concluding remarks and future perspectives

Much progress has been made in exploring the functional roles of neuropeptides in *Drosophila* over the last ten years. The present review has highlighted novel neuropeptides discovered in this period and also the accelerated use of novel and powerful genetic techniques to unravel how peptides act in CNS circuits to modulate behavior and physiology. This also extends to peptide hormones where several neurosecretory systems have been explored for roles in development, physiology and behavior. In this context, especially insulin-like peptides have attracted much attention and several layers of signaling mechanisms have been untangled that strengthen the view of an evolutionary old and conserved hormonal system.

Due to its genetic tractability and simpler organization of nervous and endocrine systems, *Drosophila* has been extensively explored for analysis of genes that may play roles in human diseases and physiological disorders or regulation of complex behaviors in mammals [see for example [1, 2, 6, 7, 68, 69, 569, 716-720]. This review has not specifically addressed the use of *Drosophila* as a disease model, although we have stressed that many of the peptide signaling pathways are conserved over evolution.

Quite a few recent investigations have ventured to determine the morphology and functions of single pairs or small populations of identifiable peptidergic neurons in the CNS. Also, several peptidergic neurosecretory systems have been delineated in addition to those employing DILPs and AKH. However, one of the pressing needs is to establish a comprehensive map of the distribution of neuropeptides in larval and adult *Drosophila* and to provide catalogs of peptidergic neurons revealed in morphological detail. At present the available data are patchy and in most cases the morphology of all individual peptidergic neurons has not been described. Even more urgent is to establish the distribution of peptide receptors at the protein level. Very few studies are available on the distribution of GPCR protein or peptide binding sites in insects. The available tools, such as the Gal4-UAS system, to reveal neurons expressing GPCRs by means of GFP suffer both from not revealing where the receptor protein is expressed in the neuron and from fidelity; does the expression truly represent that of native receptor protein (commonly a lack of independent verification method)? In mammals GPCR immunolabeling and receptor binding autoradiography have been utilized for many years; one difference probably being that more receptor protein is expressed and resolution is higher since mammalian neurons are much larger. Thus, the production of a peptidergic "connectome" in *Drosophila* is somewhat problematic at present. In principle, it would be possible to use the recently developed trans-Tango technique, which has been designed to enable tracing of neurons postsynaptic to a specific neuron type defined by a Gal4 driver [261]. This technique works well for neurons connected by conventional synapses. However, to our knowledge it has not yet been clearly established for peptidergic neurons that possibly signal by extrasynaptic transmission. Several recent studies have utilized trans-Tango to examine unbiased connectivity in circuits. In fact, two studies employed this technique to show connectivity in the sleep-wake circuit [721, 722]. Another study used this tool to show the connectivity between neurons expressing the bursicon receptor and those producing AKH [264]. However, it is not yet clear whether neuropeptides or classical neurotransmitters are mediating this connection. We obtained variable results with trans-Tango when driving the construct in a set of neurons producing leucokinin [331]. We did not visualize postsynaptic signal in several types of neurons known to express the leucokinin receptor, such as the IPCs and ITP producing ipc-1 neurons. However, we found label in sets of neurons in the SEZ. Possibly the reason is that certain LK neurons (e. g. the so called SELKs) coexpress a classical neurotransmitter and thus the neurons that are truly postsynaptic (via conventional synapses) are picked up in the trans-Tango. Clearly the trans-Tango system and its variants [723] need to be further explored for peptidergic neurons to determine its usefulness.

Another pressing question is whether all the neuroendocrine cells and/or neurons that produce a given neuropeptide cooperate to modulate or orchestrate a specific function, or does it have neuron-specific functions? For instance, do all neurons signaling with MIP act together to regulate a specific function? This probably differs between the different *Drosophila* neuropeptides. For example, it is clear that sNPF is present in a variety of neuron types in different non-overlapping parts of the brain and it has been established that the peptide acts as a co-transmitter of acetylcholine in olfactory neurons and Kenyon cells of the mushroom bodies [288, 300, 359]. Several other distinct roles of sNPF have been established: in specific synapses/circuits of the clock system [267, 280], as a modulator of insulin producing cells (IPCs) of the brain [183], in circuits of the VNC in modulation of nociception [290] and in specific neurons in the central complex sNPF modulates aspects of exploratory walking [339]. Taken together, these examples suggest that sNPF acts in a circuit-dependent manner and has distributed functions, rather than being a peptide with a unifying global function. This does not exclude that sNPF does play an important role in regulation of food search and feeding by action in circuits of the antennal lobes, on mushroom body output neurons and maybe other brain circuits [300, 301, 316, 318]. In contrast to sNPF, there are examples of neuropeptides that display more global functions as neuromodulators and/or hormones. Peptides present in few neurons or neurosecretory cells probably play such roles, although only a few comprehensive investigations have been performed. An example is leucokinin (LK) that has been studied quite extensively recently. LK is produced by a set of 22 neurosecretory cells in the abdominal ganglia and two pairs of neurons in the brain/SEZ. Classically LK was considered a diuretic hormone inducing secretion in renal tubules [81, 546, 666, 724], but more recently, genetic approaches have indicated further adult roles in food intake, regulation of stress responses, modulation of metabolism-related sleep, clock output, locomotor activity and metabolic rate, and modulation of chemosensory inputs [150, 330, 331, 347-350]. Each of the three subpopulations of the LK neurons is responsible for different parts of these regulatory mechanisms, but it was suggested that together these neurons regulate post-feeding physiology and behavior [331] (see Fig. 28). Further examples of small populations of peptidergic neurons that may underlie orchestrating functions are the four neurons producing SIFamide [162, 375]. The widely arborizing SIFamide neurons are part of a circuit integrating several peptidergic systems that generate orexogenic and anorexigenic signals and thereby they convey hunger signals or inhibit satiety signals [162]. While the SIFamide neurons were previously shown to inhibit sexual activity [375, 376], it was suggested that the neurons work antagonistically on feeding and reproduction [162]. These were only two examples, and it would be interesting to test to what extent other peptides produced by smaller and more homogeneous neuron populations also have similar global functions. Conversely, it is important to establish the possible pleiotropic roles of peptides expressed in large populations of neurons such as for instance tachykinins, DH31, Ast-C, and NPLP1.

A further interesting aspect of neuropeptide signaling is that their functional roles probably differ depending on developmental stages. A number of peptides have been analyzed in larval *Drosophila* or in pharate adults and specific functions determined that are related to molting/ecdysis or growth [99, 292, 454, 499, 515] phenomena that do not occur in adults. Yet many of the same peptides exist in adults where they obviously have other roles. Some peptidergic systems actually undergo apoptosis in pharate or very young adults: neurons producing PTTH and EH all disappear, whereas subpopulation of those producing CCAP, bursicon and corazonin die [270, 506, 725, 726]. Thus, some peptides seem to play roles only in development, while others continue to exist in adults where they have acquired novel roles. An example of a switch in function from developmental (ecdysis motor behavior) to adult roles is ETH. The ETH-producing Inka cells persist into adulthood and Ecd-dependent ETH signaling triggers production of JH and this controls ovary growth, egg production and reproduction [494]. ETH also acts on octopaminergic neurons of the oviduct to influence stress-induced reproductive arrest [496]. Finally it was shown that ETH is essential for male courtship memory via regulation of JH signaling that acts on specific dopaminergic neurons [522].

Another aspect is that the circuitry of the brain increases in complexity during metamorphosis. As an example the clock system is rudimentary in the larva (16 neurons), but highly complex in the adult (about 150 neurons). This extends also to the expression of neuropeptides in clock neurons, which diversifies during metamorphosis from two in the larva to at least 7 different ones in adults (single cell transcriptomics suggest more) [9, 273, 277]. Thus, peptide function is likely to be far more diverse and complex in adult flies than in larvae.

There are several neuropeptides that have received very little attention in *Drosophila*. Actually three of the first peptides properly identified in insects, including *Drosophila*, proctolin, extended FMRFamides and myosuppressin (DMS) are examples of understudied peptides. Other peptides were recently identified in *Drosophila* and therefore not yet functionally explored in any detail: CCHamide 1 and 2, CNMamide, ITG, Natalisin, NPLPs, Orcokinin, RYamide, and Trissin.

Quite a few novel neuropeptides have been discovered since the publication of the *Drosophila* genome [193] and the first papers on the *Drosophila* peptidome [37, 94]. In insects from other orders, especially more phylogenetically basal ones, peptides additional to those found in *Drosophila* have been identified [31, 194, 727]. Can we expect discoveries of further neuropeptides/peptide hormones in *Drosophila*? Even if that will not be the case there is a lot of work ahead to characterize the functions of those that we know do exist. With the continuously ongoing development of novel powerful genetic techniques, improved imaging methods and innovation of efficient and clever bioassays there is good hope that in the next 10 years the field will make tremendous progress.

FIGURE LEGENDS

Fig. 1. Neuropeptide production and processing. **A.** A peptidergic neuron with production steps, from gene transcription to storage of mature peptides is shown. **B.** Neuropeptides are produced from larger precursor proteins known as prepropeptides. These comprise of a signal peptide (which directs the protein to the secretory pathway), progenitors of mature peptides, spacer peptides (peptide fragments with no known biological function and non-conserved sequences) and cleavage sites (monobasic and dibasic; e. g. KR or RR). Each precursor can give rise to one or more mature neuropeptides. The number of mature peptides produced from a given precursor can vary from one insect species to another. A typical prepropeptide and its biosynthesis and processing are shown in the diagram. **C.** Different forms of post-translational modifications of peptides. Proctolin has no modifications, Ast-C is pyroglutamate (pQ) blocked and cyclic due to a disulfide bridge between C residues, AKH is blocked in both ends (pQ and amidation), DSK-1 has a Y residue that is sulfated ($-SO_3$), and CCAP is both cyclic and amidated.

Fig. 2. Identification and characterization of bilaterian peptidergic systems. The different neuropeptide / protein hormones have been classified according to the receptor type that they activate. Peptide families whose receptors have not yet been identified are grouped under orphan receptors. Protostomian animal groups are highlighted in green and deuterostomian animal groups are highlighted in pink. No deuterostomian neuropeptide family name is provided for cases in which neither the peptide nor the receptor ortholog has been identified in a deuterostome. See the legend at the bottom of the figure for explanations on the shading scheme. Abbreviations: ?, data not available; Rhod. ∂, Rhodopsin delta; RTK, receptor tyrosine kinase; RGC, receptor guanylate cyclase. Refer to Table 1 for full names of the neuropeptides. This figure is an updated version of the figure presented by [32]. Revisions based on [33, 44, 57, 62, 66, 196, 224, 728-730].

Fig. 3. Expression of neuropeptides in tissues of larval and adult *Drosophila*. The expression of each neuropeptide is color-coded: the tissue with lowest expression is in yellow, medium expression in orange and highest expression in red. Data based

on FlyAtlas (REF). Values are reported for neuropeptides that were detected in all four arrays. Neuropeptides that were undetectable in any tissue are highlighted in gray.

Fig. 4. Expression of neuropeptide receptors in tissues of larval and adult *Drosophila*. The expression of each receptor is color-coded: the tissue with lowest expression is in yellow, medium expression in orange and highest expression in red. Data based on FlyAtlas (REF). Values are reported for neuropeptides that were detected in all four arrays. Receptors that were either undetectable in any tissue or unknown for a given peptide are highlighted in gray. Note: AstCC receptor has not been deorphanized in *Drosophila* but AstCC is predicted to activate AstC receptors based on the work done in *Tribolium castaneum* [130].

Fig. 5 a and b. Schematic diagrams showing the distribution of cell bodies of various peptidergic neurons in larval CNS of *Drosophila*. Acronyms as in text (and Table 1). Note that all cell bodies are drawn with the same size for simplicity, and in some cases the minimum number of cells are drawn (some variability occurs). This figure was redrawn, revised and updated from [40, 111] and original publications listed in section 5 (and Supplementary Material files Appendix 1).

Fig. 6. DH44, leucokinin and leucokinin-receptor expressing neurons in the *Drosophila* CNS. **A** and **B**. The DH44-Gal4-driven GFP matches the distribution of DH44-immunolabeling (DH44-IR) in six median neurosecretory cells (MNCs) and 2 pairs of small neurons (asterisks) innervating the fan-shaped body (FB). **C** and **D.** Neurons expressing DH44-GFP overlap leucokinin immunoreactive (LK-IR) branches in the subesophageal zone (SEG). There are only four LK-IR neurons in the adult brain (LHLK and SELK). **E** and **F**. Distribution of the leucokinin receptor (Lkr-GFP), seen with *Lkr*-Gal4, and neurons expressing LK-IR in the larval CNS. In the abdominal neuromeres of the ventral nerve cord (VNC), 7 pairs of ABLKs are seen. Some of the median Lkr-GFP neurons in the VNC are likely motor neurons. Compiled from [331].

Fig. 7. Distribution of peptidergic neurosecretory cells in the larval CNS of *Drosophila*. The different types of neurosecretory cells are color-coded and where appropriate, their designations provided. AKH is produced in the endocrine cells of the corpora cardiaca (CC). Brain cells are clustered in median (MNC) or lateral (LNC) neurosecretory cell groups. The neurosecretory cells of the brain and subesophageal ganglion (S1–3; SEG) have axon terminations in the corpora cardiaca or corpora allata portions of the ring gland (and anterior aorta wall). The axons of the PG-LP neurons terminate in the prothoracic gland. In the ventral nerve cord (VNC), the neurosecretory cells of the thoracic neuromeres (T1–3) terminate in thoracic perisympathetic organs (not shown) and the abdominal ones (in A1–7) send axons to abdominal transverse nerves (Va) or body wall muscles (ABLKs). See Table 1 for the full names of the neuropeptides. Additional abdominal neuroendocrine cells (not shown here) are efferents with axons terminating in the body wall or intestine. These produce CCAP (some of these also MIP and bursicon), Ast-A, DILP7, ITP and PDF. This figure was redrawn and updated from [132] and [35].

Fig. 8. Peptidergic neuromodulation and cotransmission in the olfactory system. Neuromodulation in the *Drosophila* antennal lobe (AL) is shown highly schematically with only two glomeruli (dashed outlines). Inputs to the glomeruli are from olfactory sensory neurons (OSNs) of the antenna and labial palps. The OSNs synapse on projection neurons (PN) that relay signals to higher brain centers (mushroom bodies and lateral horn). The OSNs and PNs are modulated by local neurons (LNs), which form intrinsic modulatory circuits, and by extrinsic neurons that utilize several neurotransmitters and/or neuromodulators. The LNs are either GABAergic, cholinergic (Ach), or in some cases glutamatergic. The former two types are known to colocalize the neuropeptides tachykinin (TK), allatostatin-A (AstA) or myoinhibitory peptide (MIP) [285], whereas it is not known whether glutamatergic ones colocalize any peptide. The extrinsic neurons utilize SIFamide, dromyosuppressin (DMS), IPNamide (from the precursor NPLP1), CCHamide2, octopamine or serotonin (5-HT)

[285, 731-733]. It is not known whether any of these extrinsic neurons colocalize other neurotransmitters/neuropeptides. Additionally, a subpopulation of the OSNs coexpress Ach and sNPF [110, 285] and in females some OSNs with Ir-type receptors coexpress MIP [287]. Recent reports from single cell transcriptomics suggest that some PNs may express sNPF and others TK in addition to Ach [118]. This figure is updated from [9].

Figure 9. Model of the neural mechanisms in the mushroom body circuit that control food-seeking behavior. During food seeking, odors activate the Kenyon cells (KCs) that in turn activate mushroom body output neurons (MBONs). The GABAergic MBON-γ1pedc>αβ inhibits the downstream neurons that suppress food-seeking behavior, including β'2-innervating MBONs and MBON-α1. KC-to-MBON connectivity is regulated by the corresponding 6 types of dopaminergic neurons (DANs; between brackets). The different DANs are regulated by combinations of hunger and satiety signals (NPF, sNPF, AstA, Insulin and 5-HT). When flies are fed, satiety signals like insulin and AstA suppress PPL1-γ2α'1, PPL1-α'2α2, PAM-β'2α, and PAM-β2β'2α DANs. When flies are starved, hunger signals including serotonin (5HT), NPF, and sNPF activate PPL1-α3, PAM-β2β'2α, PAM-β'2α, and PPL1-γ2α'1 DANs, whereas they suppress PPL1-γ1pedc DANs. Dopamine signals pre- and post-synaptically mediated by the DAMB receptor fine-tune the KC-to-MBON connectivity and modulate the collective output of the MBONs driven by food odor. Therefore, the hunger state tunes the odor-driven output of the MBONs to regulate food-seeking behavior. DAMB, dopamine receptor, 5HT1B and 5HT2A, serotonin receptors. This figure is Fig. 12 from [316], with permission from the authors [see also license (https://creativecommons.org/licenses/by/4.0/)].

Fig. 10. Neuropeptide signaling in the central complex of *Drosophila*. Seven different neuropeptides have been identified in neurons that innervate different layers or structures of the central complex. **A.** The central complex consists of the fan-shaped body (FB), the ellipsoid body (EB), the protocerebral bridge (PB), the lateral triangle (LTR) the nodules (NO) and the ventral bodies (VBO). **B.** A set of neurons

that express the allatostatin-A receptor (AstAR1) is part of a population that induces sleep upon activation [designated sleep-inducing neurons [144]]. Their cell bodies are at position 8 in C. **C.** Location of cell bodies of peptidergic neurons innervating the central complex. Peptide acronyms are given as in text. **D.** Distribution of sNPF and its receptor snpfr1 in layers (numbered) of the fan-shaped body seen with immunolabeling and Gal4-driven GFP. A, C and D updated from [734], B edited from [735]. Original data for C from [438] and D from [110, 439].

