Supplementary Materials file

Appendix 1

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

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Brief overview of *Drosophila* neuropeptides and peptide hormones

(Appendix to section 5)

Contents

5. 1. Adipokinetic hormone (AKH)

First characterization: AKH was isolated from the CC of *Locusta migratoria* (Stone *et al.*, 1976). AKHs have 8-10 amino acids, an N-terminal pyroglutamate and a C-terminal amide (Gäde, 2009; Hauser and Grimmelikhuijzen, 2014), and most of these amino acids are critical for receptor activation (Caers *et al.*, 2012; Gäde, 2009).

Synonyms: Older synonyms that can be found in the literature are hypertrehalosaemic hormone, cardioacceleratory/hypertrehalosaemic hormone (CAH), neurohormone D (Baumann *et al.*, 1990; O'Shea and Schaffer, 1985).

Precursor gene: The first AKH gene was cloned from the locust *Schistocerca gregaria* (Schulz-Aellen *et al.*, 1989). In locusts, there are 3 AKH precursor genes that each give rise to a bioactive AKH (AKHI–III) (Van der Horst, 2003). In *Drosophila,* only 1 gene (CG1171) and AKH peptide is known (Noyes *et al.*, 1995; Schaffer *et al.*, 1990). The AKH precursors in insects encode a second peptide (AKH-Precursor Related Peptide; APRP) whose putative function, if any, remains unknown (Galikova *et al.*, 2015).

Isoforms: -

Receptor: The first AKH receptors were identified in *Drosophila* (CG11325) and *Bombyx mori* (Park *et al.*, 2002; Staubli *et al.*, 2002). The AKH receptors are orthologous to the vertebrate GnRH receptors (Lindemans *et al.*, 2009; Mirabeau and Joly, 2013).

Distribution: In *Drosophila* and other insects, AKH is only produced by the glandular cells of the CC (Isabel *et al.*, 2005; Kim and Rulifson, 2004; Lee and Park, 2004; Van der Horst, 2003). In locusts, the three AKHs encoded on separate genes are colocalized (Vroemen *et al.*, 1998). The *Drosophila* AKH receptor (AKH-R) is expressed by adipocytes of the fat body, and a subset of sweet sensing gustatory neurons (Bharucha *et al.*, 2008; Jourjine *et al.*, 2016).

Functions: AKH induces mobilization of lipids, carbohydrates and proline from stores (such as the fat body and muscle) during flight/locomotion, reproduction, development and stress (Bednarova *et al.*, 2013; Gäde, 2009; Gäde and Auerswald, 2003; Gäde *et al.*, 1997; Galikova *et al.*, 2015; Grönke *et al.*, 2007; Lee and Park, 2004). AKH has also been reported to stimulate heart rate, inhibit protein and lipid synthesis, stimulate locomotor activity and induce muscle contractions in various insects (Gäde, 2009; Gäde and Auerswald, 2003; Grönke *et al.*, 2007; Hauser and Grimmelikhuijzen, 2014; Wicher *et al.*, 2006). In *Drosophila,* AKH is orexigenic and plays roles in carbohydrate and lipid metabolism as well as in nutritional and oxidative stress responses, and it extends lifespan under starvation conditions (Bednarova *et al.*, 2013; Bharucha *et al.*, 2008; Galikova *et al.*, 2015; Galikova *et al.*, 2017; Post *et al.*, 2018; Waterson *et al.*, 2014). Furthermore, AKH was shown to induce contractions of the crop in *Drosophila* (Solari *et al.*, 2017).

Related peptides: AKH is a paralog of corazonin, which has been identified in insects including *Drosophila*, as well as ACP found in several insects, but not *Drosophila* (Hauser and Grimmelikhuijzen, 2014; Kaufmann and Brown, 2006; Kaufmann *et al.*, 2009; Li *et al.*, 2008; Siegert, 1999; Tian *et al.*, 2016;

Zandawala *et al.*, 2018b). A relative in crustaceans is RPCH, and GnRH in vertebrates (Hauser and Grimmelikhuijzen, 2014; Li *et al.*, 2008; Li *et al.*, 2016).

5. 2. Allatostatin-A (Ast-A)

First characterization: Four peptides of the insect Ast-A type were isolated from brain extracts of the cockroach *Diploptera punctata* and named allatostatins since they inhibit JH biosynthesis by the cockroach corpora allata (Woodhead *et al.*, 1989). The Ast-A type peptides are characterized by an FGLamide C-terminus. Thus, these peptides are also referred to as FGLamide-related allatostatins or cockroach-type allatostatins.

Synonyms: FGLa allatostatin (FGLa/AST)

Precursor gene: The *D. punctata* Ast-A precursor gene encodes 13 Ast-A peptides (Donly *et al.*, 1993), but the number of peptides encoded by Ast-A precursor varies between species (Bendena *et al.*, 2012). In *Drosophila,* the Ast-A precursor (CG13633) encodes 4 sequence-related peptides (Ast-A1-4) (Baggerman *et al.*, 2002; Lenz *et al.*, 2000b; Vanden Broeck, 2001).

Receptor: In *Drosophila,* there are two Ast-A receptors (CG2672; DAR-1 and CG10001; DAR-2) both of which are related to galanin receptors of mammals (Birgul *et al.*, 1999; Jekely, 2013; Larsen *et al.*, 2001; Lenz *et al.*, 2000a; Mirabeau and Joly, 2013).

Isoforms: There are 4 in *Drosophila* (Ast-A1-4), up to 13 in the cockroach *D. punctata*

Distribution: Ast-A peptides are expressed in both neurons of the CNS and endocrine cells in the midgut (Carlsson *et al.*, 2010; Hergarden *et al.*, 2012; Veenstra, 2009b; Veenstra *et al.*, 2008; Yoon and Stay, 1995). Ast-A-like immunoreactivity was detected in the brain, subesophageal zone (SEZ) and the VNC of *D. melanogaster* (Carlsson *et al.*, 2010; Hergarden *et al.*, 2012; Santos *et al.*, 2007; Yoon and Stay, 1995). Furthermore, Ast-A is expressed by various neurosecretory cells both in the brain and in peripheral nerves of the VNC (Yoon and Stay, 1995), and can thus function as a neurohormone as well as a neuromodulator in certain brain centers. It is also expressed in cockroach hemocytes (Skinner *et al.*, 1997).

Functions: Only in cockroaches, crickets and termites the Ast-A peptides inhibit JH biosynthesis (Stay and Tobe, 2007). Myoinhibitory effects of Ast-A have been shown in several insect species, (Lange *et al.*, 1995; Robertson *et al.*, 2012; Zandawala and Orchard, 2015). In *Drosophila,* Ast-A also regulates food search, feeding, metabolism and sleep (Chen *et al.*, 2016; Donlea *et al.*, 2017; Hentze *et al.*, 2015; Hergarden *et al.*, 2012; Tsao *et al.*, 2018; Wang *et al.*, 2012a).