Fig. 11. Neuropeptides in clock neurons in the *Drosophila* brain. **A.** The different types of clock neurons in one brain hemisphere. There are lateral ventral neurons (s-LNv and l-LNv), lateral dorsal neurons (LNd), dorsal neurons (DN1-DN3), and a set of lateral posterior neurons (LPN). aMe, accessory medulla. This panel is from [280], but originally published in a slightly different form in [448]. **B.** Expression of Tim-Gal4-driven GFP (green) and immunolabeling for ion transport peptide (ITP; magenta), from [280]. **C**. Neuropeptides in LNd and LNv neurons are colocalized in different patterns. The figure is compiled from data in [280] and [277]. Note that the s-LNvs also produce the amino acid transmitter glycine [279] and l-LNvs the cytokine Upd1 [278]. **D**. The clock output generates daily activity with peaks in the morning (M) and evening (E) and low activity at night and mid day. This activity is generated by clock neurons that act as morning (M) and evening (E1-E3) oscillators. These express different combinations of neuropeptides and some interactions between LNvs and other neurons are known to be by means of pigment-dispersing factor (PDF) shown in red arrows. The roles of other peptides are less known so far. This figure is compiled in part from data in [277].

Fig. 12. A scheme depicting PDF-, sNPF-, and light-mediated interactions that orchestrate sequential Ca^{2+} activity phases in different pacemaker groups of the *Drosophila* clock. Each pacemaker group is represented by one neuron. The position of cells in the day-night circle (yellow–gray) indicates the peak phase of Ca^{2+}. Both PDF and sNPF signals inhibit the target neurons and suppress these from being active when the sender neurons (s-LNv for PDF; s-LNv and LNd for sNPF) are

active. Light cycles act together with PDF to delay Ca^{2+} phases in LNds. This figure is from [9] which was redrawn from [267].

Fig. 13. A scheme depicting neuropeptides modulating different aspects of *Drosophila* reproduction. Reproduction is shown here as courtship, mating, post-mating responses and reproductive physiology. Peptides are shown in black boxes (including insulin signaling, IIS). Specific events/behaviors/physiology during reproduction are shown in blue boxes. Black arrows depict stimulatory input, red bars indicate inhibition and blue arrow indicates an unknown mechanism. ETH is regulated by 20-OH ecdysone (20E). For acronyms and references to the original data, see text.

Fig. 14. Neurons and neuropeptides part of the ecdysis circuit in *Drosophila*. **A.** A schematic of the larval CNS depicting sets of peptidergic neurons expressing the ecdysis triggering hormone receptor A isoform (ETHR-A). These neurons are activated by ETH following its release from the epitracheal Inka cells (not shown in A). **B.** The different sets of neurons are activated sequentially after ETH release from Inka cells. Note that some neurons express more than one neuropeptide. Acronyms: AstCC, allatostatin-CC; burs, bursicon; CCAP, crustacean cardioactive peptide; EH, eclosion hormone; ETH, ecdysis triggering hormone; FMRFa, FMRFamide; MIP, myoinhibitory peptide. This figure is an updated version of a figure in [35] which was originally based on [292].

Fig. 15. Insulin producing cells (IPCs) in the larval and adult CNS. **A.** Larval IPCs (*dilp2*-Gal4-driven GFP) with a list of peptides and receptors expressed. There are 14 cell bodies (cb) and a set of axon terminations in the aorta and ring gland. SEG, subesophageal zone. **B.** Overview of IPCs in larval CNS and their terminations in the ring gland (RG). **C.** The adult IPCs (*dilp1*-Gal4-driven GFP) with two sets of dendrites (Dendr 1 and 2), 14 cell bodies (cb) and a list of peptides and receptors expressed. Note that the receptors differ between the larva and adult stages (some of the differences could be due to only one of the stages investigated for several of

the receptors - ligands). In adults there are 6 more MNCs expressing DILP2: the DH44 producing cells [275]. **D.** The IPCs in their entire extent within the brain (inversed image from Gal4-driven GFP). The arrow indicates the exit site of axons to the corpora cardiaca and other peripheral sites. **E.** DILP7-expressing neurons of the adult ventral nerve cord revealed by Gal4-driven GFP. Two of the lateral cell bodies in abdominal neuromere 1 (A1) are indicated by asterisks. Most of the 20 DILP7 neurons are obscured by GFP labeled neuronal branches. A bundle of DILP7 expressing axons (Ax) exit the ganglion posteriorly, destined for the hindgut. **F.** DILP7-immunolabeled neurons in the same region as in E. Two neurons labeled with asterisks correspond to the ones in E. A cluster of posterior neurons (pCb) is seen, some of which give rise to axons innervating the hindgut. **G**. Immunolabeling with an antiserum to a mosquito insulin receptor reveals a general weak labeling of neuropil, as well as strong labeling in a set of 14 neurons (ABLKs) known to produce the peptide leucokinin. This figure is updated from [736].

Fig. 16. Factors that regulate production and release of DILPs from IPCs in the *Drosophila* larva. Three tissues release regulatory factors (red circles 1-3). From corpora cardiaca (CC) AKH is released in a glucose-dependent manner. The fat body releases TNF Eiger, adiponectin, DILP6 and stunted and the midgut releases CCHamide2. The box shows the receptors expressed by the IPCs (ligands in brackets). For references to the original data see text.

Fig. 17. Scheme depicting pathways that regulate insulin-producing cells (IPCs) in the adult brain of *Drosophila*. Blue arrows depict stimulatory inputs and red bars show inhibitory ones. Dashed black line indicates incompletely known mechanisms. The IPCs are regulated by neurons in the brain releasing serotonin (5-HT), octopamine (OA), dopamine (DA), allatostatin-A (AstA), leucokinin (LK), short neuropeptide F (sNPF), and tachykinin (TK), as well as GABA. The fat body is nutrient sensing and releases adiponectin-like polypeptide, Upd2, and DILP6 after carbohydrate intake. Upd2 acts (inhibitory) on GABAergic brain neurons and thereby relieves inhibition of the IPCs. Adiponectin and DILP6 act directly on the IPCs.

Another factor FIT (female-specific independent of transformer) is a protein-specific signal released from the fat body after a protein meal. The corpora cardiaca (CC), under conditions of low sugar, releases limostatin (Lst) and adipokinetic hormone (AKH) and thereby inhibits release of DILPs. The intestine is likely to have nutrient-sensing cells and to release peptide hormones into the circulation. Two gut peptides have been shown to act on IPCs, allatostatin A (AstA) and CCHamide2 (CCHa2), whereas bursicon (Burs) from the gut acts on brain neurons, which in turn act on CC to diminish AKH production (asterisk and dashed line to indicate indirect action via brain). There may be other gut peptides that act on the CC or brain neurons that in turn act on IPCs (e. g. DH31 and neuropeptide F; not shown here). For references to the original data see text.

Fig. 18. Insulin signaling during larval growth and development. The insulin-producing cells (IPCs) release DILPs in a nutrient-dependent fashion. These act to regulate tissue growth. DILP release and activity of circulating DILPs are under five types of control (red circles 1-5): (1) modulatory factors from corpora cardiaca in ring gland (RG), from brain neurons and intestine; (2) inhibitory control by insulin-binding proteins such as secreted decoy of insulin receptor (SDR) as well as (3) acid-labile subunit (ALS) and Imp-L2. DILP6 is released from fat body. Finally DILP8 is released from damaged imaginal discs (4) and acts to block production of ecdysone (Ecd) and 20-OH Ecdysone (20E) from the RG via action on interneurons that block PTTH release. The IPCs are also regulated by 20E (5), which affects DILP2 production and IPCs in turn regulate production of Ecd in the RG [602]. Ecd is converted to 20E in the fat body. Reduced 20E production slows development and allows regeneration of the damaged disc. Redrawn, slightly altered and updated from [524].

Fig. 19. Insulin signaling, metabolism and reproduction. Scheme showing insulin signaling components and some of the feedbacks in control of energy allocation and reproductive maturation in *Drosophila*. The insulin-producing cells (IPCs) release DILPs (dark blue arrows) into the circulation and target tissues such as the corpora allata (CA), muscle, fat body and ovaries. The CA produces juvenile hormone (JH),

which acts on fat body to trigger vitellogenin (Vg) production (for export to ovaries) and on the ovaries to regulate oocyte maturation. JH and 20-hydroxy ecdysone (20E, produced in ovaries) are mutually inhibitory in action on ovaries. DILPs acting on fat body also regulate nutrient/energy (e) storage. Partly antagonistic to DILPs, AKH from corpora cardiaca (CC) mobilizes nutrient/energy (e). Feedbacks onto IPCs are provided from CC cells by means of AKH (red arrow) and from fat body by means of DILP6 and probably other factors. Production and release of DILPs is under further control of short neuropeptide F (sNPF) from brain neurons (DLPs) and other modulators (not shown here). The DLPs also produce corazonin that acts of the fat body to regulate stress-related energy reallocation. Nutrient sensing occurs in IPCs (1) by glucose transporters coupled to carbohydrate metabolism and ATP-sensitive K^+-Channels, (2) possibly by DLP neurons via fructose receptors (Gr43b), and (3) by nutrient sensors in the fat body. The modulators (4) from brain neurons are shown in Figures 13 and 15. For references to the original data see text.

Fig. 20. Distribution and actions of diuretic hormones in adult *Drosophila*. A schematic depiction of the location of peptidergic neurons and gut endocrine cells expressing the classical insect diuretic hormones: CAPA, diuretic hormone 31 (DH31), diuretic hormone 44 (DH44) and leucokinin (LK). Following release from these neurosecretory cells, these peptides act on their receptors, which are localized in one of two cell-types in the Malpighian (rental) tubules, the principal cells or stellate cells (visualized here using *LKR > mcd8GFP*). Different peptides act via different second messengers to alter the activity of ion pumps or channels. The orange rectangles represent aquaporin channels, the blue represent chloride channels and the red represents a *Kir* potassium channel. Abbreviations: CC, corpora cardiaca; CA, corpora allata; VNC, ventral nerve cord; SJ, septate junction; V, V-type ATPase. The Malpighian tubule model is adapted from [737]. Image of localization of *LKR* in stellate cells is from [331].

Fig. 21. Internal state initiates foraging and decisions are made at several other checkpoints that may lead to food ingestion. In a simplified scheme thirst and hunger

are regulated by two sets of neurons, ISNs (interoceptive SEZ neurons) and ITP-producing neurons (ITP; ipc-1). The two sets of neurons are in principle antagonistic on drinking and food ingestion (thirst and hunger). ITP increases thirst, but depresses hunger [333], and ISNs induce the opposite [310]. The ISNs are activated by low osmolality, sensed by the Nanchung (Nan) cat ion channels, or AKH released due to low carbohydrate levels and acting on the AKH receptor (AKHR) [310]. The inputs to the ITP neurons are not known, but they respond to desiccation of the fly. The ITP neurons also inhibit excretion [333]. The box below shows the behavior sequence triggered by internal and external signals. Several of these behaviors are modulated by neuropeptides, including DILPs, as described in the text. See also sections on olfaction, taste, mushroom bodies and locomotion.

Fig. 22. Neuropeptides that modulate aspects of feeding. A number of neuromodulators and peptide hormones regulate feeding in different ways. The neuromodulators in black and red units are produced by identified neurons: dopamine (DA) in DL1 neurons (for foraging) and in ventral unpaired neurons (for meal initiation), neuropeptide F (NPF) in non-clock NPF neurons, short neuropeptide F (sNPF) in olfactory sensory neurons (OSNs), DTK (tachykinin; TK) in local interneurons (LNs) of the antennal lobe, DSK in insulin-producing cells (IPCs) and adipokinetic hormone (AKH) in cells of corpora cardiaca. Note that in starved flies (low insulin signaling) the DTK signaling is inhibiting an olfactory channel mediating aversive odors and thereby increases foraging [301]. The other peptides Hugin-pyrokinin (hugin), allatostatin A (AstA), leucokinin (LK) and myoinhibitory peptide (MIP, also know as allatostatin B) are produced by several neurons types and it is not known which sets of neurons mediate the feeding responses. DILPs from IPCs contribute to inhibition of foraging, meal initiation and food ingestion by action on different neuron groups (red). Note that DILPs inhibit the sNPF and DTK signaling in OSNs by regulating receptor expression. The dashed red line indicates that mechanisms for DILP action on food ingestion are not clear. Finally, a leptin-like peptide (unpaired 1; Upd1) is produced by l-LNv clock neurons, also known to produce pigment-dispersing factor (PDF). Upd1 inhibits foraging and meal initiation

via the Upd1 receptor domeless expressed on certain NPF neurons [278]. Not shown in this figure is a set of SIFamide neurons, which is known to play a high level role in coordinating orexigenic and anorexigenic signals and thereby regulate the responsiveness of food odor sensing olfactory sensory neurons and orchestrate appetitive behavior [162]. This figure was updated from [23], which in turn was compiled from data in [680]. See text for further details and references.

Fig. 23. A model of the neuropeptides and neurotransmitters involved in starvation-dependent food seeking and food consumption. Starvation promotes food seeking via two components: increased perception of food cues and increased food exploration (hyperactivity, foraging). Octopaminergic brain neurons expressing the AKH and insulin receptors (AKHR$^+$ and dInR$^+$) are important for starvation-induced hyperactivity. Food perception is modulated by several neuropeptides (sNPF, NPF, DTK and DILPs) and dopamine, which alter the activity of gustatory neurons (Gr5a and Gr66a) and olfactory neurons (Or42b and Or85a). Food consumption is modulated by several types of brain neurons releasing peptides including NPF, sNPF, LK, Ast-A and hugin. The regulation of starvation-induced hyperactivity is independent from that of food consumption, and vice versa. This figure is redrawn from [311].

Fig. 24. Hugin expressing neurons antagonistically regulate feeding and locomotion in larvae. **A.** There are four morphologically distinct classes of hugin neurons: hugin-PC (protocerebrum) shown in green, hugin-VNC (ventral nerve cord) in blue, hugin-RG (ring gland) in red and hugin-PH (pharynx) in orange (asterisks mark exit sites of axon innervating muscles). **B.** Electron microscopic serial section (ssTEM) reconstruction of hugin neurons and their synaptic sites in *Drosophila* first instar larvae. **C.** Side view of the larval CNS. Hugin neurons reside in the subesophageal zone (SEZ) and send axon projections to the ring gland (RG), pars intercerebralis and the VNC. **D.** Hugin neurons antagonistically modulate feeding (decrease) and locomotion (increase). This figure is slightly redrawn and assembled from Fig. 1 and 2 in [64], see license https://creativecommons.org/licenses/by/4.0/.

Fig. 25. A scheme depicting the organization of the digestive tract in adult *Drosophila*. The *Drosophila* gut spans across the entire thorax and abdomen and is comprised of the foregut, midgut, Malpighian (renal) tubules and hindgut. The midgut is comprised of five different cell types: muscle cells, stem cells, enteroblasts, enterocytes and enteroendocrine cells. Ten neuropeptides/peptide hormones are expressed in the adult *Drosophila* enteroendocrine cells: allatostatin A, allatostatin B, allatostatin C, bursicon alpha, CCHamide-1, CCHamide-2, diuretic hormone 31, neuropeptide F, orcokinin-B and tachykinin. This figure was redrawn from [696].

Fig. 26. Neuropeptides, peptide hormones and their receptors in the intestine. In the midgut enteroendocrine cells (EEs) produce neuropeptides/peptide hormones in a region-specific manner. Four midgut regions are shown here. Peptides produced are shown in blue text, whereas peptide receptors (GPCRs) are shown in red text. DH31 is diuretic hormone 31. There are also EEs producing tachykinin in the anterior hindgut. Two AstA (CG2872 and CG10001) and two AstC receptors (CG7285 and CG13702) are known. DTKR is a tachykinin receptor (CG7887), GPA2/GPB5-R (CG7665; Lgr1) is a receptor for the glycoproteins GPA2/GPB5, PDF-R (CG13758) is a receptor of pigment-dispersing hormone and NPLP1-R is a receptor for peptides derived from the neuropeptide-like precursor 1. Many of the EEs express more than one peptide (see also Fig. 23). For references to the original data see text.

Fig. 27. Neuropeptides and peptide hormones associated with the intestine and peripheral neurohemal areas. The retrocerebral complex in the anterior intestine consists of the corpora cardiaca (CC), corpora allata (CA) and the hypercerebral ganglion (HG). Axons from neurons and neurosecretory cells of the median and lateral neurosecretory cells of the brain, as well as of the frontal ganglion (these structures are not shown) run into this complex (at asterisk) and terminate on CC, CA, the aorta, crop and anterior intestine (foregut, proventriculus and midgut). The CC cells produce AKH and limostatin (Lst), whereas neurons in the HG produce sNPF and those of CA release juvenile hormone. Brain neurosecretory cells produce

peptide hormones that can be released by the retrocerebral complex and neurohemal areas associated with its nerves: allatostatin A (AstA), corazonin, diuretic hormone 44 (DH44), *Drosophila* insulin-like peptides (DILP2, 3 and 5), drosulfakinin (DSK), dromyosuppressin (DMS), ion transport peptide (ITP) and pyrokinin (PK). In addition the neuroendocrine cells producing ITP also produce tachykinin and sNPF, but is not known whether these peptides are released into the circulation or act locally in the retrocerebral complex. Neurosecretory cells in the abdominal ganglia produce peptides released by axon terminations on the hindgut: AstA, crustacean cardioactive peptide (CCAP), ITP, pigment-dispersing factor (PDF) and proctolin. Finally, thoracic neuroendocrine cells send axon terminations to neurohemal areas in the dorsal neural sheath of the thoracic ganglia that release extended FMRFamides (dFMRFa) and abdominal cells have peripheral axon terminations/release sites for the peptides Capa/PK, GPA2/GPB5 (glycoproteins) and leucokinin. References are given in the text.

Fig. 28. Leucokinin (LK) signaling from a small set of neurons coordinates several functions related to feeding and metabolism. There are 22 neurons (LKn) in the CNS producing LK, designated LHLK, SELK and ABLK. Dashed arrows indicate proposed pathways. The ABLKs are neurosecretory and presumed to release LK into the circulation (via 3, 4). By these hormonal routes LK may act on brain IPCs (via 3) to affect insulin production/release and hence affect metabolism, stress responses and food intake or (via 4) act on peripheral targets such as gut, renal tubules and heart and thereby regulating water and ion balance and related stress responses [331]. The SELKs may affect feeding directly or indirectly via action on IPCs (2), ITP-producing neurons (ITPn) or unidentified neurons. The LHLKs are glucose sensing and have been shown to activate IPCs (1) and thereby regulate metabolism associated activity and sleep, probably via other interneurons downstream IPCs [350]. The signaling between IPCs and other brain neurons could be by DILP2 [see [629]] or possibly colocalized classical neurotransmitters (CT). Among the likely targets of IPCs are the ITP-producing ITPn neurons (see section 8. 2. 3). Thus, LHLKs may regulate IPCs, which in turn activate ITPn and thereby affect central and

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peripheral signaling with DILPs, ITP, sNPF and TK. A recent analysis of *Lk* and *Lkr* mutants suggest that the three types of LK neurons act together to modulate a range of actions that together establish post-feeding homeostasis. This figure is updated from [331] and incorporates findings from [350].

Supplementary materials Files

Supplementary materials File: Table 1. Flygut-seq EE peptide receptor expression: Expression of receptors for enteroendocrine cell-produced peptides in various regions and cell-types of the adult *Drosophila* midgut. The midgut is divided into five distinct domains (R1-R5) according to Buchon et al 2013. It is comprised of five different cells: visceral muscles (VM), intestinal stem cells (ISC), enteroblasts (EB), enterocytes (EC) and enteroendocrine (EE) cells. The expression of each receptor is color-coded: the tissue with lowest expression is in yellow, medium expression in orange and highest expression in red. The expression of allatostatin A receptor 1 could not be detected. Data based on Flygut-seq [738].

Supplementary materials File: Appendix 1. Brief overview of *Drosophila* neuropeptides and peptide hormones (Appendix to section

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Note that references 739-1018 are associated with the Supplementary Materials File Appendix 1

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Figure 1

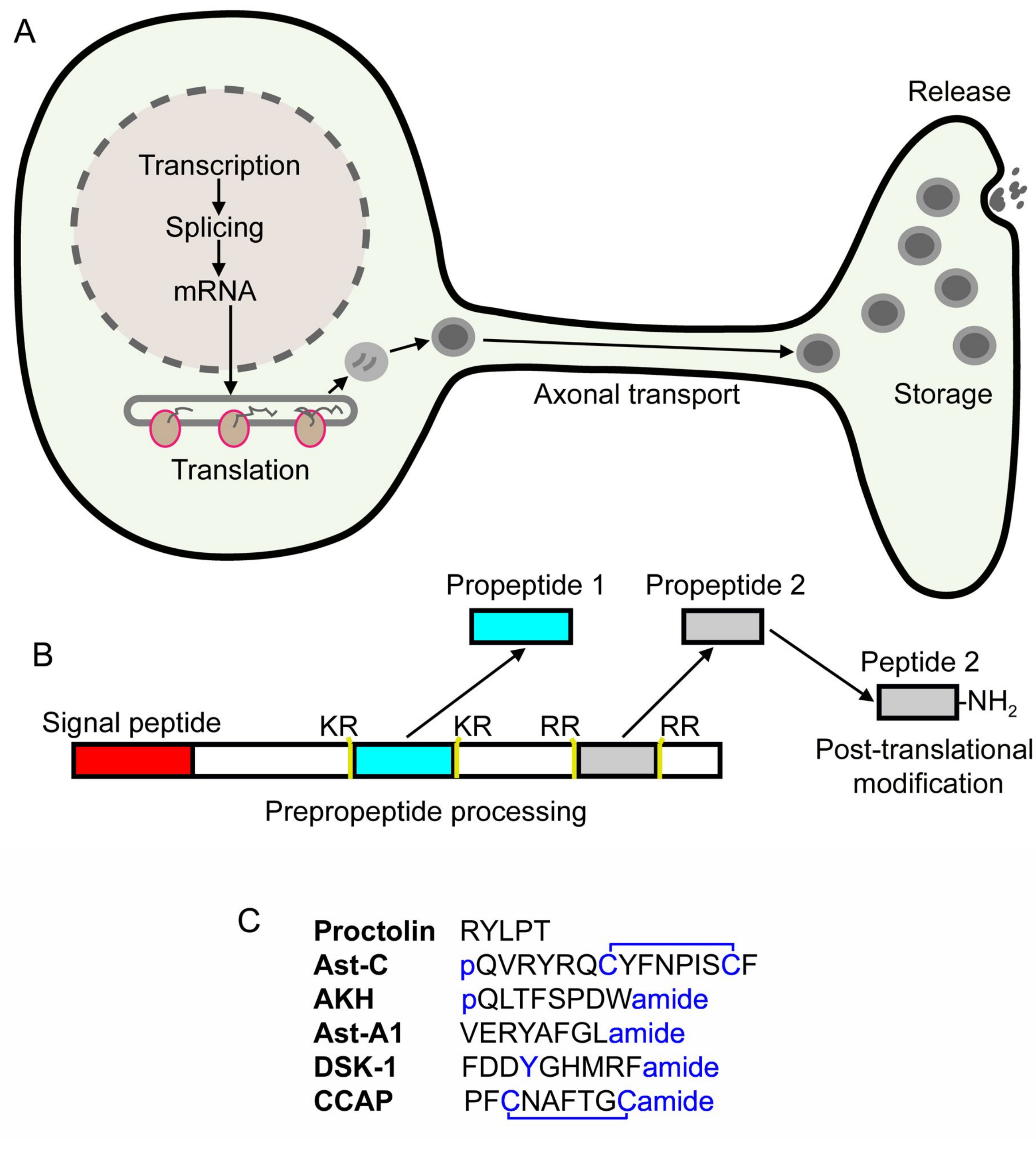
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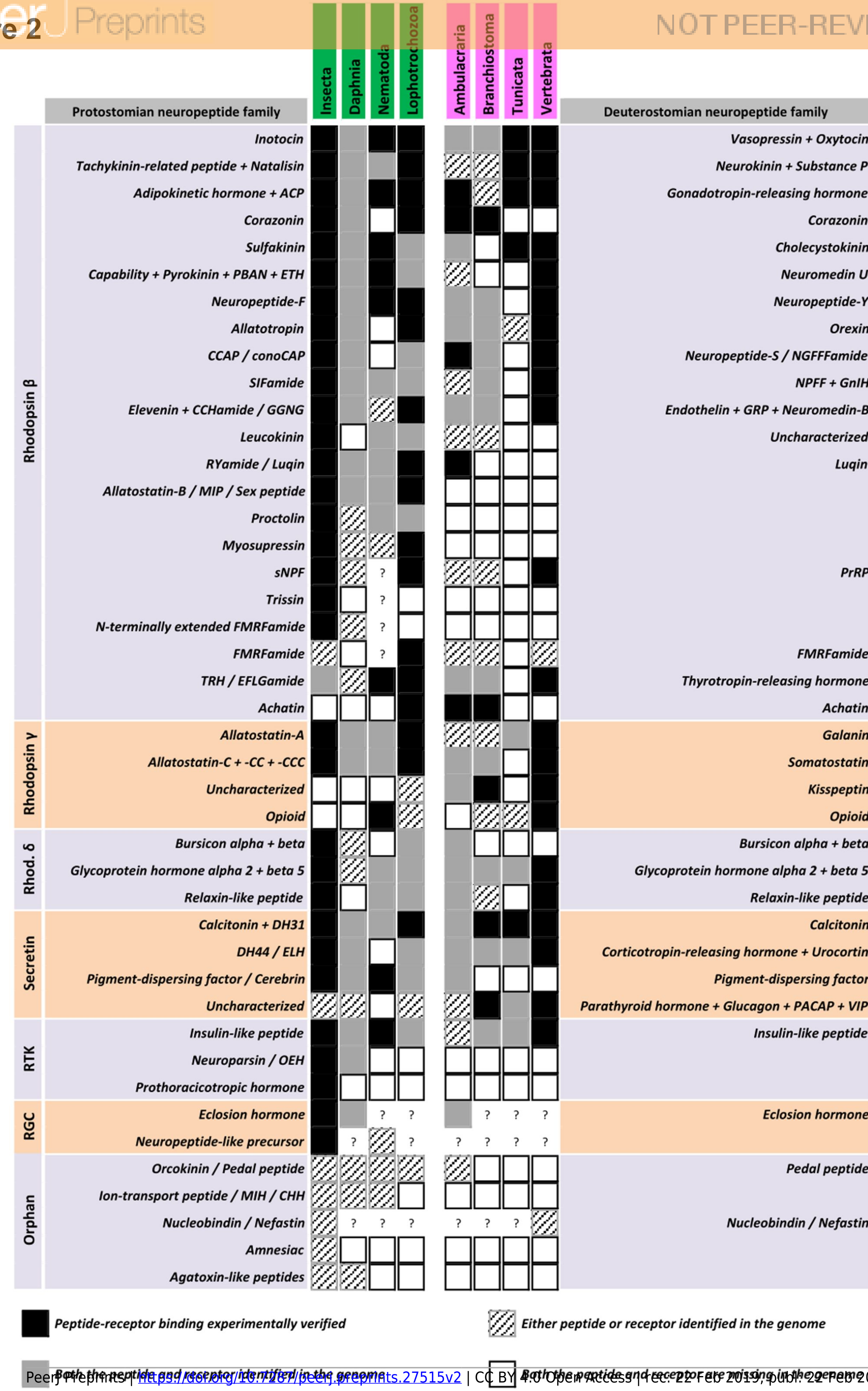
Figure 2

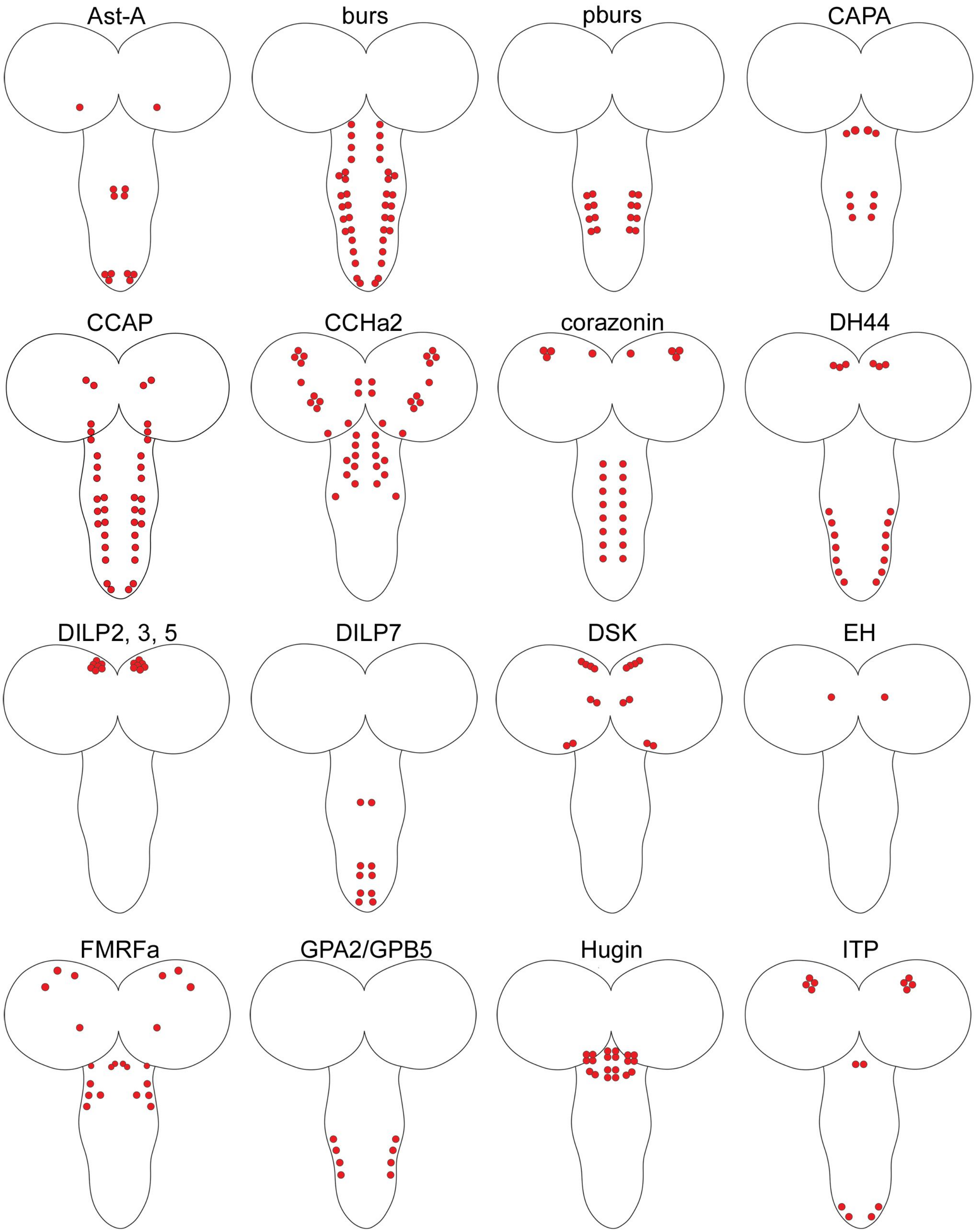

Insecta
Daphnia
Nematoda
Lophotrochozoa
Ambulacraria
Branchiostoma
Tunicata
Vertebrata
Protostomian neuropeptide family
Deuterostomian neuropeptide family
Rhodopsin β
Inotocin
Vasopressin + Oxytocin
Tachykinin-related peptide + Natalisin
Neurokinin + Substance P
Adipokinetic hormone + ACP
Gonadotropin-releasing hormone
Corazonin
Corazonin
Sulfakinin
Cholecystokinin
Capability + Pyrokinin + PBAN + ETH
Neuromedin U
Neuropeptide-F
Neuropeptide-Y
Allatotropin
Orexin
CCAP / conoCAP
Neuropeptide-S / NGFFFamide
SIFamide
NPFF + GnIH
Elevenin + CCHamide / GGNG
Endothelin + GRP + Neuromedin-B
Leucokinin
Uncharacterized
RYamide / Luqin
Luqin
Allatostatin-B / MIP / Sex peptide
Proctolin
Myosupressin
sNPF
PrRP
Trissin
N-terminally extended FMRFamide
FMRFamide
FMRFamide
TRH / EFLGamide
Thyrotropin-releasing hormone
Achatin
Achatin
Rhodopsin γ
Allatostatin-A
Galanin
Allatostatin-C + -CC + -CCC
Somatostatin
Uncharacterized
Kisspeptin
Opioid
Opioid
Rhod. δ
Bursicon alpha + beta
Bursicon alpha + beta
Glycoprotein hormone alpha 2 + beta 5
Glycoprotein hormone alpha 2 + beta 5
Relaxin-like peptide
Relaxin-like peptide
Secretin
Calcitonin + DH31
Calcitonin
DH44 / ELH
Corticotropin-releasing hormone + Urocortin
Pigment-dispersing factor / Cerebrin
Pigment-dispersing factor
Uncharacterized
Parathyroid hormone + Glucagon + PACAP + VIP
RTK
Insulin-like peptide
Insulin-like peptide
Neuroparsin / OEH
Prothoracicotropic hormone
RGC
Eclosion hormone
Eclosion hormone
Neuropeptide-like precursor
Orphan
Orcokinin / Pedal peptide
Pedal peptide
Ion-transport peptide / MIH / CHH
Nucleobindin / Nefastin
Nucleobindin / Nefastin
Amnesiac
Agatoxin-like peptides
Peptide-receptor binding experimentally verified
Either peptide or receptor identified in the genome
Both the peptide and receptor identified in the genome
Both the peptide and receptor are missing in the genome

Peptide gene (peptide acrnoym)	Annotation	Head	Eye	Brain	VNC	Crop	Midgut	Hindgut	Tubule	Fat body	Salivary gland	Heart	Ovary	Virgin Spermatheca	Mated Spermatheca	Testis	Accessory glands	Carcass	CNS	Midgut	Hindgut	Tubule	Fat body	Salivary gland	Trachea
Adipokinetic hormone (AKH)	CG1171	528		913	163														93						
Allatostatin A (AstA)	CG13633	173	20	741	1455	14	195	222		28				24	22			47	255	200	157			13	
Allatostatin B (AstB; MIP)	CG6456	261	18	743	196		40									12			222	373					
Allatostatin C (AstC)	CG14919	1073		1930	924		1442	83		15									456	470					
Allatostatin CC (AstCC)	CG14920																		34						
Bursicon (Burs alpha)	CG13419						114		28										114	41		32			
Partner of bursicon (Burs beta)	CG15284																		58						
Capability (CAPA; periviscerokinin)	CG15520	252	38	908	1843														422						
CCHamide 1	CG14358			82	239		74	30						23						46					
CCHamide 2	CG14375	413	86	122	260		344	26		1923		519		1609	1787			410	121	443	37		1517	26	
Corazonin	CG3302	266		1103															551						
CNMamide	CG13936																								
Crustacean cardioactive peptide (CCAP)	CG4910			34	103														87						
Diuretic hormone 31 (DH31; CT/DH)	CG13094	242	19	930	1383		114												372	232	21				
Diuretic hormone 44 (DH44; CRF/DH)	CG8348	174		655	124											77			231		14	65			
Ecdysis triggering hormone (ETH)	CG18105																		27						2003
Eclosion hormone	CG5400																		168						
FMRFamide	CG2346	58		318	3250														358						
GPA2	CG17878																								
GPB5	CG40041	39		145	469			17							17	11			122			13			
Hugin	CG6371	289		1104															336						
Ion transport peptide (ITP)	CG13586	368	332	1135	195	39	41	83	93	51	45	1081		24	26	10	38	143	233	46	83	129	21	18	275
Insulin-like peptide 1	CG13173																								
Insulin-like peptide 2	CG8167	507		1608															638						
Insulin-like peptide 3	CG14167	77		322			107												70	141					
Insulin-like peptide 4	CG6736																								
Insulin-like peptide 5	CG33273	185		683			12												631			286			
Insulin-like peptide 6	CG14049	150	60	98	68					73		66	24	54	44	40		70	62		13	24	1916	184	
Insulin-like peptide 7	CG13317			161									16						36						
Insulin-like peptide 8	CG14059												181												
Kinin (leucokinin)	CG13480			166	1538														393						
Limostatin	CG8317	923	469	24	24	34	16	246		2897		1893		3603	2814	28		1824		41	183	76	6073	53	265
Myosuppressin	CG6440	1311	88	2823	187			181		158		2361			62		2509	92	836						
Natalisin	CG34388	66		175															57						
Neuropeptide F (NPF)	CG10342	261		806			339												289						
Neuropeptide-like precursor 1 (NPLP1)	CG3441	289	20	1020	3692					17				18	17			48	1043						
Neuropeptide-like precursor 2 (NPLP2)	CG11051	5980	7227	1651	1519	7248	127	3238	554	7049	246	9447	25	6177	6065	29	116	8320	30	99	1312	134	710	853	1610
Neuropeptide-like precursor 3 (NPLP3)	CG13061	4628	8949	33	39					25		130						3477				18			
Neuropeptide-like precursor 4 (NPLP4)	CG15361	69	2539	19		50		118		51		140		33	42			85	637	164	406		35	2749	5890
Orcokinin	CG13565	450	46	1297	2405		36												463	14					
Pigment-dispersing factor (PDF)	CG6496	368		1365	540														121						
Proctolin	CG7105	49		225	944														229						90
Prothoracicotropic hormone (PTTH)	CG13687	23	38	20	29		19	33	50			23				45			60			24	23		
RYamide	CG40733																								
Sex peptide (SP)	CG17673															100	8631	95							
short neuropeptide F (sNPF)	CG13968	311	11	997	398												35		372	21					
SIFamide (SIFa)	CG4681															741									
Sulfakinin	CG18090	1531	1051	2365															290						
Tachykinin	CG14734	149	26	695	114		356	138											64	94	320				
Trissin	CG14871	81		297	204														57						