Related peptides: Ast-A is orthologous to vertebrate galanin (Mirabeau and Joly, 2013). Ast-A and galanin are also evolutionary related to kisspeptin and although kisspeptin-like receptors have been identified in invertebrate genomes, no kisspeptin ortholog has yet been identified in invertebrates (Felix *et al.*, 2015).

5. 3. Allatostatin-B (Ast-B), or myoinhibitory peptide (MIP)

First characterization: The first Ast-B type peptide was isolated from CNS extracts of *Locusta migratoria* (Schoofs *et al.*, 1991). It was named locust-myoinhibiting peptide (Lom-MIP) due to its inhibitory action on spontaneous contractions of locust hindgut and oviduct. Later, four Ast-B peptides were isolated from the cricket, *Gryllus bimaculatus* that were found to inhibit JH biosynthesis by the CA, and were thus dubbed allatostatins (Lorenz *et al.*, 1995). A gene encoding an Ast-B precursor (CG6456) was cloned from *Drosophila* (Williamson *et al.*, 2001a). The *Drosophila* precursor encodes 5 copies of sequence related Ast-Bs (Ast-B1-5). This copy number was later found to vary between species (Bendena and Tobe, 2012).

Synonyms: myoinhibitory peptides (MIPs), W(X_6)Wamides and cricket-type allatostatins

Precursor gene: The first Ast-B/MIP encoding gene (CG6456) was cloned from *Drosophila* (Williamson *et al.*, 2001a).

Isoforms: 5 Ast-B/MIP peptides in *Drosophila* (Williamson *et al.*, 2001a).

Receptor: The first Ast-B/MIP receptor was identified in *Bombyx mori* (Yamanaka *et al.*, 2010) and soon afterwards in *D. melanogaster* (CG16752 or the synonym CG12731) (Kim *et al.*, 2010). Interestingly, this Ast-B/MIP receptor was already known as a receptor for sex peptide in *Drosophila* (Yapici *et al.*, 2008).

Distribution: *Drosophila* Ast-Bs/MIPs are expressed in both the CNS and gut (Carlsson *et al.*, 2010; Veenstra, 2009b; Wang *et al.*, 2012a; Williamson *et al.*, 2001a). MIPs are expressed in neurons throughout the CNS, including the antennal lobe, lamina of the optic lobe and a subset of neurons in the VNC that regulate ecdysis behavior (Carlsson *et al.*, 2010; Jang *et al.*, 2017; Kim *et al.*, 2006a; Kolodziejczyk and Nässel, 2011; Min *et al.*, 2016).

Functions: Ast-Bs/MIPs function as allatostatins in *G. bimaculatus, Tenebrio mollitor* and *Tribolium castaneum* (Abdel-latief and Hoffmann, 2010, 2014; Lorenz *et al.*, 1995). They are myoinhibitory in various insect species (Blackburn *et al.*, 1995; Lange *et al.*, 2012; Schoofs *et al.*, 1991), and in *Bombyx mori,* Ast-Bs/MIPs inhibit ecdysteroid production by prothoracic glands (Hua *et al.*, 1999; Yamanaka *et al.*, 2010). In *Drosophila,* Ast-Bs/MIPs regulate satiety in adults and during development they act in a neuronal network that regulates ecdysis behavior (Kim *et al.*, 2006b; Min *et al.*, 2016). In mated *Drosophila* females, Ast-B/MIP was found in a subset of the olfactory sensory neurons (OSNs) that express Ir-type olfactory receptors and acts as a co-transmitter of acetylcholine in a sensory channel that detects polyamines (Hussain *et al.*, 2016). Moreover, female-specific MIP interneurons in the abdominal ganglia regulate mating receptivity (Jang *et al.*, 2017).

Related peptides: Ast-B/MIPs do not have a vertebrate ortholog (Jekely, 2013). However, Ast-B/MIPs are evolutionary related to the lophotrochozoan GWamides and cnidarian LWamides. Moreover, they are structurally related to sex peptide, which is only found in a few *Drosophila* species (Kim *et al.*, 2010; Poels *et al.*, 2010).

5. 4. Allatostatin-C (Ast-C)

First characterization: Ast-C peptides were first identified in *Manduca sexta* where it displays inhibitory action on JH biosynthesis in CA of another lepidopteran, *Heliothis virescens* (Kramer *et al.*, 1991). Ast-C peptides posses two cysteine residues that form a disulfide bridge that is essential for biological activity, and have the characteristic C-terminal pentapeptide sequence PISCF (Bendena and Tobe, 2012).

Synonyms: PISCF-related allatostatins (PISCF/Ast), *Manduca* type allatostatins and moth-type allatostatins.

Precursor gene: An Ast-C-encoding gene was first cloned from the moth *Pseudaletia unipuncta* (Jansons *et al.*, 1996) and later (CG14919) in *Drosophila* (Williamson *et al.*, 2001b). Ast-C precursors in insects contain a single copy of the mature peptide (Veenstra, 2009a).

Isoforms: -

Receptor: Two Ast-C receptors were identified in *Drosophila*, Drostar1 (CG7285) and Drostar2 (CG13702), and found to be related to the vertebrate somatostatin receptors (Kreienkamp *et al.*, 2002). These receptor genes seems to have arisen from a gene duplication in Diptera since insects other than *Drosophila* and mosquitoes only have a single Ast-C receptor (Mayoral *et al.*, 2010).

Distribution: Ast-C is expressed in the neurons of the CNS and endocrine cells of the gut in *Drosophila* (Park *et al.*, 2008; Williamson *et al.*, 2001b; Zitnan *et al.*, 1993). Similar to their vertebrate homolog, somatostatin, they are brain-gut peptides.

Functions: Peptides of Ast-C type are known to be allatostatic in dipterans and lepidopterans in a stage-specific manner (Bendena and Tobe, 2012; Li *et al.*, 2006; Verlinden *et al.*, 2015; Wang *et al.*, 2012b). Ast-C peptides also display myoinhibitory action in *Drosophila* and the moth *Lacanobia oleracea* (Matthews *et al.*, 2007; Price *et al.*, 2002). In *Drosophila,* Ast-C furthermore modulates nociception and immunity (Bachtel *et al.*, 2018). Finally, Ast-C decreases food ingestion and growth in the pea aphid *Acyrthosiphon pisum* (Down *et al.*, 2010).

Related peptides: Ast-C is orthologous to vertebrate somatostatin (Jekely, 2013; Mirabeau and Joly, 2013). Ast-C is paralogous to Ast-CC and Ast-CCC (Veenstra, 2016).

5. 5. Allatostatin-CC (Ast-CC) or allatostatin double C

First characterization: Allatostatin-CC (Ast-CC) was identified by mining genome and expressed sequence tag (EST) databases from several arthropods, including *Drosophila* (Veenstra, 2009a). Similar to its paralog Ast-C, arthropod Ast-CCs have two cysteine residues, suggesting that the peptide becomes cyclized by means of a disulfide bridge.

Synonyms: allatostatin double C.

Precursor gene: The gene encoding a single Ast-CC (CG14920) is a paralog of the allatostatin C (Ast-C) gene.

Isoforms: -

Receptor: The first Ast-C receptors, Drostar1 and 2, were identified and characterized in *Drosophila* (Kreienkamp *et al.*, 2002). In the beetle *Tribolium castaneum*, there is a somatostatin-like GPCR, that can be activated by both Ast-C and Ast-CC, and that is related to the two *Drosophila* Ast-C receptors (Audsley *et al.*, 2013). The *Drosophila* Ast-C receptors, however, have not been tested for activation with Ast-CC.

Distribution: In larvae of *Drosophila*, Ast-CC is expressed in bilateral pairs of segmental neurons in abdominal neuromeres also producing Ast-B (MIP), bursicon, and CCAP (Kim *et al.*, 2015). These peptidergic neurons are part of a larval circuit initiating the switch from pre-ecdysis to ecdysis behavior, but a specific role of Ast-CC in this circuit has not been determined (Kim *et al.*, 2015).

Functions: In several arthropods including *Drosophila*, tsetse flies, the termite *Zootermopsis nevadensis* and the crayfish *Procambarus clarkii,* the Ast-CC encoding precursors have an N-terminal signal anchor sequence instead of the signal peptide (Veenstra, 2015). Thus, it was suggested that in these species tethered Ast-CC could function in a juxtacrine manner instead of being secreted as an endocrine or paracrine peptide. In other species, such as *T. castaneum*, *Rhodnius prolixus* and *Apis mellifera,* the Ast-CC precursors posses a canonical signal peptide and may produce secreted peptides (Veenstra, 2009a). No specific function of Ast-CC is known to date.

Related peptides: Ast-CC is paralogous to Ast-C and Ast-CCC (Veenstra, 2016). Consequently, Ast-CC is orthologous to vertebrate somatostatin.

5. 6. Bursicon and partner of bursicon, or bursicon α and β

First characterization: Bursicon was discovered as a tanning factor and partially purified from blowflies (*Sarcophaga bullata,* now known as *Neobellieria bullata*) in the 1960s (Fraenkel and Hsiao, 1962; Fraenkel *et al.*, 1966). The full sequence and structure of bursicon was determined about 40 years later in *Drosophila* (Luo et al., 2005; Mendive et al., 2005). Bursicon is a heterodimer consisting of two cystine knot polypeptides, bursicon (burs;

CG13419) and partner of bursicon (pburs; CG15284), these peptides are also known as bursicon α and β (Mendive *et al.*, 2005).

Synonyms: bursicon α and β

Precursor gene: Two genes (burs; CG13419) and (pburs; CG15284) were identified in *Drosophila* (Luo *et al.*, 2005; Mendive *et al.*, 2005).

Isoforms: -

Receptor: The bursicon receptor (CG8930; Lgr2) is a GPCR with a large ectodomain containing leucine-rich repeats (LGRs) (Luo *et al.*, 2005; Mendive *et al.*, 2005).

Distribution: Burs and pburs expression has been revealed in neurons of the brain and ventral nerve cord in *Drosophila*, *Periplaneta americana*, the cricket *Teleogryllus commodus, Anopheles gambiae* and *Manduca sexta* (Dai *et al.*, 2008; Dewey *et al.*, 2004; Honegger *et al.*, 2008; Honegger *et al.*, 2011; Luo *et al.*, 2005). In *Drosophila*, burs and pburs are localized in abdominal neurons also expressing CCAP, and these neurons undergo apoptosis in the adult fly soon after final eclosion (Honegger *et al.*, 2011; Peabody *et al.*, 2008). Moreover, burs is also expressed in the midgut enteroendocrine cells (Scopelliti *et al.*, 2014).

Functions: Bursicon was isolated as a factor inducing cuticle-tanning in insects (Fraenkel *et al.*, 1966). Furthermore, bursicon induces both wing expansion and tanning in *Drosophila, M. sexta,* and *S. bullata* (Dai *et al.*, 2008; Luo *et al.*, 2005; Mendive *et al.*, 2005; Peabody *et al.*, 2008). Bursicon, in addition to regulating ecdysis motor behavior and post ecdysis physiology, is known to activate the NF-κB transcription factor relish and thereby an innate immune response during molting in *Drosophila* (An *et al.*, 2012) and in larvae and adults of the mosquito *Aedes aegypti* (Zhang *et al.*, 2017). *Drosophila* burs is also expressed in gut enteroendocrine cells where it controls local stem cell quiescence (Scopelliti *et al.*, 2014). Moreover, burs is released from these enteroendocrine cells in response to dietary sugars and regulates metabolic homeostasis (Scopelliti *et al.*, 2018).

Related peptides: Bursicon α and β do not have a vertebrate ortholog.

5. 7. Capability (Capa), a precursor encoding periviscerokinins and a pyrokinin

First characterization: A Capa-type peptide was isolated from *Manduca sexta* and originally named cardioacceleratory peptide 2b (CAP_{2b}) based on its ability to stimulate heart contractions *in vitro* (Huesmann *et al.*, 1995). A *Drosophila* CAP_{2b} peptide was isolated soon afterwards and shown to stimulate fluid secretion by Malpighian tubules (Davies *et al.*, 1995). These and related peptides are now referred to as Capa peptides after the discovery of the gene, *Capability* (*Capa*) in *Drosophila* that encodes two CAP_{2b} type peptides, designated Capa-1 and Capa-2 (Kean *et al.*, 2002). The Capa gene also codes for a pyrokinin (PK-1) – see also entry for pyrokinins.

Synonyms: CAP_{2b}, periviscerokinins [see (Wegener *et al.*, 2002)].

Precursor gene: *Capability* (*Capa;* CG15520) in *Drosophila* (Kean *et al.*, 2002). The Capa precursor contains Capa-1 and Capa-2, which have a characteristic C-terminal AFPRVamide, but also a pyrokinin peptide (Capa-PK or PK-1) with an FXPRLamide C-terminus.