Figure 4

Peptide gene	Peptides	Receptor	Head	Eye	Brain	VNC	Crop	Midgut	Hindgut	Tubule	Fat body	Salivary gland	Heart	Ovary	Virgin Spermatheca	Mated Spermatheca	Testis	Accessory glands	Carcass	CNS	Midgut	Hindgut	Tubule	Fat body	Salivary gland	Trachea
Adipokinetic hormone (AKH)	AKH	CG11325	415	184	18	16	20		28		1943		593		1247	1575			503			21		861	32	
Allatostatin A (AstA)	AstA 1-4	CG2872	47	147	143	88														45						
		CG10001	14	40			117	157	263	54			45							29	103	196	48			
Allatostatin B (AstB; MIP) and Sex peptide	MIP 1-5 and SP	CG16752	183	35	478	1034			31	144	34		15	9	1683	1724			71	71	21	24				
Allatostatin C (AstC) and AstCC #	AstC and AstCC	CG7285			31																					
		CG13702																								
Burs alpha and Burs beta	Burs and pBurs	CG8930			13	18									22	30				7				104		
Capability (CAPA; periviscerokinin)	CAPA-PVK 1-2	CG14575			14	14		15	17	513	16					12			20	9		10	176			
	CAPA-PK	CG9918	16				12										9		39							17
CCHamide 1	CCHa 1	CG30106							37																	
CCHamide 2	CCHa 2	CG14593															16									
Corazonin	CRZ	CG10698	72	40	55	40	12				579	138	406						410	78					979	
CNMamide	CNMa	CG33696	13		53	21		11												8	14					
Crustacean cardioactive peptide (CCAP)	CCAP	CG6111																								
Diuretic hormone 31 (DH31; CT/DH)	DH31	CG32843	56	17	245	195	78	185	54	992			70						20	73	202	22	35			
		CG4395			14																					
Diuretic hormone 44 (DH44; CRF/DH)	DH44	CG8422	32		154	127														39						
		CG12370	47	18	137	101	210	110	122	411	14		43			11				77	34	141	372	72		
Ecdysis triggering hormone (ETH)	ETH 1-2	CG5911																							69	
Eclosion hormone	EH	CG10738			23															16						18
FMRFamide	FMRFa 1-8	CG2114			17	16																				
GPA2 and GPB5	GPA2 and GPB5	CG7665	77	72	74	31	27		986	75		517	10		17	19	39	20	19	9		751	68		61	
Hugin	Hug-PK	CG8795			24	34	95											40		18						
		CG8784			18															15						
Ion transport peptide (ITP)	ITP, ITPL 1-2	Unknown																								
Insulin-like peptides 1-7	DILP 1-7	CG18402	46	89	101	108	84	58	75	47	163	57	92	102	80	83	24	43	62	204	55	64	84	72	64	73
Insulin-like peptide 8	DILP 8	CG31096			38	19														36						
Kinin (leucokinin)	Drosokinin	CG10626	23		78	109			58	349					22	27				78	25	666	348			
Limostatin		CG9918	16				12										9		39							17
Myosuppressin	DMS	CG8985					364																			
		CG13803			17		72																			
Natalisin		CG6515			60	33														40						
Neuropeptide F (NPF)	NPF	CG1147	20		86	66	36	21	12	108							14			69	11		45			
Neuropeptide-like precursor 1 (NPLP1)	NPLP1-VQQ	CG8742	136	137	113	139	516	349	631	584	103	615	137	596	77	82	44	204	155	138	473	876	496	351	320	178
Neuropeptide-like precursor 2 (NPLP2)		Unknown																								
Neuropeptide-like precursor 3 (NPLP3)		Unknown																								
Neuropeptide-like precursor 4 (NPLP4)		Unknown																								
Orcokinin		Unknown																								
Pigment-dispersing factor (PDF)	PDF	CG13758	69	76	51		286		96				57									135				
Proctolin	Proctolin	CG6986																								
Prothoracicotropic hormone (PTTH)	PTTH	CG1389									61		46	292					64							
RYamide	dRYa 1-2	CG5811							223																	
short neuropeptide F (sNPF)	sNPF 1-4	CG7395	82	62	313	191			18		19		19		55	73		34		94		29	15		12	
SIFamide (SIFa)	SIFa	CG10823	14	15	91	55									13					28						
Sulfakinin	DSK 1-2	CG42301																								
		CG32540																								
Tachykinin		CG7887			70	37	38		28				14							39	18	20	44			
Trissin		CG34381	25		62	50	48													24						

Figure 5A


Ast-A
burs
pburs
CAPA
CCAP
CCHa2
corazonin
DH44
DILP2, 3, 5
DILP7
DSK
EH
FMRFa
GPA2/GPB5
Hugin
ITP

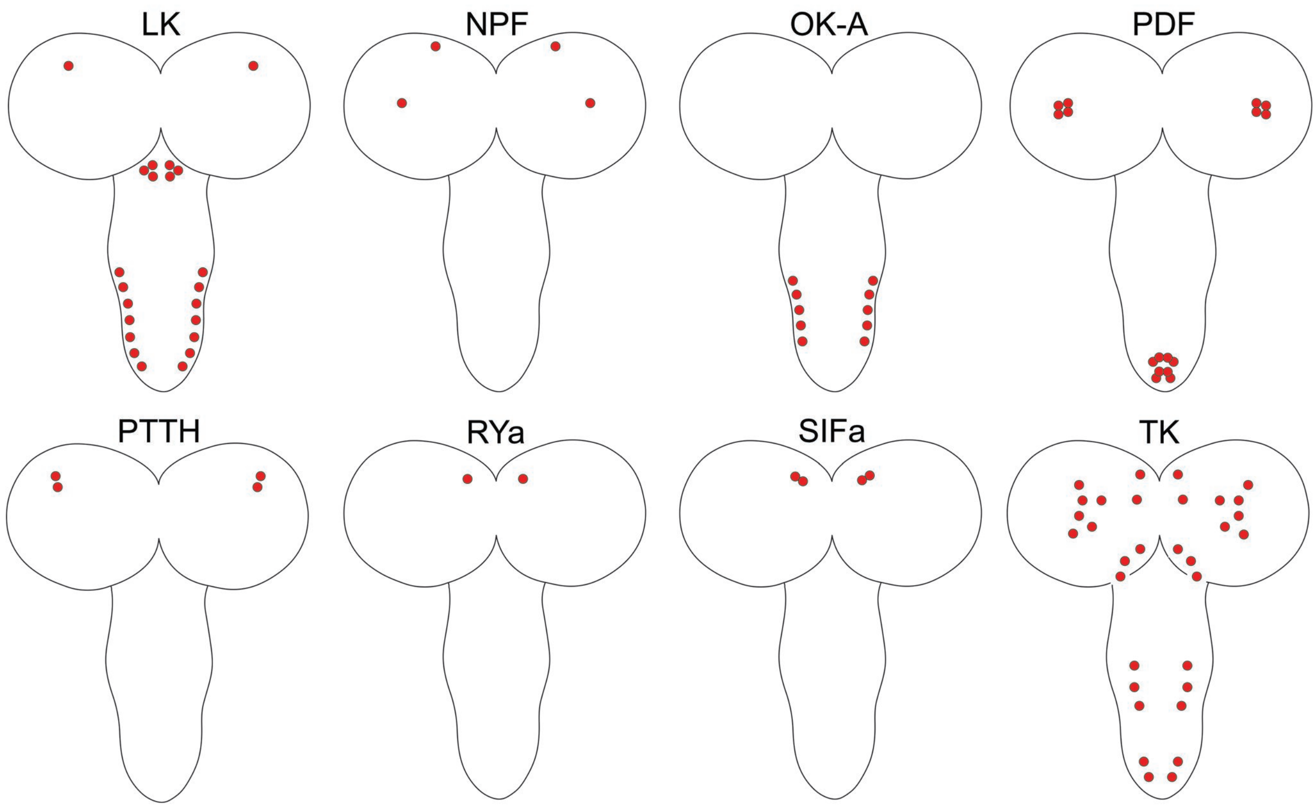

LK
NPF
OK-A
PDF
PTTH
RYa
SIFa
TK

Figure 6

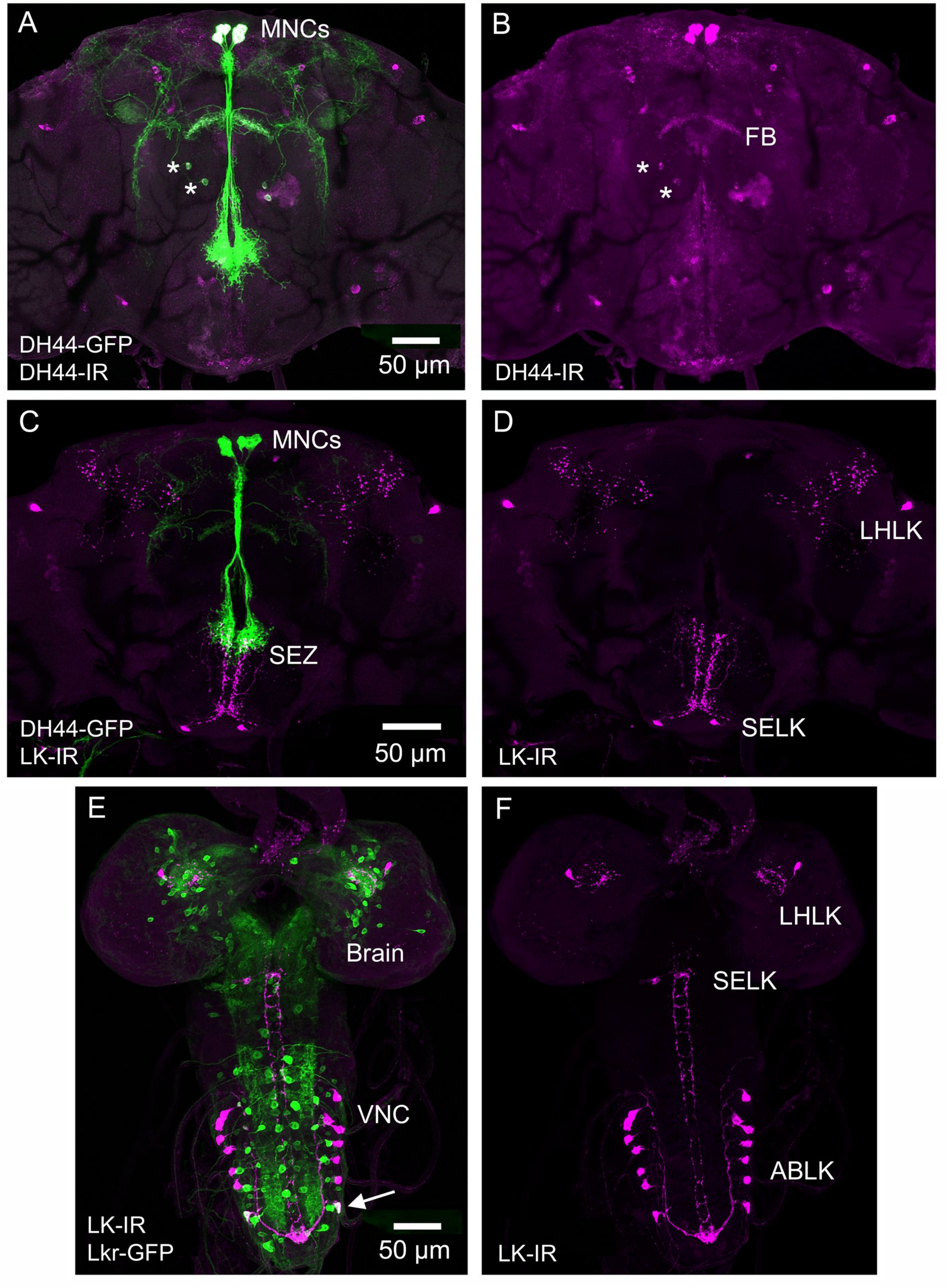
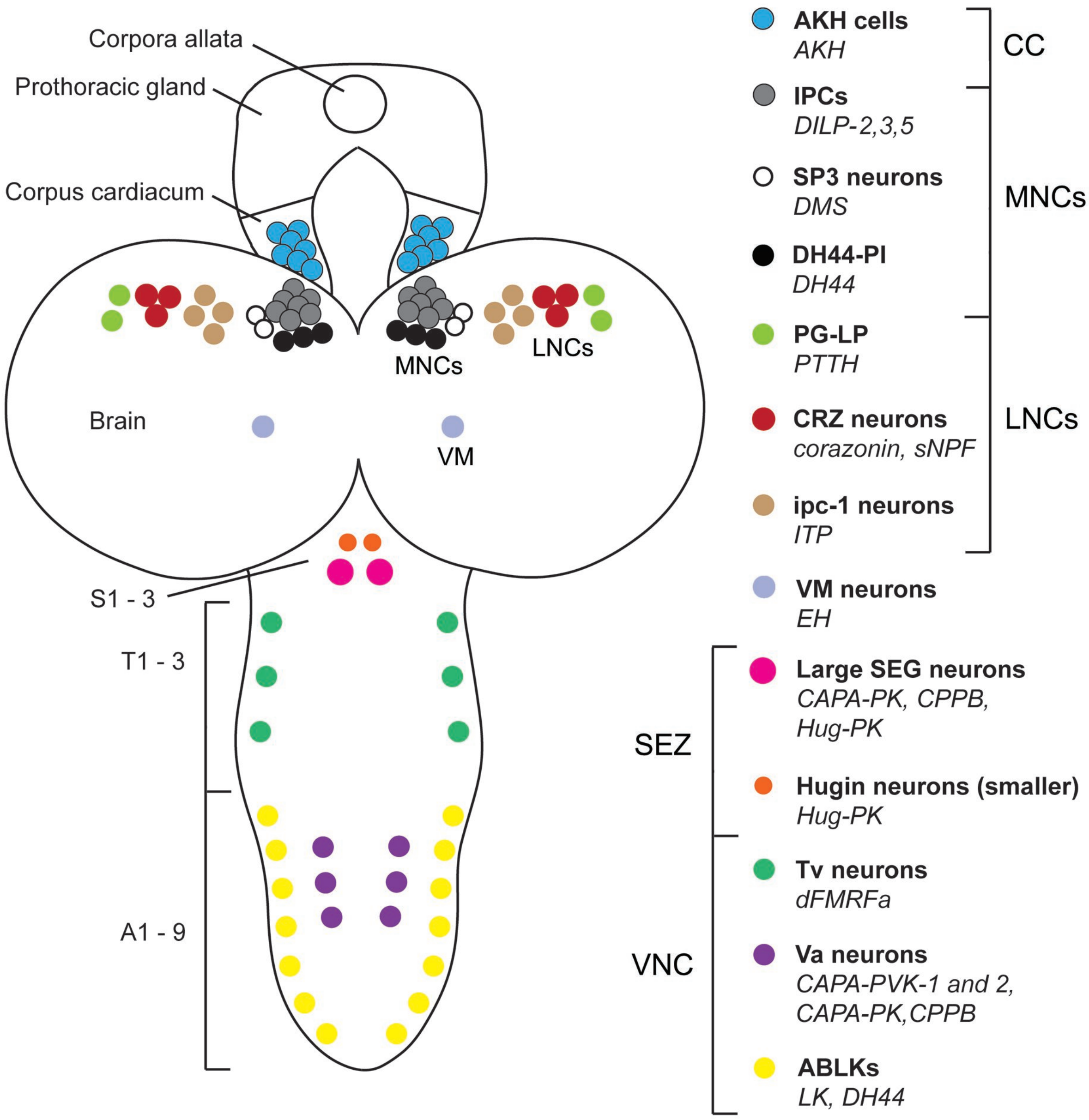

A
MNCs
*
*
DH44-GFP
DH44-IR
50 µm
B
FB
*
*
DH44-IR
C
MNCs
SEZ
DH44-GFP
LK-IR
50 µm
D
LHLK
SELK
LK-IR
E
Brain
VNC
LK-IR
Lkr-GFP
50 µm
F
LHLK
SELK
ABLK
LK-IR

Figure 7



Corpora allata
Prothoracic gland
Corpus cardiacum
MNCs
LNCs
Brain
VM
S1 - 3
T1 - 3
A1 - 9
AKH cells
AKH
CC
IPCs
DILP-2,3,5
SP3 neurons
DMS
MNCs
DH44-PI
DH44
PG-LP
PTTH
CRZ neurons
corazonin, sNPF
LNCs
ipc-1 neurons
ITP
VM neurons
EH
Large SEG neurons
CAPA-PK, CPPB, Hug-PK
SEZ
Hugin neurons (smaller)
Hug-PK
Tv neurons
dFMRFa
VNC
Va neurons
CAPA-PVK-1 and 2, CAPA-PK,CPPB
ABLKs
LK, DH44