Isoforms: Capa-1 and Capa-2

Receptor: Capa peptides and pyrokinins activate distinct receptors and are, thus, part of two distinct signaling systems, even though the peptides are encoded on the same gene. A Capa receptor (CapaR; CG14575) was first identified in *Drosophila* (Iversen *et al.*, 2002; Park *et al.*, 2002) and is ancestrally related to vertebrate neuromedin U receptors (Terhzaz *et al.*, 2012). The Capa-PK receptor (CG9918) (Park *et al.*, 2002) was also shown to be a receptor of the unrelated peptide limostatin (Alfa *et al.*, 2015). Pyrokinin-type neuropeptides, including Capa-PK and their receptors, as well as limostatin, are discussed under separate headings (sections 5. 21 and 5. 33).

Distribution: In *Drosophila,* the Capa peptides are expressed by three pairs of large neurosecretory cells in the anterior abdominal neuromeres (A2-4) of the ventral nerve cord (Kean *et al.*, 2002). These cells have axon terminations in perisympathetic organs (neurohemal organs) in the larva and in a plexus in the neural sheath of the abdominal ganglion and abdominal nerve in the adult (Santos *et al.*, 2006), suggesting that these so-called Va neurons can release peptide into the circulation. In some insects Capa peptides are also expressed in neurons of the brain and subesophageal zone (Loi *et al.*, 2001; Loi and Tublitz, 2004; Paluzzi and Orchard, 2010).

Functions: Capa peptides are generally diuretic and stimulate secretion in Malpighian tubules of several insect species (Halberg *et al.*, 2015). This signaling also has an effect on desiccation and cold stress tolerance in *Drosophila* (Terhzaz *et al.*, 2015). Interestingly, Capa peptides in the blood-sucking bug *Rhodnius prolixus* and mosquito *Aedes aegypti* are anti-diuretic at low doses (Paluzzi *et al.*, 2008; Sajadi *et al.*, 2018). Also in *Drosophila* Capa peptides can at low concentrations be antidiuretic and disrupt cold tolerance (MacMillan *et al.*, 2018). Capa peptides are furthermore known to be myotropic (Wegener *et al.*, 2002), but the function of the Capa-PK has not yet been revealed (see section 5. 33 on pyrokinins).

Related peptides: Capa peptides are structurally related to pyrokinin, PBAN and ETH. The vertebrate ortholog of these peptides is neuromedin U.

5. 8. CCHamide-1 and CCHamide-2 are encoded by separate genes

First characterization: Genomic BLAST searches identified a gene encoding CCHamide in *Bombyx mori* and some other insects (Roller et al., 2008). All insects with a sequenced genome have been found to have two genes, each coding for a unique CCHamide (CCHamide-1 and CCHamide-2) (Hansen *et al.*, 2011; Ida *et al.*, 2011a; Roller *et al.*, 2008). These peptides were named CCHamides due to the presence of two conserved cysteine residues, which form a disulfide bridge, and an amidated histidine (H) at the C-terminus (Roller et al., 2008). The peptides were also chemically isolated and sequenced from *Drosophila* (Ida *et al.*, 2012).

Synonyms: -

Precursor gene: There are two genes in *Drosophila*, CCHamide-1 (CG14358) and CCHamide-2 (CG14375), as also seen in other insects (Hansen *et al.*, 2011; Ida *et al.*, 2011a; Roller *et al.*, 2008).

Isoforms: -

Receptor: Two receptors, CCHamide-1 receptor (CG30106) and CCHamide-2 receptor (CG14593), specific for each of the peptides, were found in *Drosophila* (Hansen *et al.*, 2011).

Distribution: In *Drosophila,* both CCHamide-1 and 2 are expressed in the CNS as well as the midgut (Li *et al.*, 2013; Sano *et al.*, 2015a; Veenstra and Ida, 2014). In the CNS, CCHamide-1 is expressed in a subset of clock neurons called anterior dorsal neuron 1 (Fujiwara *et al.*, 2018). In the midgut, CCHamide-1 and 2 are each produced in distinct cell populations, with the exception of few enteroendocrine cells in the posterior midgut where both were colocalized (Veenstra and Ida, 2014). CCHamide-2 is also highly expressed in the *Drosophila* fat body (FlyAtlas). The CCHamide-2 receptor is expressed by insulin-producing cells in the *Drosophila* brain (Sano *et al.*, 2015b).

Functions: In *Drosophila,* CCHamide-2 mutants display reduced feeding both in larvae and adults (Ren *et al.*, 2015) and the peptide increases the motivation to feed (Ida *et al.*, 2012). In addition, their morning and evening locomotor activity was reduced. This altered feeding affects levels of insulin-like peptide in the brain, which in turn seems to affect growth and developmental timing (Ren *et al.*, 2015; Sano *et al.*, 2015b). It has been postulated that CCHamide-2 is a carbohydrate-induced signal from fat body and/or intestine that activates insulin signaling (Sano *et al.*, 2015b). The CCHamide-1 mutants were not affected in the above assays (Ren *et al.*, 2015). In *Drosophila,* CCHamide-1 signaling modulates odor perception in starved flies and thereby increases odor attraction (Farhan *et al.*, 2013). Moreover, CCHamide-1 modulates the timing of activity and sleep through interactions with PDF signaling (Fujiwara *et al.*, 2018)

Related peptides: CCHamides are structurally related to protostomian elevenin and GGNG peptides that are found in Lophotrochozoa (Jekely, 2013; Veenstra, 2010). Although not apparent based on the peptide sequence alone, CCHamides are evolutionary related to neuromedin B, endothelin and gastrin-releasing peptide in vertebrates (Jekely, 2013; Mirabeau and Joly, 2013).

5. 9. CNMamide

First characterization: CNMamide (CNMa; CG13936) was identified in a database search of the *Drosophila* genome (Jung *et al.*, 2014). Its name derives from a conserved C-terminal Cys-Asp-Met-amide. The peptide contains two cysteine residues, suggesting that the peptide is cyclized by means of a disulfide bridge

Synonyms: -

Precursor gene: The *Drosophila* CNMa precursor (CG13936) encodes one CNMamide (Jung *et al.*, 2014).

Isoforms: Two alternative splicing variants (CG13936-PB and CG13936-PD) are found in *Drosophila*. CG13936-PB is predicted to produce pQYMSPCHFKICNM-amide where as CG13936-PD is predicted to result in an N-terminal extended isoform (NYQYMSPCHFKICNM-amide) (Jung *et al.*, 2014).

Receptor: The *Drosophila* CNMamide receptor (CNMaR) is encoded by CG33696. Other insects seem to have two CNMamide receptor paralogs, although these have yet to be characterized (Jung *et al.*, 2014).

Distribution: CNMamide is expressed in a fairly large number of neurons in the brain (60 neurons) and VNC (57 neurons) of *Drosophila* (Jung *et al.*, 2014).

Functions: Knockdown of CNMa in the fly increases the latency to sperm ejection by females after copulation [data in supplemental material of (Lee *et al.*, 2015)].

Related peptides: -

5. 10. Corazonin (CRZ)

First characterization: Corazonin was identified from CC extract of the cockroach, *Periplaneta americana* using an assay monitoring effects on heart contractions (Veenstra, 1989). Corazonin and its prepropeptide are structurally similar to the insect AKHs and the two are likely to have originated following gene duplication in Urbilateria (Tian *et al.*, 2016). Insect corazonin peptides have an N-terminal pyroglutamate and are C-terminally amidated. The corazonin sequence is well conserved among insects.

Synonyms: -

Precursor gene: A corazonin-encoding gene (CG3302) was cloned from *Drosophila* (Veenstra, 1994).

Isoforms: -

Receptor: A corazonin receptor (CG10698) was first discovered in *Drosophila* (Cazzamali *et al.*, 2002; Park *et al.*, 2002).

Distribution: In adult *Drosophila* and in other insects, corazonin is expressed by sets of lateral neurosecretory cells of the brain that have axon terminations in the neurohemal organs of corpora cardiaca and the anterior aorta (Cantera *et al.*, 1994; Hou *et al.*, 2018; Lee *et al.*, 2008a; Veenstra and Davis, 1993). *Drosophila* adult males also express corazonin in 2-3 pairs of interneurons in the abdominal ganglia (Tayler *et al.*, 2012). In *Drosophila* and blowfly larvae, corazonin is also expressed in segmental interneurons of the VNC (Cantera *et al.*, 1994; Lee *et al.*, 2008a), but these cells undergo apoptosis after adult eclosion (Lee *et al.*, 2008a). In *Drosophila,* the corazonin receptor is expressed in the fat body and salivary glands, as well as sets of neurons in the CNS (Kubrak *et al.*, 2016; Sha *et al.*, 2014).

Functions: Corazonin has several diverse functions in different insects. These include triggering ecdysis in moths, effects on locust gregarization and coloration, coordination of sperm transfer in *Drosophila*, and different roles in stress responses and metabolism (including ethanol metabolism) in *Drosophila* (Kim *et al.*, 2004; Kubrak *et al.*, 2016; Sha *et al.*, 2014; Tawfik *et al.*, 1999; Tayler *et al.*, 2012; Verlinden *et al.*, 2009; Zhao *et al.*, 2010).

Related peptides: Corazonin is paralogous to AKH, ACP, RPCH, and GnRH family of peptides (Tian *et al.*, 2016). Corazonin has no orthologs in vertebrates (Zandawala *et al.*, 2018b).

5. 11. Crustacean cardioactive peptide (CCAP)

First characterization: Crustacean cardioactive peptide (CCAP) was identified in the shore crab, *Carcinus maenas* (Stangier *et al.*, 1987) and was later found in *Locusta migratoria* (Stangier *et al.*, 1989). The CCAPs are cyclic due to an internal disulphide bridge.

Synonyms: -

Precursor gene: A CCAP coding gene was first discovered in the genome of *Drosophila* (CG4910) and was later cloned from *Manduca sexta* (Hewes and Taghert, 2001; Loi *et al.*, 2001; Vanden Broeck, 2001). This precursor codes for a single CCAP peptide.

Isoforms: -

Receptor: A CCAP receptor (CG6111) was characterized in *Drosophila* (Cazzamali *et al.*, 2003; Park *et al.*, 2002). The CCAP receptors are orthologs of vertebrate Neuropeptide S receptors and echinoderm NGFFFamide receptors (Mirabeau and Joly, 2013; Semmens *et al.*, 2016).

Distribution: Expression of CCAP has been mapped to neurons throughout the nervous system in several insects including *Drosophila*, *L. migratoria*, *Rhodnius prolixus*, *M. sexta* and the stick insect *Baculum extradentatum* (da Silva and Lange, 2006; Draizen *et al.*, 1999; Lange and Patel, 2005; Lee and Lange, 2011; Loi *et al.*, 2001), and CCAP neurons have been found to innervate the gut and other peripheral tissues (Donini *et al.*, 2002). In some insects, but not in *Drosophila,* CCAP is furthermore expressed in endocrine cells of the midgut (Lange and Patel, 2005; Mikani *et al.*, 2015). In *Drosophila,* most of the CCAP expressing neurons undergo apoptosis after adult eclosion (Draizen *et al.*, 1999). Many of the CCAP neurons in the larval abdominal neuromeres of the VNC co-express bursicon (Kim *et al.*, 2006b; Luan *et al.*, 2006).

Functions: CCAP is cardioactive in several insect species (da Silva *et al.*, 2011; Dulcis *et al.*, 2001; Dulcis *et al.*, 2005; Lee *et al.*, 2013; Lee and Lange, 2011). CCAP is important in initiating the ecdysis motor program both in holo- and hemimetabolous insects (Arakane *et al.*, 2008; Gammie and Truman, 1997; Kim *et al.*, 2006a; Kim *et al.*, 2006b; Lee *et al.*, 2013). Furthermore, CCAP stimulates alpha-amylase and protease activities in the midgut of *P. americana* (Matsui *et al.*, 2013) and induces contractions of muscles in the hindgut and oviduct (Donini and Lange, 2002; Lee and Lange, 2011). In *Drosophila,* it has been shown that targeted ablation of CCAP-containing neurons causes defects in execution and circadian timing of ecdysis behavior (Park *et al.*, 2003a).

Related peptides: CCAP is orthologous to Neuropeptide S in vertebrates, conoCAP in lophotrochozoans and NGFFFamide in echinoderms (Mirabeau and Joly, 2013; Moller *et al.*, 2010; Semmens *et al.*, 2015). CCAP/Neuropeptide S family is distantly related to the vasopressin/oxytocin neuropeptides (Semmens *et al.*, 2016)

5. 12. Diuretic hormone 31 (DH31), or calcitonin-like diuretic hormone

First characterization: A DH31 peptide was first isolated from brains of the cockroach *Diploptera punctata* by assaying secretion in Malpighian tubules (MTs) (Furuya *et al.*, 2000). Due to this peptide comprising 31 amino acids and diuretic activity, it was designated DH31. The peptide shares the Pro-amide C-terminus with vertebrate peptide calcitonin, but lacks the disulfide bridge typical of calcitonins.

Synonyms: calcitonin-like diuretic hormone.

Precursor gene: The *Drosophila* DH31 encoding gene (CG13094) was found in a genome search (Coast *et al.*, 2001).

Isoforms: -

Receptor: The first DH31 receptor (Family B type GPCR; CG17415) was characterized in *Drosophila* (Johnson *et al.*, 2005). A more recent study identified two DH31 receptors in the kissing bug, *Rhodnius prolixus* and showed that there are two DH31 receptors in most insects, including *Drosophila* (Zandawala, 2012; Zandawala *et al.*, 2013). The second *Drosophila* DH31 receptor is encoded by *Hector* (CG4395) although it has not been functionally characterized (Zandawala, 2012).