Figure 8

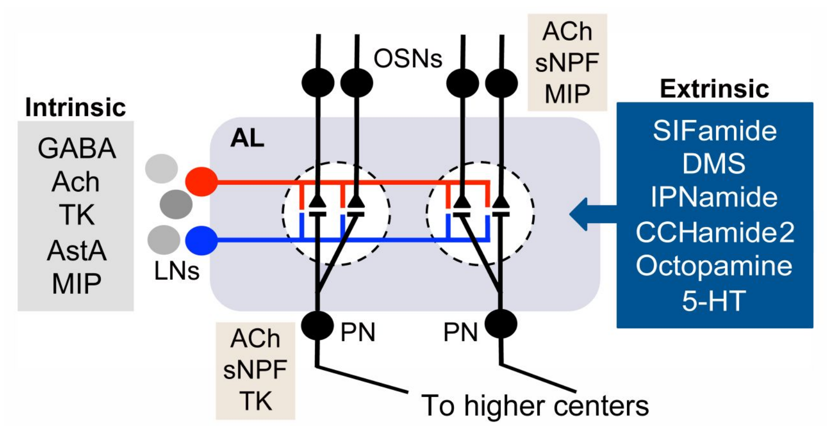
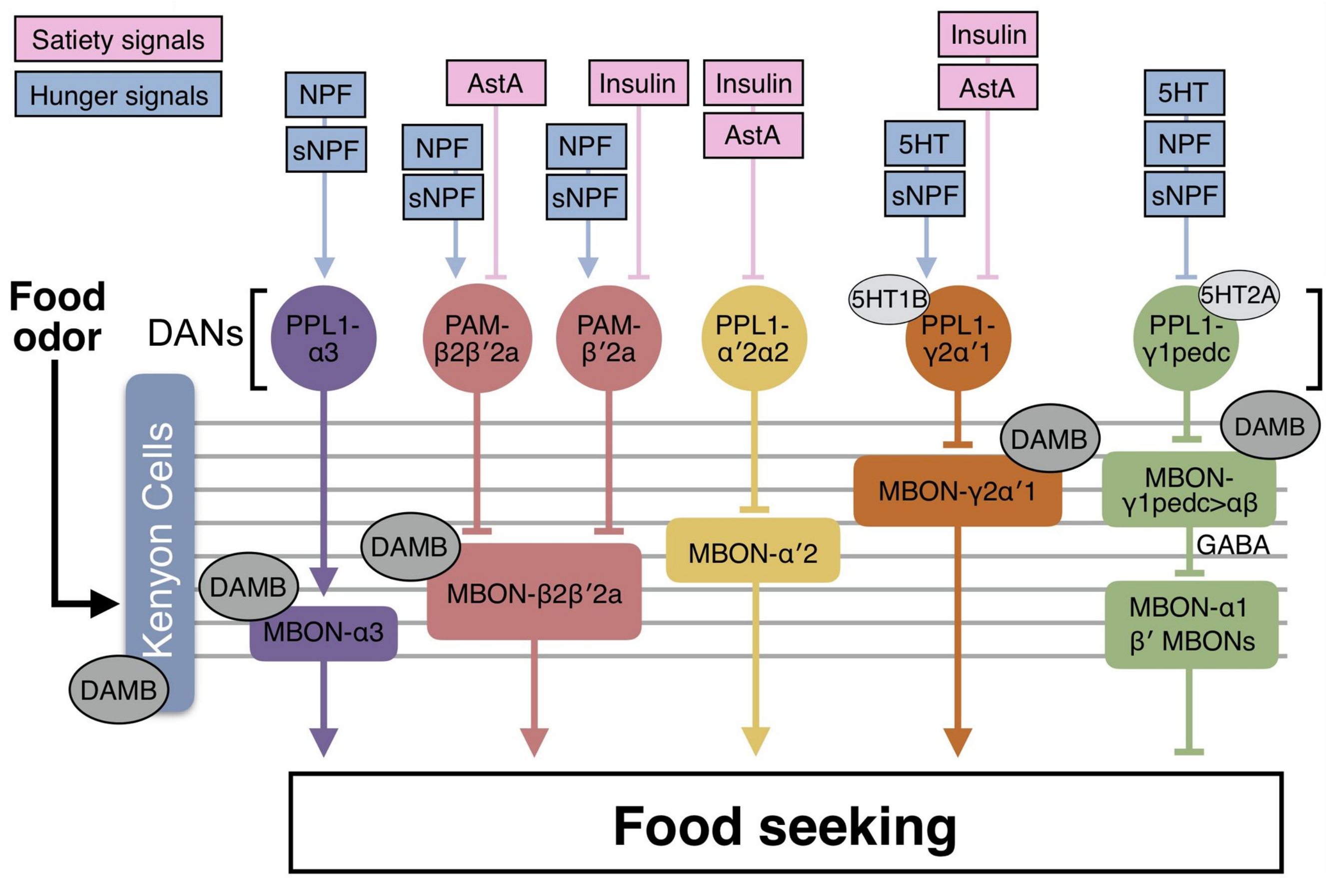

Intrinsic
GABA
Ach
TK
AstA
MIP
LNs
AL
OSNs
ACh
sNPF
MIP
Extrinsic
SIFamide
DMS
IPNamide
CCHamide2
Octopamine
5-HT
PN
PN
ACh
sNPF
TK
To higher centers

Figure 9



Satiety signals
Hunger signals
NPF
sNPF
AstA
NPF
sNPF
Insulin
NPF
sNPF
Insulin
AstA
Insulin
AstA
5HT
sNPF
5HT
NPF
sNPF
Food odor
DANs
PPL1-α3
PAM-β2β′2a
PAM-β′2a
PPL1-α′2α2
5HT1B
PPL1-γ2α′1
5HT2A
PPL1-γ1pedc
Kenyon Cells
DAMB
DAMB
DAMB
DAMB
DAMB
MBON-α3
MBON-β2β′2a
MBON-α′2
MBON-γ2α′1
MBON-γ1pedc>αβ
GABA
MBON-α1 β′ MBONs
Food seeking

Figure 10

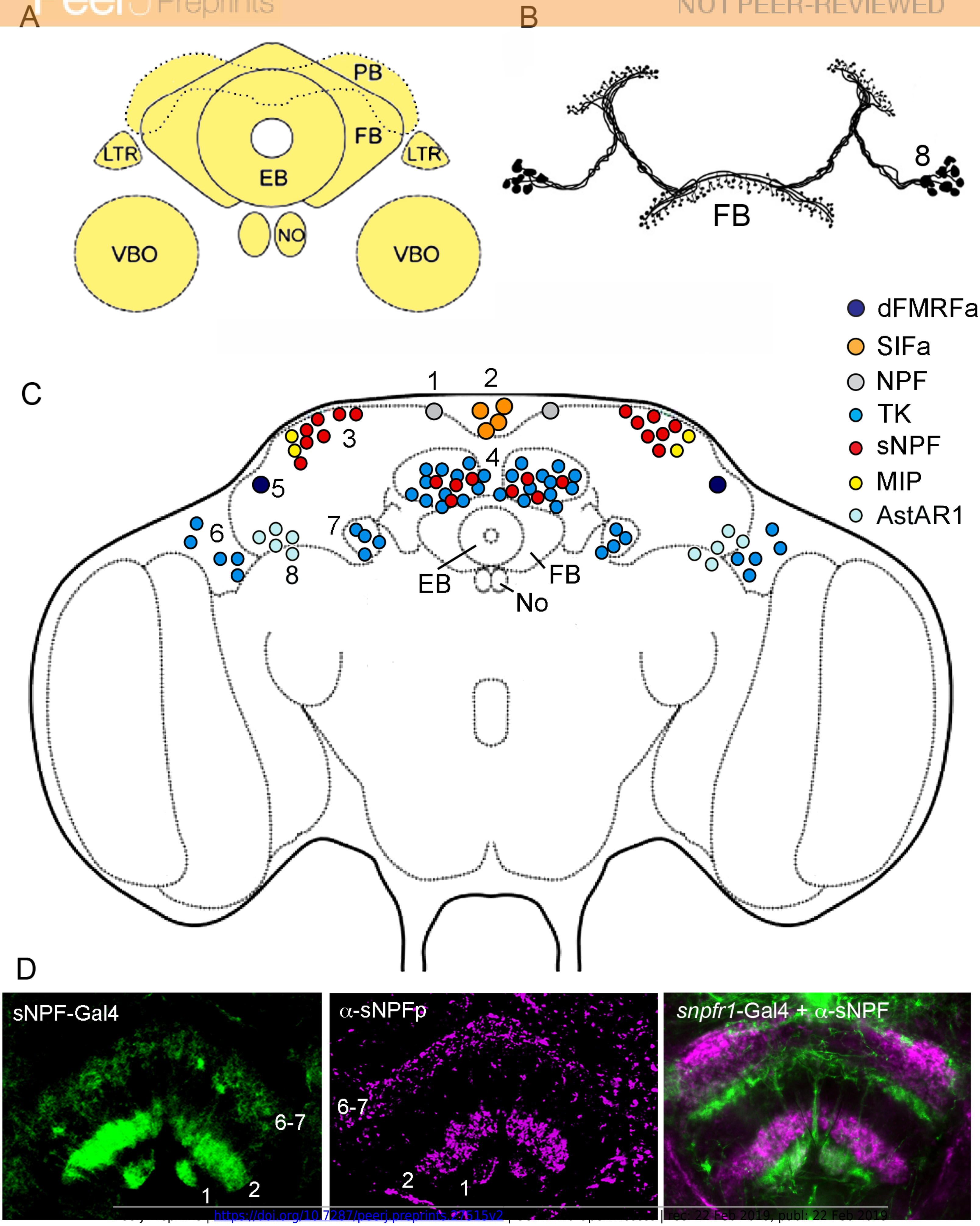

A
PB
FB
LTR
LTR
EB
NO
VBO
VBO
B
8
FB
C
dFMRFa
SIFa
NPF
TK
sNPF
MIP
AstAR1
1
2
3
4
5
6
7
8
EB
FB
No
D
sNPF-Gal4
6-7
1
2
α-sNPFp
6-7
2
1
snpfr1-Gal4 + α-sNPF

Figure 11

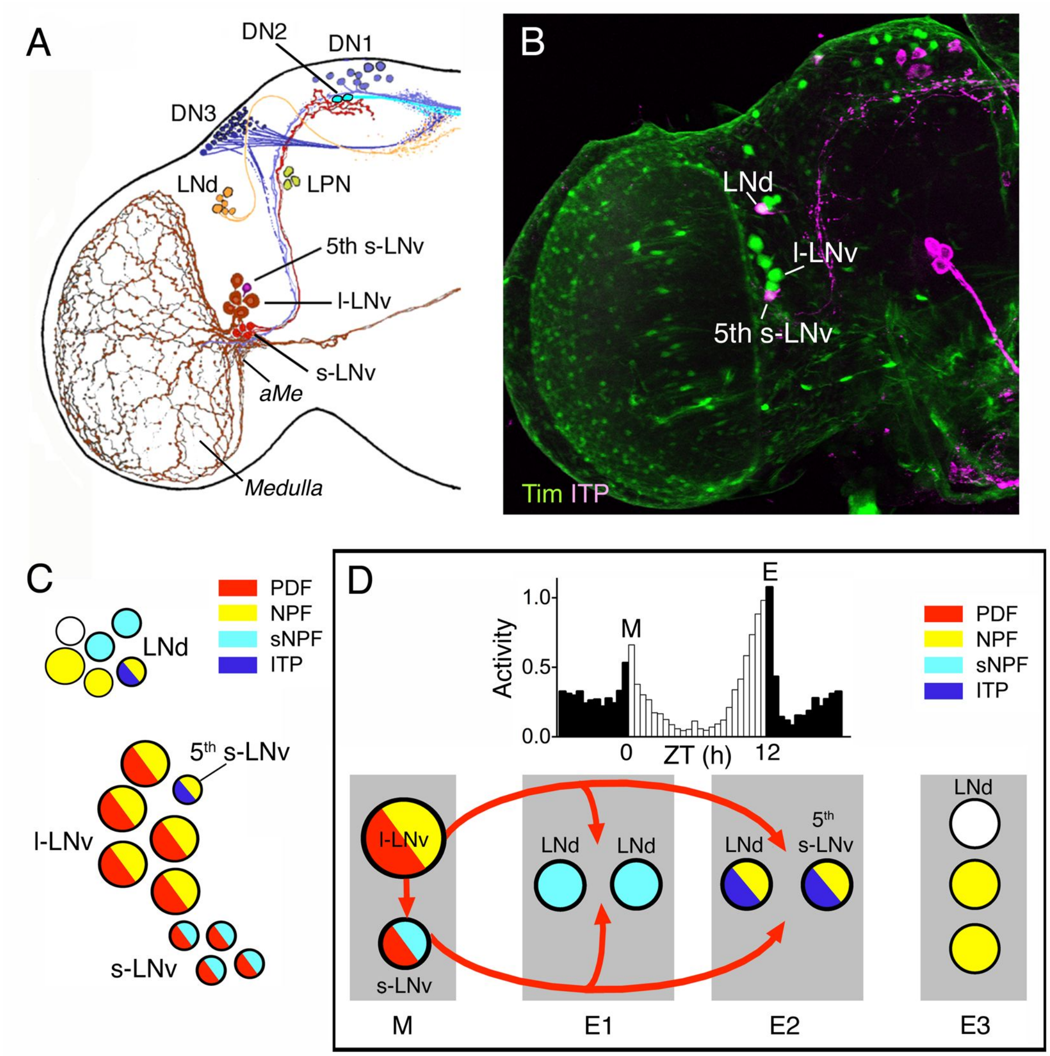

A
DN2
DN1
DN3
LNd
LPN
5th s-LNv
l-LNv
s-LNv
aMe
Medulla
B
LNd
l-LNv
5th s-LNv
Tim ITP
C
PDF
NPF
sNPF
ITP
LNd
5th s-LNv
l-LNv
s-LNv
D
E
1.0
M
Activity
0.5
0.0
0
ZT (h)
12
PDF
NPF
sNPF
ITP
l-LNv
s-LNv
LNd
LNd
LNd
5th s-LNv
LNd
M
E1
E2
E3

Figure 12

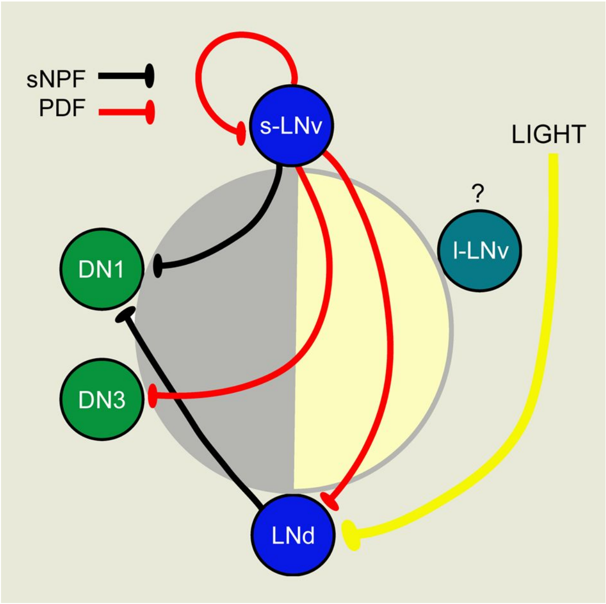
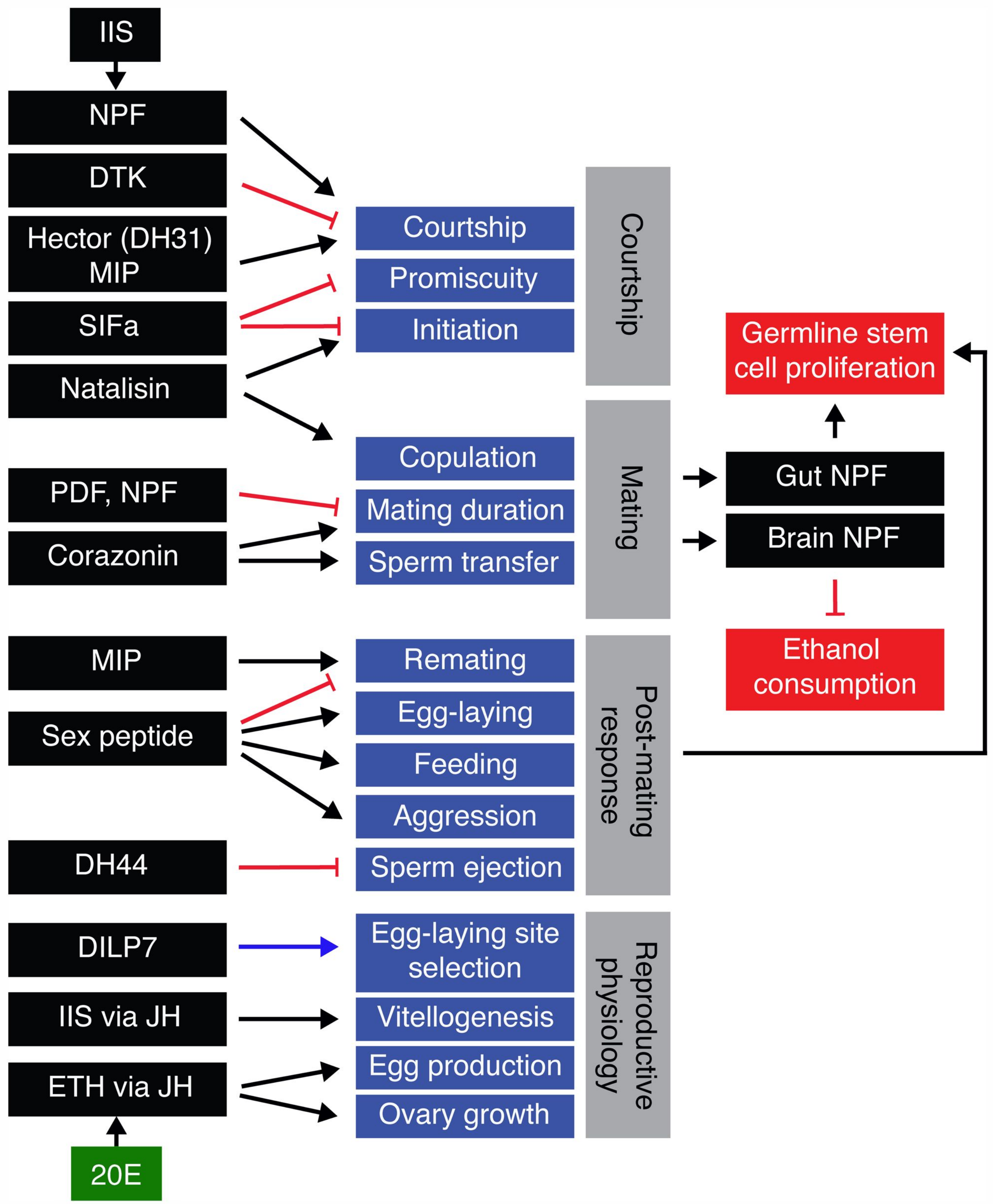