Distribution: DH31 is expressed by neurons and neurosecretory cells in the brain and abdominal ganglia of several insect species, including *Drosophila* (Kunst *et al.*, 2014; Park *et al.*, 2008; Te Brugge *et al.*, 2005; Te Brugge and Orchard, 2008; Zandawala *et al.*, 2011). DH31 has also been found in enteroendocrine cells of the *Drosophila* midgut (Veenstra, 2009b; Veenstra *et al.*, 2008). These DH31-expressing gut cells were found to be activated after ingestion of amino acid or protein-rich diet, indicating a nutrient sensing function (Park *et al.*, 2016).

Functions: In addition to its diuretic activity, it was shown in several insect species that DH31 can induce contractions in muscles, of the hindgut, midgut and salivary glands (LaJeunesse *et al.*, 2010; Orchard, 2009; Te Brugge and Orchard, 2008). In *Drosophila,* gut-derived DH31 stimulates gut contractions that results in expulsion of opportunistic bacteria (Benguettat *et al.*, 2018; LaJeunesse *et al.*, 2010). The DH31 expressing enteroendocrine cells are activated by dietary proteins and amino acids suggesting that DH31 signaling is involved in nutrient sensing (Park *et al.*, 2016). Moreover, DH31 signaling also plays roles in male courtship and circadian control of sleep (Kunst *et al.*, 2014; Li *et al.*, 2011). The DH31 receptor was found to be expressed on corazonin-producing lateral neurosecretory cells in the *Drosophila* brain, indicating that DH31 may control hormone release (Johnson *et al.*, 2005). Finally, DH31 acts on clock neurons to decrease night-onset temperature preferences in *Drosophila*, and it does so by activating the promiscuous PDF receptor (Goda *et al.*, 2016).

Related peptides: DH31 originated in the protostomian lineage following duplication of the calcitonin peptide (Conzelmann *et al.*, 2013). Calcitonin signaling system is found in vertebrates, lophotrochozoans and some insects (Veenstra, 2014).

5. 13. Diuretic hormone 44 (DH44)

First characterization: The first diuretic hormone of insects was isolated from the moth *Manduca sexta* heads and displayed considerable sequence similarity to corticotropin-releasing factor (CRF) of vertebrates (Kataoka *et al.*, 1989). This *M. sexta* peptide consisted of 41 amino acids and was thus named Manse-DH41. In *Drosophila,* the homologous peptide has 44 residues and is named DH44.

Synonyms: corticotropin-releasing factor-related diuretic hormone (CRF/DH) and diuretic hormone.

Precursor gene: The first precursor gene encoding a CRF/DH was cloned from *M. sexta* (Digan *et al.*, 1992). In *Drosophila,* there is one DH44 gene, encoded by CG8348 (Cabrero *et al.*, 2002). In the beetle *Tribolium castaneum,* there are two peptides (Trica-DH37 and Trica-DH47) and *Bombyx mori* has three peptides (Bommo-DH34, Bommo-DH41 and Bommo-DH45), that are known to be the result of alternate splicing (Roller *et al.*, 2008).

Isoforms: In Bombyx three isoforms.

Receptor: The first CRF/DH receptor was identified in *M. sexta* (Reagan *et al.*, 1993). In *Drosophila* (and some other insects)*,* there are two CRF/DH receptors (Dh44-R1, CG8422 and Dh44-R2, CG12370) that are functionally distinct (Cardoso *et al.*, 2014; Hector *et al.*, 2009; Johnson *et al.*, 2004; Johnson *et al.*, 2005). CRF/DH receptors belong to the family of secretin-like GPCRs (subfamily B1).

Distribution: In *Drosophila* and other insects, CRF/DH is expressed in median neurosecretory cells of the brain and segmentally arranged lateral neurosecretory cells in the abdominal ganglia (Cabrero *et al.*, 2002; Cannell *et al.*, 2016; Te Brugge *et al.*, 1999; Veenstra and Hagedorn, 1991; Zandawala *et al.*, 2018a). The abdominal neurons co-express leucokinin in some insect species, including *Drosophila* (Chen *et al.*, 1994a; Te Brugge *et al.*, 2001; Zandawala *et al.*, 2018a). CRF-DH immunoreactivity has been found in endocrine cells of the intestine of locusts and the beetle *Tenebrio molito*r (Johard *et al.*, 2003; Wiehart *et al.*, 2002), but not in *Drosophila*.

Functions: DH44 and other CRF/DHs have well-established roles in fluid secretion in insects both *in vivo* and *in vitro* (Cannell *et al.*, 2016; Furuya *et al.*, 2000; Kay *et al.*, 1992; Te Brugge *et al.*, 2011b; Zandawala *et al.*, 2018a). CRF/DHs also induce satiety in *Schistocerca gregaria* and *M. sexta* (Keeley *et al.*, 1992; Van Wielendaele *et al.*, 2012), initiate pre-ecdysis in *M. sexta* (Kim *et al.*, 2006a), delay oocyte growth in *S. gregaria* (Van Wielendaele *et al.*, 2012). In *Drosophila,* DH44 modulates rest-activity rhythms and control sperm ejection and storage (Cavanaugh *et al.*, 2014; King *et al.*, 2017; Lee *et al.*, 2015). Furthermore, the six DH44 producing MNCs display endogenous glucose sensing and their activation facilitates sugar ingestion and excretion (Dus *et al.*, 2015). These cells also promote food consumption by sensing dietary amino acids via an amino acid transporter (CG13248) (Yang *et al.*, 2018). It was shown that the DH44 producing MNCs receive inputs from clock neurons and form an output pathway from the brain regulating locomotor activity (Cavanaugh *et al.*, 2014). Finally, DH44-R1 knockdown leads to hyper aggressive flies (Kim *et al.*, 2018b).

Related peptides: DH44 is orthologous to the vertebrate CRF. DH44 is related to the egg-laying hormone in lophotrochozoans (Mirabeau and Joly, 2013).

5. 14. Ecdysis-triggering hormone (ETH) and pre-ecdysis-triggering hormone (PETH)

First characterization: Ecdysis-triggering hormone (ETH) was discovered in *Manduca sexta* where it is produced by peritracheal cells, also known as Inka cells (Zitnan *et al.*, 1996). As the name indicates, the peptide acts on the CNS to trigger ecdysis behavior. ETH has a characteristic PRXamide C-terminus.