Figure 13


IIS
NPF
DTK
Hector (DH31)
MIP
SIFa
Natalisin
PDF, NPF
Corazonin
MIP
Sex peptide
DH44
DILP7
IIS via JH
ETH via JH
20E
Courtship
Promiscuity
Initiation
Copulation
Mating duration
Sperm transfer
Remating
Egg-laying
Feeding
Aggression
Sperm ejection
Egg-laying site selection
Vitellogenesis
Egg production
Ovary growth
Courtship
Mating
Post-mating response
Reproductive physiology
Germline stem cell proliferation
Gut NPF
Brain NPF
Ethanol consumption

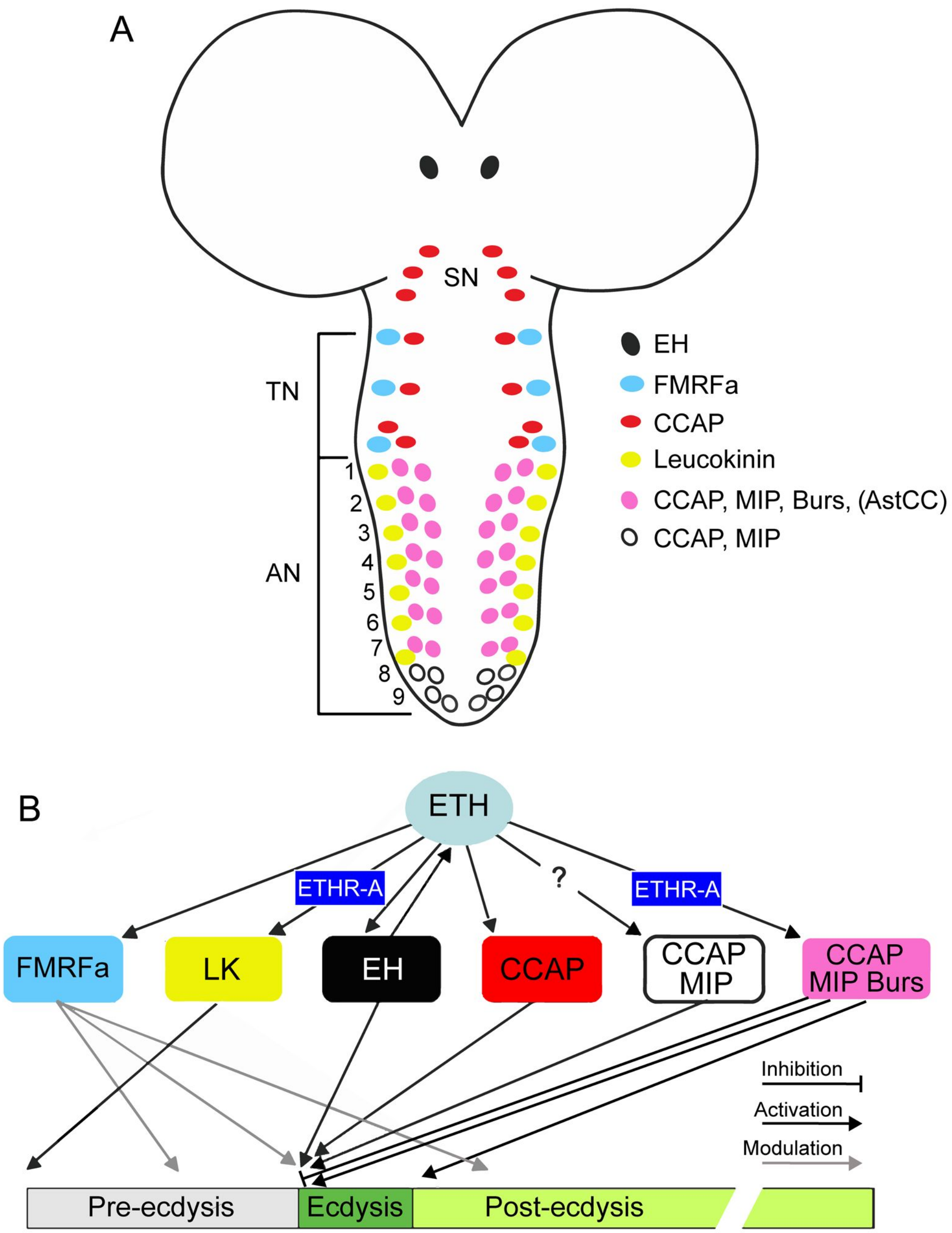
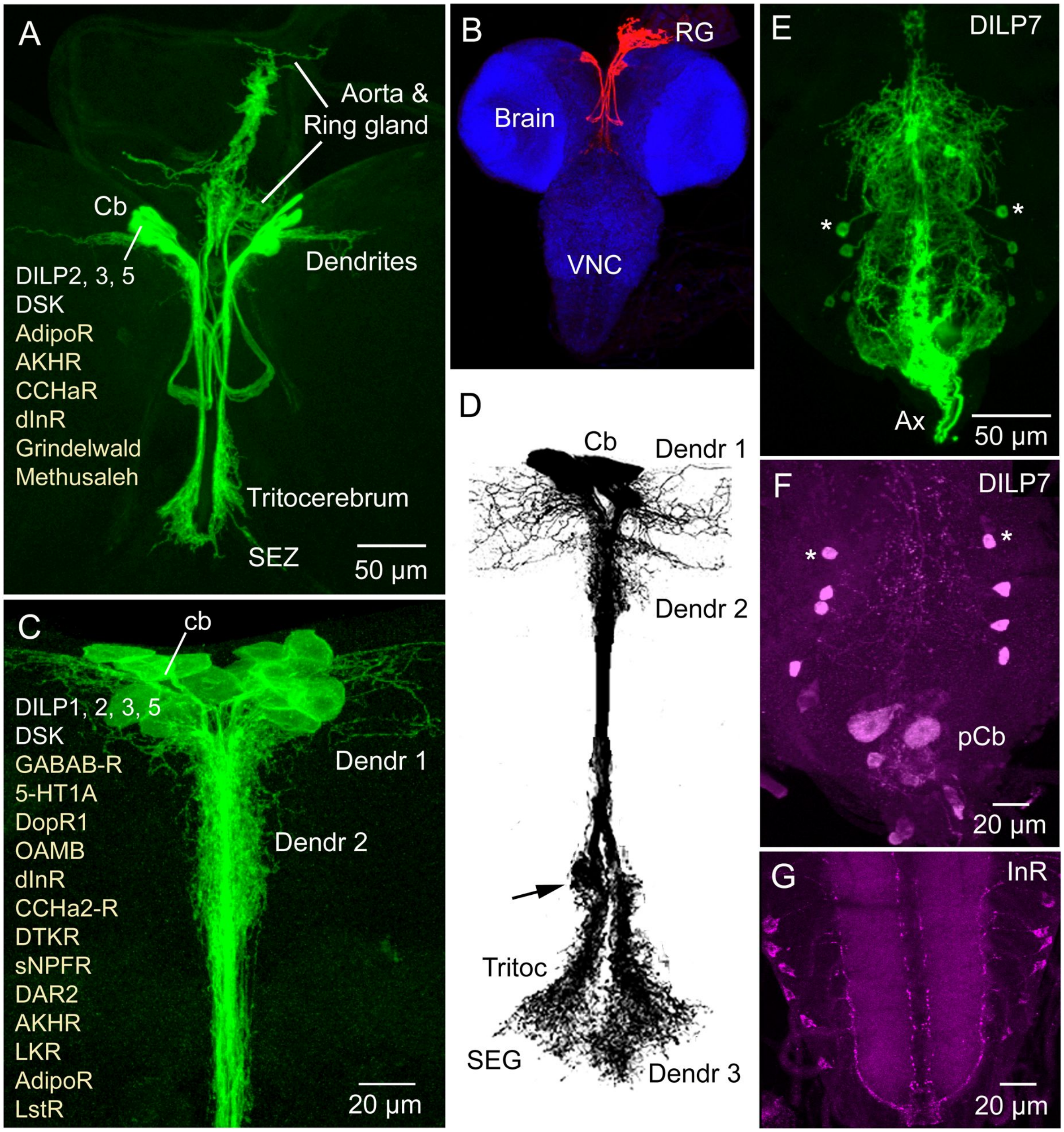

A
SN
TN
AN
1
2
3
4
5
6
7
8
9
EH
FMRFa
CCAP
Leucokinin
CCAP, MIP, Burs, (AstCC)
CCAP, MIP
B
ETH
ETHR-A
?
ETHR-A
FMRFa
LK
EH
CCAP
CCAP MIP
CCAP MIP Burs
Inhibition
Activation
Modulation
Pre-ecdysis
Ecdysis
Post-ecdysis

Figure 15


A
Aorta &
Ring gland
Cb
Dendrites
DILP2, 3, 5
DSK
AdipoR
AKHR
CCHaR
dInR
Grindelwald
Methusaleh
Tritocerebrum
SEZ
50 µm
B
RG
Brain
VNC
C
cb
DILP1, 2, 3, 5
DSK
GABAB-R
5-HT1A
DopR1
OAMB
dInR
CCHa2-R
DTKR
sNPFR
DAR2
AKHR
LKR
AdipoR
LstR
Dendr 1
Dendr 2
20 µm
D
Cb
Dendr 1
Dendr 2
Tritoc
SEG
Dendr 3
E
DILP7
Ax
50 µm
F
DILP7
pCb
20 µm
G
InR
20 µm

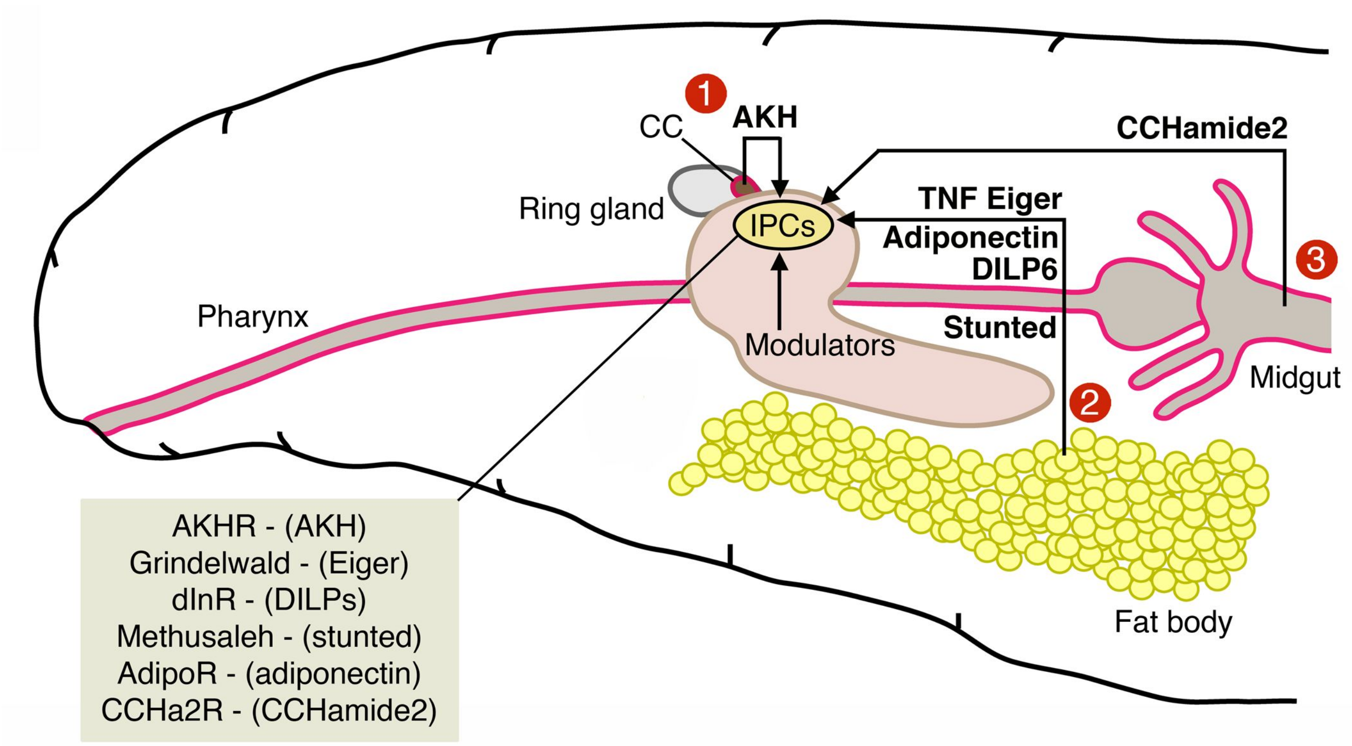

1
CC
AKH
CCHamide2
Ring gland
IPCs
TNF Eiger
Adiponectin
DILP6
3
Pharynx
Stunted
Modulators
Midgut
2
Fat body
AKHR - (AKH)
Grindelwald - (Eiger)
dInR - (DILPs)
Methusaleh - (stunted)
AdipoR - (adiponectin)
CCHa2R - (CCHamide2)

Figure 17

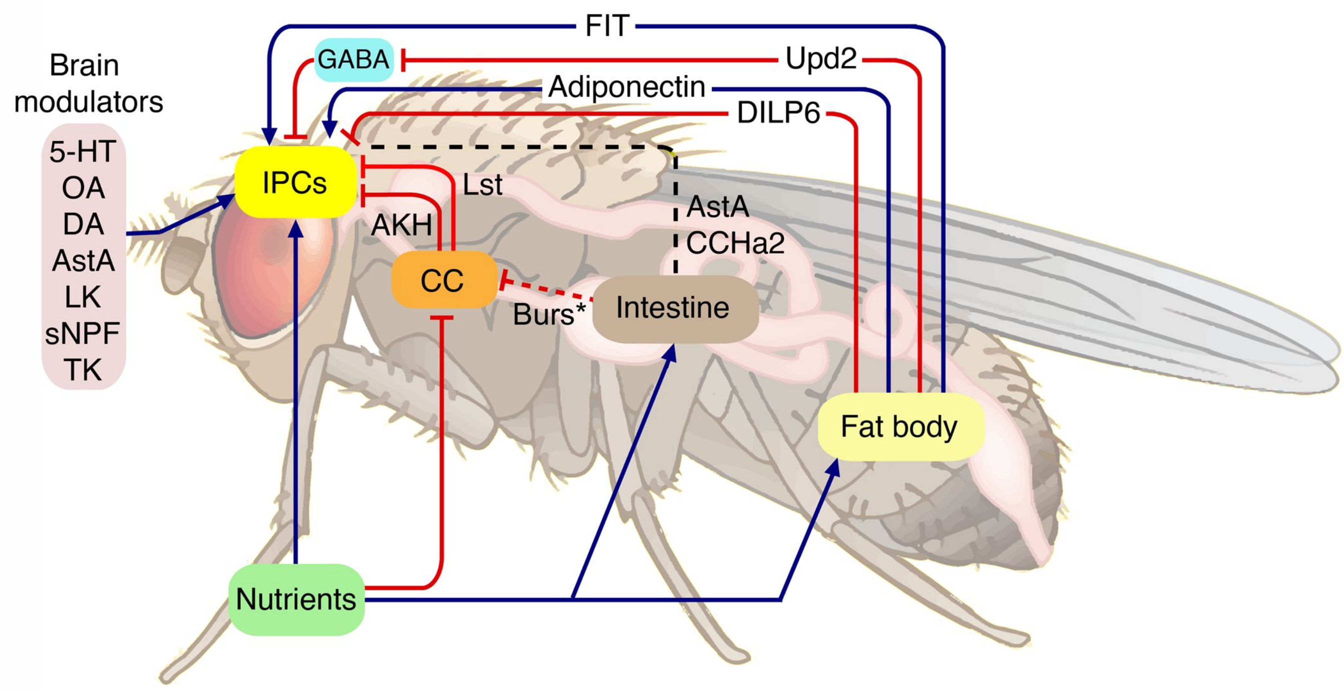


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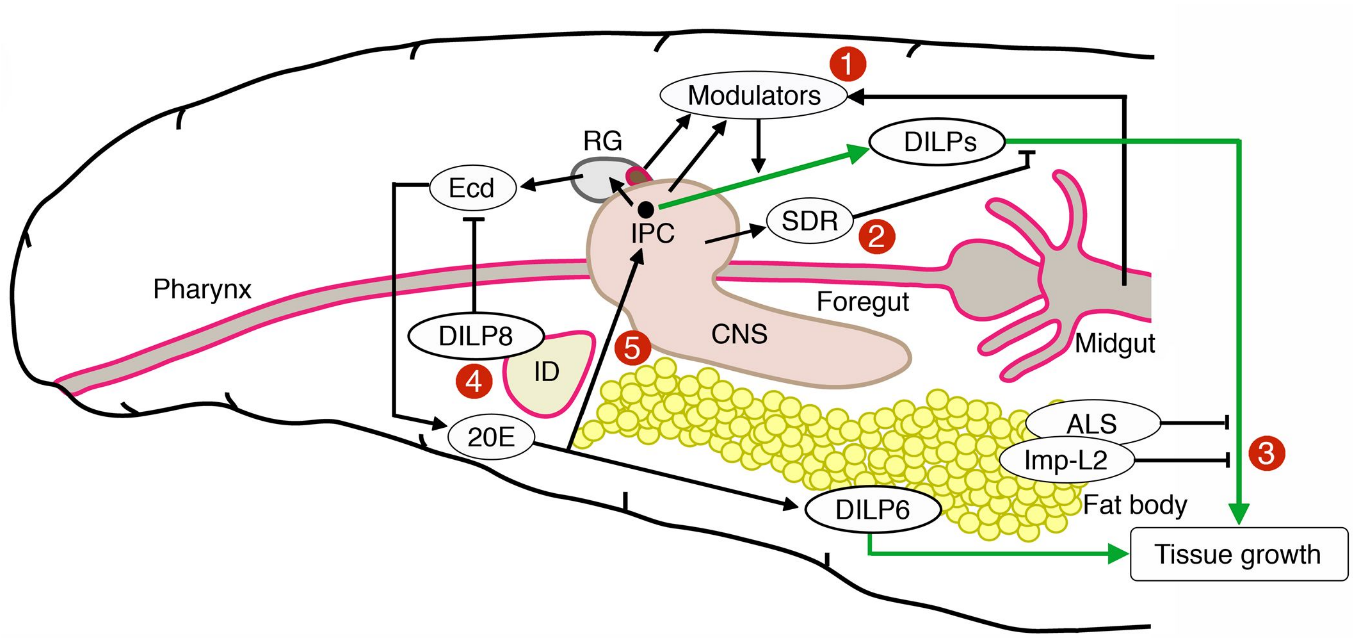
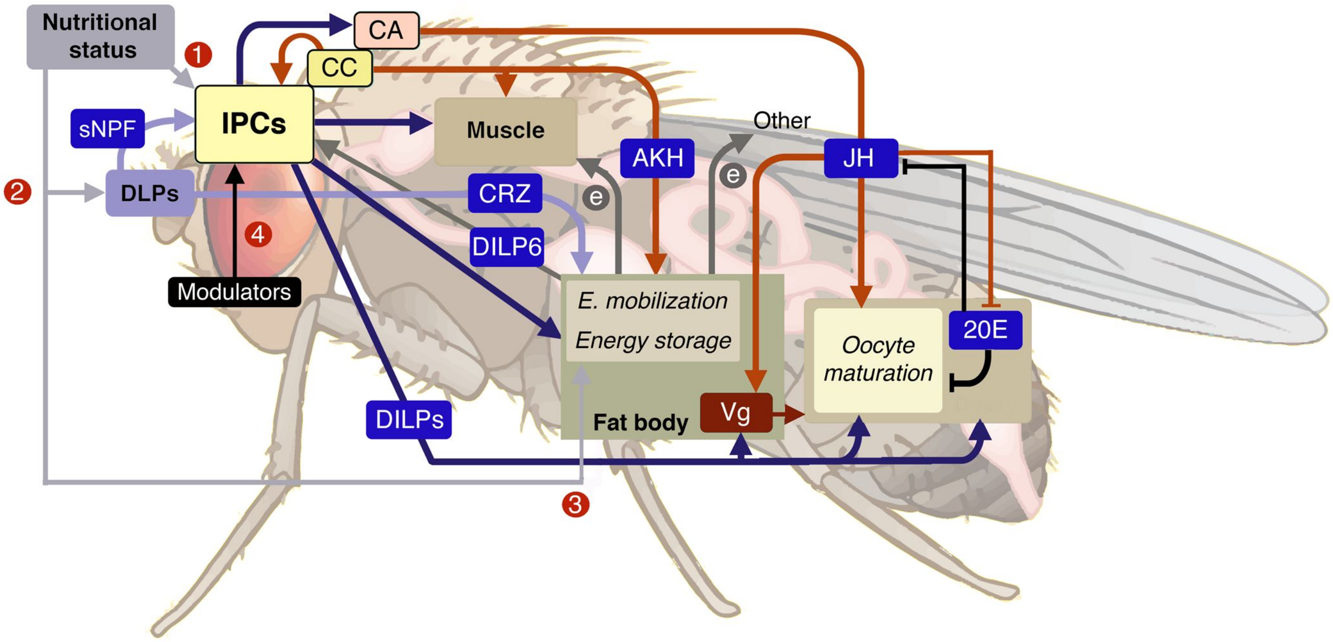
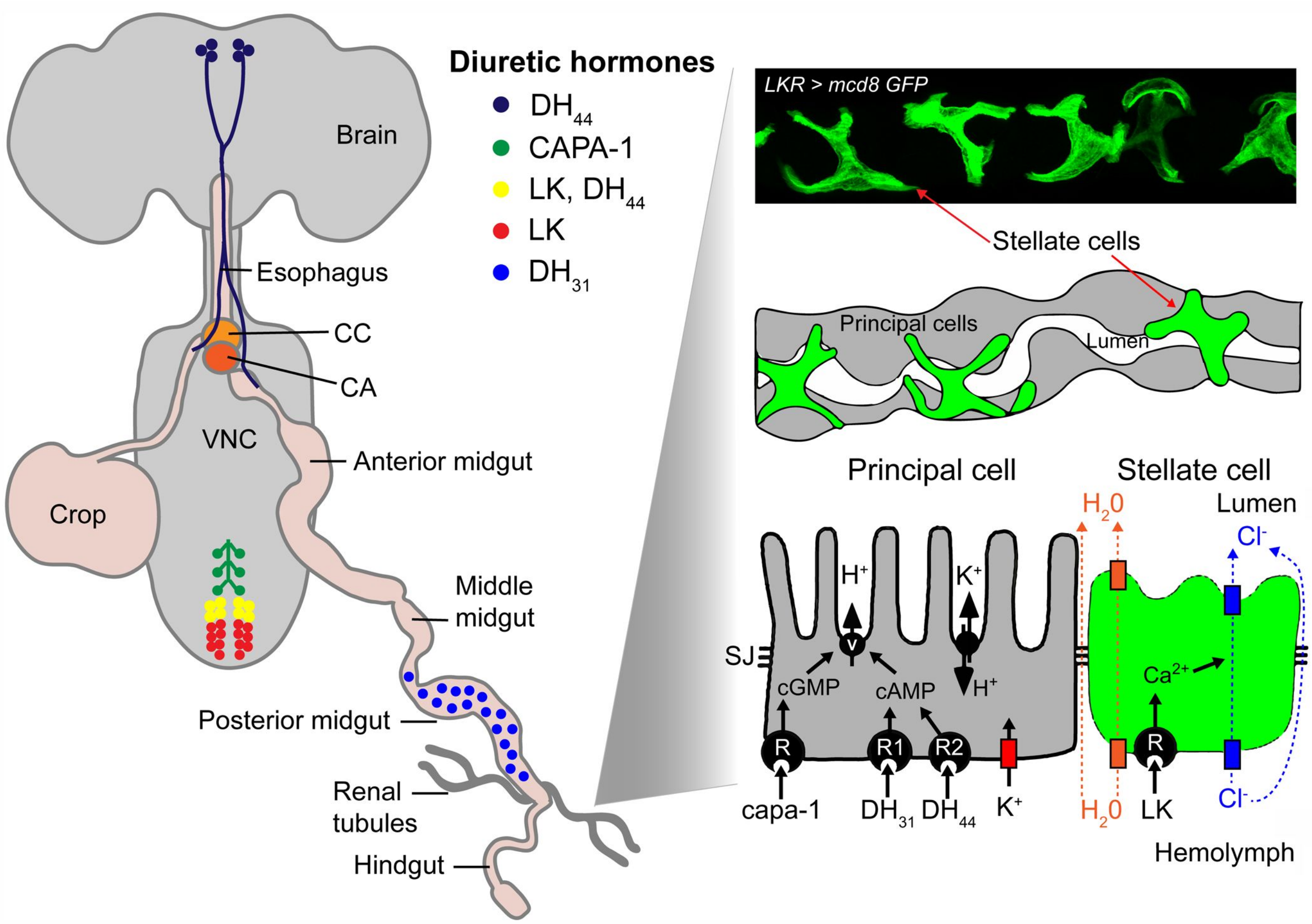
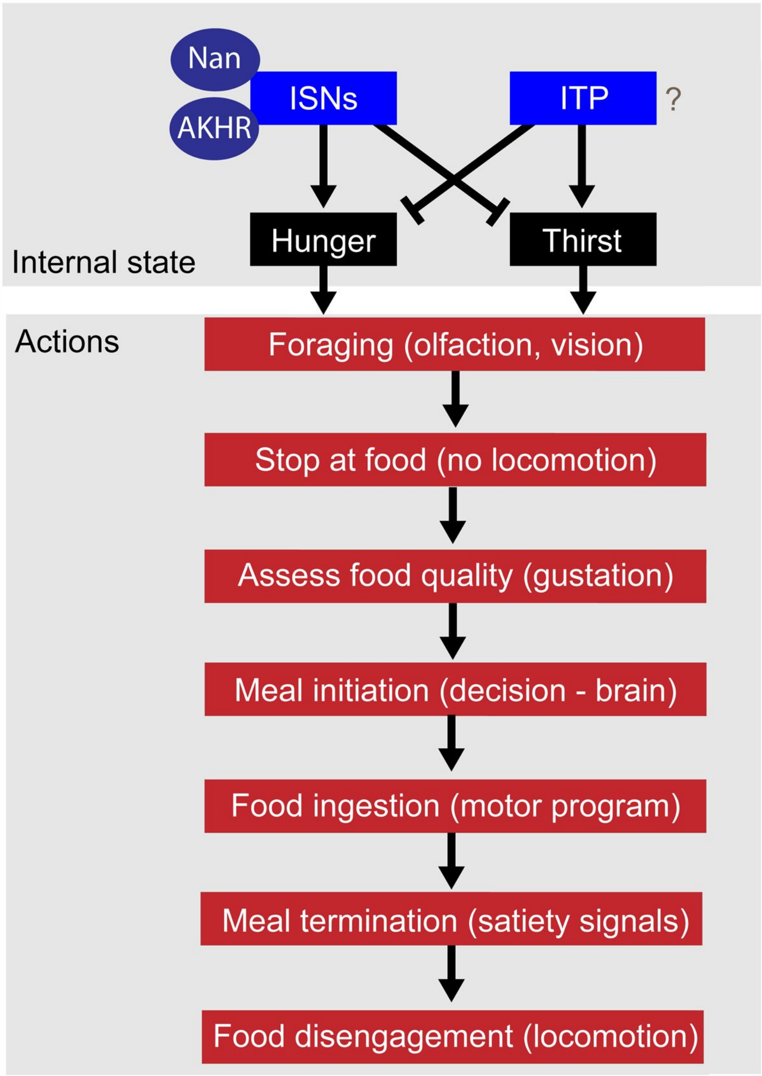
Figure 18


1
Modulators
DILPs
RG
Ecd
IPC
SDR
2
Pharynx
Foregut
CNS
Midgut
DILP8
ID
4
5
ALS
Imp-L2
3
20E
DILP6
Fat body
Tissue growth


Nutritional status
1
2
3
4
sNPF
DLPs
IPCs
CA
CC
Muscle
AKH
Other
JH
CRZ
DILP6
e
e
Modulators
E. mobilization
Energy storage
Oocyte maturation
20E
DILPs
Fat body
Vg


Diuretic hormones
DH44
CAPA-1
LK, DH44
LK
DH31
Brain
Esophagus
CC
CA
VNC
Crop
Anterior midgut
Middle midgut
Posterior midgut
Renal tubules
Hindgut
LKR > mcd8 GFP
Stellate cells
Principal cells
Lumen
Principal cell
Stellate cell
H20
Lumen
Cl-
H+
K+
SJ
v
cGMP
cAMP
H+
Ca2+
R
R1
R2
R
capa-1
DH31
DH44
K+
H20
LK
Cl-
Hemolymph


Nan
AKHR
ISNs
ITP
?
Hunger
Thirst
Internal state
Actions
Foraging (olfaction, vision)
Stop at food (no locomotion)
Assess food quality (gustation)
Meal initiation (decision - brain)
Food ingestion (motor program)
Meal termination (satiety signals)
Food disengagement (locomotion)

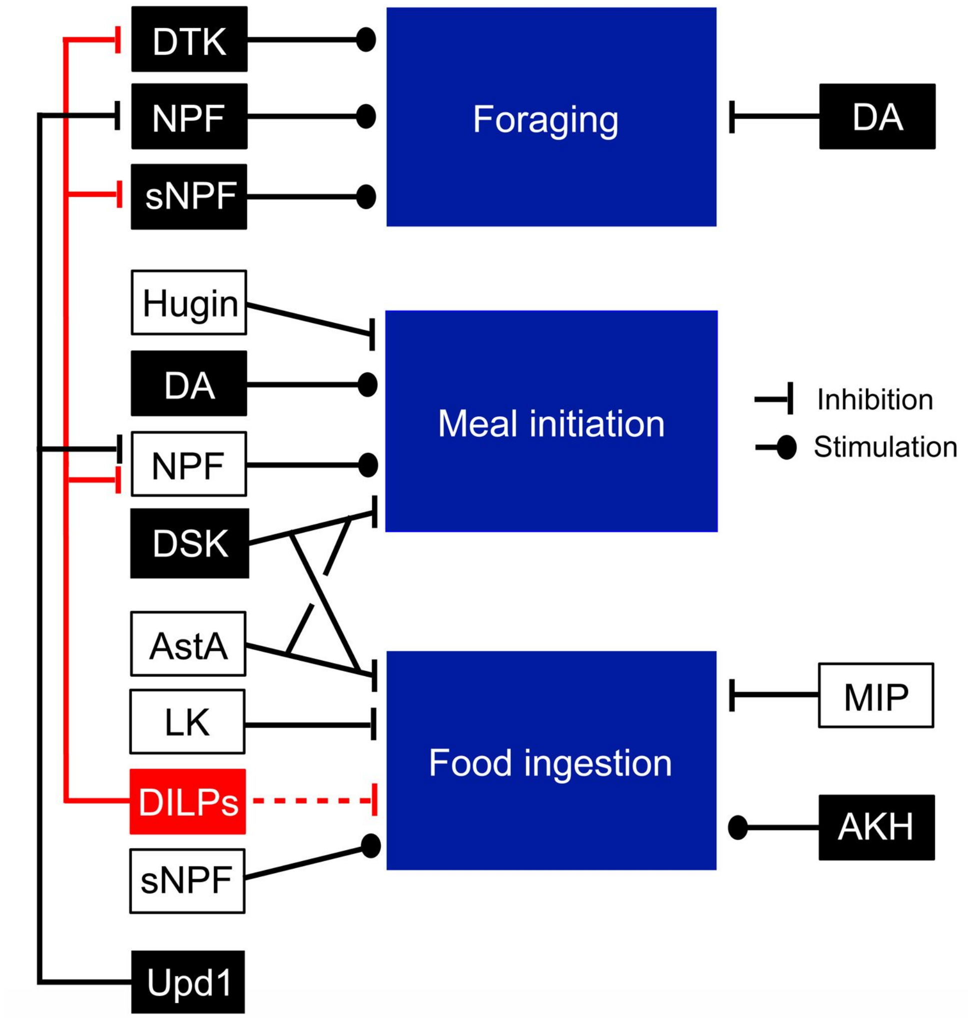
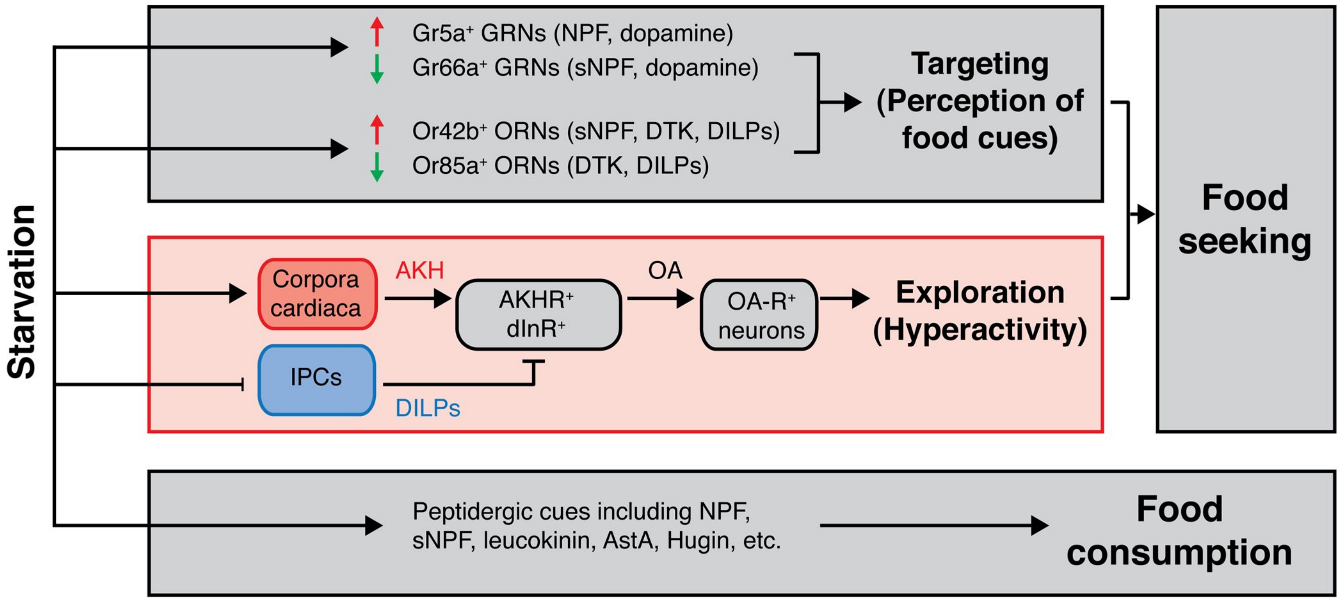
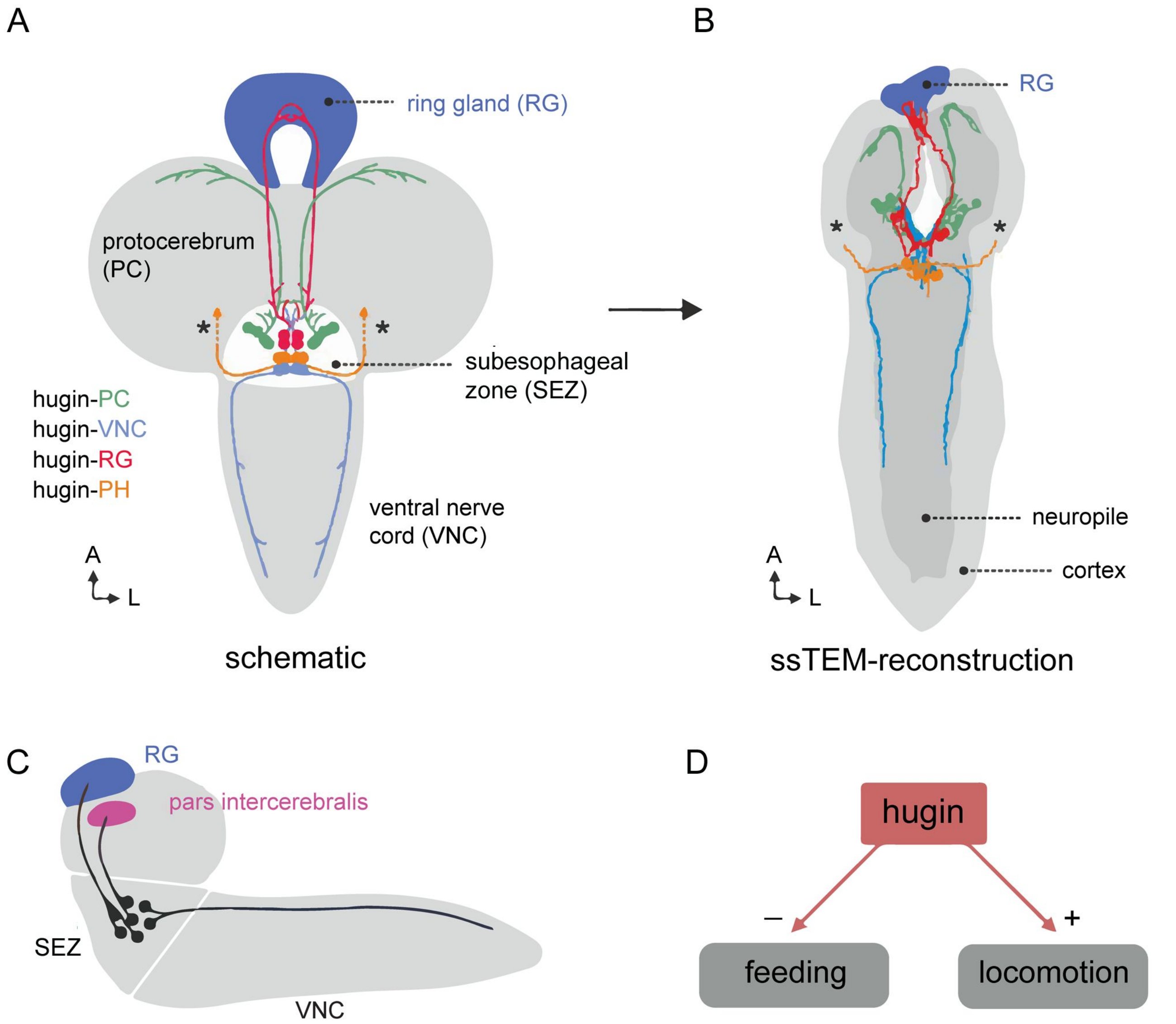
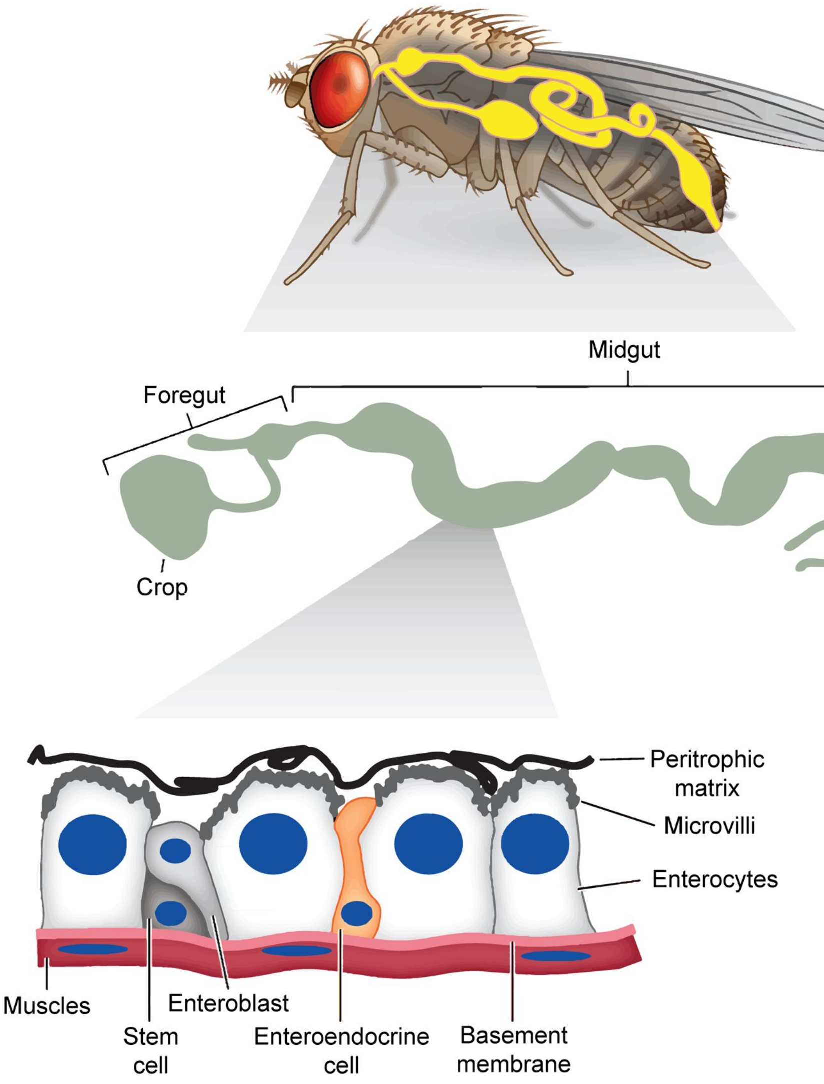