Synonyms: -

Precursor gene: The first ETH precursor gene was cloned in *M. sexta,* and then in *Drosophila* (CG18105) (Park *et al.*, 1999; Zitnan *et al.*, 1996). In *Drosophila,* the precursor encodes two ETH-like peptides (ETH1 and ETH2), whereas in *M. sexta* it encodes two distinct peptides, ETH and preecdysis-triggering hormone, PETH. The two peptides in both species are functionally distinct.

Isoforms: ETH1 and ETH2

Receptor: The first ETH receptor (CG5911) was identified in *Drosophila* (Iversen et al., 2002) and is homologous to the vertebrate neuromedin U receptors (Jekely, 2013). In *Drosophila,* this receptor gene gives rise to two transcript variants of the ETH receptor that display differences in ligand sensitivity, cellular distribution and they have distinct roles during ecdysis behavior (Diao *et al.*, 2016; Park *et al.*, 2003b).

Distribution: In *Drosophila*, ETH1 and ETH2 can be found together in 18 peritracheal cells that resemble Inka cells (O'Brien and Taghert, 1998; Zitnan *et al.*, 2003). The ETH promoter contains an Ecd response element and can be transcriptionally regulated by Ecd (Park *et al.*, 1999; Zitnan *et al.*, 1996).

Functions: The two *M. sexta* peptides play different roles in behavior: PETH initiates pre-ecdysis I, and ETH triggers pre-ecdysis II and ecdysis behavior (Zitnan *et al.*, 1996). In the silkmoth *Bombyx mori*, both peptides can initiate the entire behavioral sequence (Zitnan *et al.*, 2002). *Drosophila* ETH1 is more potent than ETH2, and these peptides play a role in tracheal air filling and the ecdysis sequence (Zitnan *et al.*, 2007). Recent studies have also indicated functions of the ETH system in adult flies. The Inka cells persist into adulthood and Ecd-dependent ETH signaling triggers production of JH and thereby controls ovary growth, egg production and reproduction (Meiselman *et al.*, 2017). In addition to affecting JH release, ETH also acts on octopaminergic neurons of the oviduct to influence stress-induced reproductive arrest (Meiselman *et al.*, 2018). Another study showed that ETH is essential for male courtship memory via regulation of JH signaling that acts on specific dopaminergic neurons (Lee *et al.*, 2017b).

Related peptides: ETH is structurally related to myomodulin (found in Lophotrochozoa), Capa, pyrokinin and PBAN. The vertebrate ortholog of these peptides is neuromedin U.

5. 15. Eclosion hormone (EH)

First characterization: EH was isolated from *Manduca sexta* and *Bombyx mori* where it is a 63 amino acid peptide (Kataoka *et al.*, 1987; Kono *et al.*, 1990). It was known earlier that EH alters the timing of adult emergence in silkworms, *B. mori* (Truman and Riddiford, 1970). Insect EHs have six cysteine residues forming three disulfide bridges (Zitnan *et al.*, 2007).

Synonyms:

Precursor gene: The first EH gene was identified in *M. sexta* and subsequently in *Drosophila* (CG5400) (Horodyski *et al.*, 1993; Horodyski *et al.*, 1989).

Isoforms: -

Receptor: An EH receptor was identified in the Oriental fruit fly *Bactrocera dorsalis* (Chang *et al.*, 2009). This receptor is a guanylyl cyclase that is expressed in epitracheal (Inka) cells. The *Drosophila* ortholog of this receptor is encoded by CG10738; however, this receptor has not yet been functionally characterized.

Distribution: Only two pairs of neurons in the brain of *M. sexta* and *B. mori* produce EH, whereas in *Drosophila,* there is one pair of EH expressing neurons (Copenhaver and Truman, 1986; Horodyski *et al.*, 1993; Horodyski *et al.*, 1989; McNabb *et al.*, 1997). In all these species EH neurons descend into the VNC, but also with axonal processes terminating in neurohemal areas.

Functions: EH is involved in triggering ecdysis behavior in insects (Ewer, 2005). In *M. sexta,* hormonal EH induces the release of ETH from Inka cells and initiates a cascade of neuronal activities in several types of peptidergic neurons (Zitnan *et al.*, 2007). In *Drosophila,* EH was found to play an important role in ecdysis behavior, but is surprisingly not essential for completion of ecdysis since flies with EH knockdown still undergo ecdysis (McNabb *et al.*, 1997).

Related peptides: EH is not found in vertebrates but an EH ortholog is present in echinoderms (Zandawala *et al.*, 2017).

5. 16. FMRFamide (FMRFa), or extended FMRFamides

First characterization: A cardioexcitatory peptide of the FMRFamide type was first isolated and sequenced from the clam *Macrocallista nimbosa* (Price and Greenberg, 1977). The name is derived from the characteristic FMRFamide C-terminal sequence, and over the years numerous peptides with variants of this C-terminus were identified in insects and other invertebrates [see (Nichols, 2003; Orchard *et al.*, 2001; Walker *et al.*, 2009)]. Only with the identification of genes encoding precursors of peptides with FMRFamide-like sequences it was clear that there are at least five distinct genes each with structurally and functionally distinct peptides with corresponding receptors [see (Bauknecht and Jekely, 2015; Jekely, 2013; Mirabeau and Joly, 2013; Nässel and Winther, 2010)]. These are dealt with in this review under the headings: FMRFamide, myosuppressins, neuropeptide F (NPF), short neuropeptide F (sNPF) and sulfakinins. In contrast to molluskan precursors, the *Drosophila* (and other insects) FMRFamide precursor does not give rise to the tetrapeptide FMRFamide, but extended peptide forms, such as DPKQDFMRFamide. Thus, the insect peptides of this group can be referred to as extended FMRFamides.

Synonyms: -

Precursor gene: The gene encoding the FMRFamide precursor in *Drosophila* (CG2346) was the first insect neuropeptide gene to be cloned (Nambu *et al.*, 1988; Schneider and Taghert, 1988). The FMRFamide gene in *Drosophila* species encodes multiple sequence-related peptides each with 7-10 amino acids, and these isoform numbers vary between species [see (Wegener and Gorbashov, 2008)].

Isoforms: In *Drosophila melanogaster* there are 8 isoforms, dFMRFa-1-8.

Receptor: Two independent studies identified the *Drosophila* FMRFamide receptor (CG2114) (Cazzamali and Grimmelikhuijzen, 2002; Meeusen *et al.*, 2002).