DTK
NPF
sNPF
Foraging
DA
Hugin
DA
NPF
DSK
Meal initiation
Inhibition
Stimulation
AstA
LK
DILPs
sNPF
Food ingestion
MIP
AKH
Upd1

Figure 23

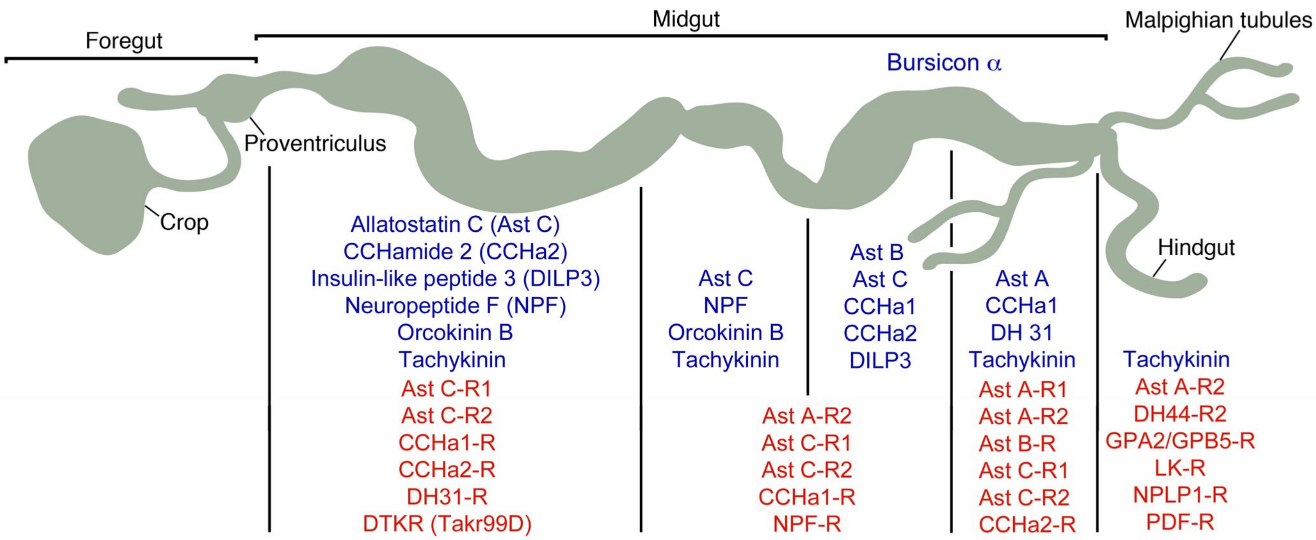

Starvation
Gr5a+ GRNs (NPF, dopamine)
Gr66a+ GRNs (sNPF, dopamine)
Or42b+ ORNs (sNPF, DTK, DILPs)
Or85a+ ORNs (DTK, DILPs)
Targeting (Perception of food cues)
Corpora cardiaca
AKH
AKHR+ dInR+
OA
OA-R+ neurons
Exploration (Hyperactivity)
IPCs
DILPs
Food seeking
Peptidergic cues including NPF, sNPF, leucokinin, AstA, Hugin, etc.
Food consumption

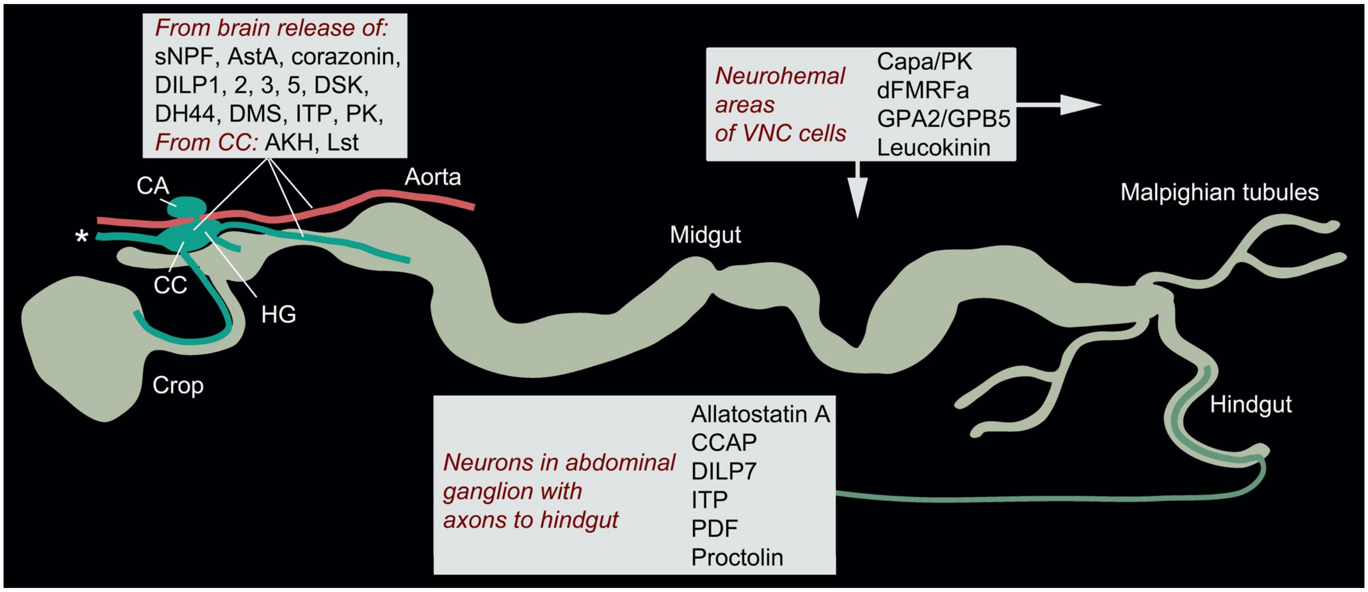

A
ring gland (RG)
protocerebrum
(PC)
*
*
subesophageal
zone (SEZ)
hugin-PC
hugin-VNC
hugin-RG
hugin-PH
ventral nerve
cord (VNC)
A
L
schematic
B
RG
*
*
neuropile
cortex
A
L
ssTEM-reconstruction
C
RG
pars intercerebralis
SEZ
VNC
D
hugin
–
+
feeding
locomotion

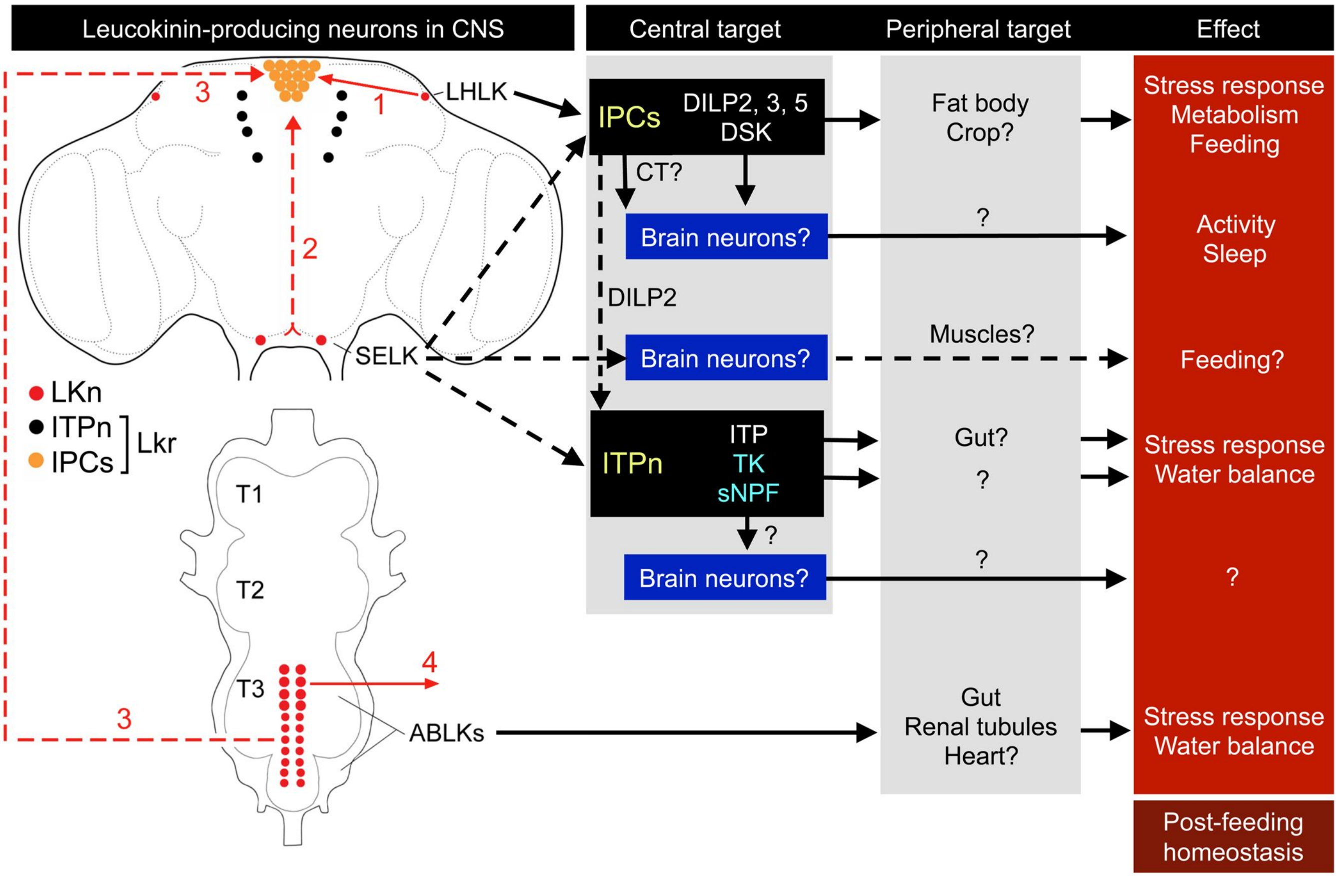


***Drosophila* neuropeptides**

- Allatostatin A
- Allatostatin B
- Allatostatin C
- Bursicon alpha
- CCHamide-1
- CCHamide-2
- Diuretic hormone 31
- Neuropeptide F
- Orcokinin-B
- Tachykinin


Foregut
Midgut
Malpighian tubules
Bursicon α
Proventriculus
Crop
Hindgut
Allatostatin C (Ast C)
CCHamide 2 (CCHa2)
Insulin-like peptide 3 (DILP3)
Neuropeptide F (NPF)
Orcokinin B
Tachykinin
Ast C-R1
Ast C-R2
CCHa1-R
CCHa2-R
DH31-R
DTKR (Takr99D)
Ast C
NPF
Orcokinin B
Tachykinin
Ast B
Ast C
CCHa1
CCHa2
DILP3
Ast A-R2
Ast C-R1
Ast C-R2
CCHa1-R
NPF-R
Ast A
CCHa1
DH 31
Tachykinin
Ast A-R1
Ast A-R2
Ast B-R
Ast C-R1
Ast C-R2
CCHa2-R
Tachykinin
Ast A-R2
DH44-R2
GPA2/GPB5-R
LK-R
NPLP1-R
PDF-R


From brain release of:
sNPF, AstA, corazonin,
DILP1, 2, 3, 5, DSK,
DH44, DMS, ITP, PK,
From CC: AKH, Lst
Neurohemal areas of VNC cells
Capa/PK
dFMRFa
GPA2/GPB5
Leucokinin
CA
*
CC
HG
Aorta
Crop
Midgut
Malpighian tubules
Hindgut
Neurons in abdominal ganglion with axons to hindgut
Allatostatin A
CCAP
DILP7
ITP
PDF
Proctolin



Leucokinin-producing neurons in CNS
Central target
Peripheral target
Effect
LHLK
SELK
ABLKs
LKn
ITPn
IPCs
Lkr
T1
T2
T3
1
2
3
4
IPCs
DILP2, 3, 5
DSK
CT?
DILP2
Brain neurons?
ITPn
ITP
TK
sNPF
Fat body
Crop?
Muscles?
Gut?
Gut
Renal tubules
Heart?
?
Stress response
Metabolism
Feeding
Activity
Sleep
Feeding?
Stress response
Water balance
Post-feeding
homeostasis