Distribution: Immunohistochemical studies with FMRFamide antisera must be treated with caution due to the sequence similarity between *bona fide* FMRFamides and peptides derived from other precursors/genes that share the C-terminus sequence, such as myosuppressins, NPF, sNPF and sulfakinins. However, *in situ* hybridization established sets of FMRFamide transcript expressing neurons in the brain and VNC of *Drosophila* (O'Brien *et al.*, 1991; Schneider *et al.*, 1993a; Schneider *et al.*, 1993b). Combined with immunohistochemistry it was found that there are three pairs of large neurosecretory cells (Tv neurons) in the thoracic neuromeres. These send axon terminations to segmental neurohemal organs in the larva and neurohemal release sites along the entire dorsal surface of the VNC of adults [see (Lundquist and Nässel, 1990; Nässel *et al.*, 1988; Schneider *et al.*, 1993b)]. There are also FMRFamide expressing interneurons in the *Drosophila* brain, including the optic lobes (Taghert, 1999; Taghert *et al.*, 2000).

Functions: FMRFamides have been found to be myostimulatory or modulatory on various muscles in several insect species, including *Drosophila* (Dunn and Mercier, 2005; Hewes *et al.*, 1998; Lange and Cheung, 1999; Orchard *et al.*, 2001; Sedra and Lange, 2014; Suggs *et al.*, 2016). In the blowfly *Calliphora vomitoria,* FMRFamides induce fluid secretion from salivary glands (Duve *et al.*, 1992). In *Drosophila*, FMRFamide containing neurons are part of the circuitry regulating ecdysis behavior (Kim *et al.*, 2006b). Another function of FMRFamide and its receptor in larvae is to modulate glutamatergic neurons that are required in nutrient (amino acid) dependent induction of pupariation (Jayakumar *et al.*, 2018). Surprisingly little is known in adult flies about the function of FMRFamide or the neurons producing it, except that it promotes stress-induced sleep (Lenz *et al.*, 2015) and that the FMRFamide receptor is required in dopaminergic neurons necessary for sustained flight (Ravi *et al.*, 2018).

Related peptides: The family of extended FMRFamides is arthropod-specific (Bauknecht and Jekely, 2015).

5. 17. Glycoprotein A2 (GPA2) and Glycoprotein B5 (GPB5)

First characterization: Homologs of the glycoproteins GPA2 and GPB5 have been identified in *Drosophila* (Sudo *et al.*, 2005) (Hsu *et al.*, 2002). Insect GPA2 and GPB5 each contain 10 highly conserved cysteine residues. These participate in the formation of a cystine-knot structure, characteristic of glycoprotein hormones (Paluzzi *et al.*, 2014; Sudo *et al.*, 2005). The proteins GPA2 and GPB5 form a heterodimer.

Synonyms: -

Precursor gene: In *Drosophila,* GPA2 (CG17878) and GPB5 (CG40041) encoding genes were identified (Hsu *et al.*, 2002; Sudo *et al.*, 2005).

Isoforms: -

Receptor: In *Drosophila,* the GPA2/GPB5 heterodimer activates a leucine-rich repeat-containing receptor (LGR1; CG7665) (Sudo *et al.*, 2005).

Distribution: In *Drosophila* larvae, GPA2/GPB5 transcripts are expressed in four pairs of bilateral cells in the first four abdominal neuromeres (Sellami *et al.*, 2011). These cells are also found in the adults. GPB5-GAL4 also drives expression in a pair of cells in the pars intercerebralis of the brain and another pair of cells in the subesophageal ganglion (Sellami *et al.*, 2011). The receptor LGR1 is expressed mainly in the hindgut and salivary glands [FlyAtlas; (Chintapalli *et al.*, 2007)]. It is also highly expressed in the gut enteroendocrine cells and muscles [Flygut-*seq*; (Dutta *et al.*, 2015)].

Functions: In *Drosophila*, genetic ablation of GPA2/GPB5 cells decreases survival during development (Sellami *et al.*, 2011). It was also proposed that GPA2/GPB5 may function as an anti-diuretic hormone since its receptor is enriched in the hindgut which is associated with ion and water homeostasis (Sellami *et al.*, 2011). This is supported by a more recent study in the mosquito *Aedes aegypti* where it was shown that GPA2/GPB5 regulates ion transport across the hindgut (Paluzzi *et al.*, 2014).

Related peptides: GPA2/GPB5 orthologs are found throughout Bilateria (Jekely, 2013). GPA2/GPB5 are distantly related to vertebrate follicle-stimulating hormone (FSH), luteinizing hormone (LH), chorionic gonadotropin (CG) and thyroid-stimulating hormone (TSH) (Rocco and Paluzzi, 2016).

Hugin-pyrokinin is presented under pyrokinins (Section 5. 30)

5. 18. Insulin-like peptides (ILPs), encoded by multiple genes

First characterization: The first insulin-like peptide (ILP) was isolated from the silkmoth *Bombyx mori* and named Bombyxin (Nagasawa *et al.*, 1986). ILPs have been identified in all investigated insect species. In *Drosophila,* 8

ILPs (DILP1-8) have been found, each encoded on a separate gene [see (Brogiolo *et al.*, 2001; Colombani *et al.*, 2012; Garelli *et al.*, 2012; Grönke *et al.*, 2010; Liu *et al.*, 2016; Okamoto *et al.*, 2009; Slaidina *et al.*, 2009)]. Of these, two (DILP7 and 8) are structurally related to mammalian relaxin, one is an insulin-growth factor (IGF)-like (DILP6), and the others are insulin-like (DILP1-5) peptides. Insulins and ILPs typically are heterodimers formed by A and B chains each with about 20 and 30 amino acids, respectively. The insulin-like precursor also generates a C-peptide. The A- and B-chains contain six cysteine residues. These are located at highly conserved sites and both external and internal disulfide bridges are crucial for forming a conserved folded structure. The IGFs are single chain peptides with internal cysteine bridges and consist of A and B chains with the C-peptide retained.

Synonyms: Bombyxin

Precursor gene: The first genes encoding ILP precursors were identified in *B. mori* and the locust *Locusta migratoria* (Adachi *et al.*, 1989; Kawakami *et al.*, 1989; Lagueux *et al.*, 1990). Each gene encodes one ILP precursor, even when multiple ILPs are present in a species. The number of ILP encoding genes in each species varies and range between 1 (e. g. in locusts) and 38 (*B. mori*) (Badisco *et al.*, 2008; Mizoguchi and Okamoto, 2013). In *Drosophila,* DILP1-DILP8 are encoded on the genes CG13173 (dilp1), CG8167 (dilp2), CG14167 (dilp3), CG6736 (dilp4), CG33273 (dilp5), CG14049 (dilp6), CG13317 (dilp7) and CG14059 (dilp8) [see (Brogiolo *et al.*, 2001; Colombani *et al.*, 2012; Garelli *et al.*, 2012; Grönke *et al.*, 2010; Liu *et al.*, 2016; Okamoto *et al.*, 2009; Slaidina *et al.*, 2009)].

Isoforms: -

Receptor: The ILPs of insulin- and IGF-type are presumed to act on receptor tyrosine kinases (Brogiolo *et al.*, 2001; Fernandez *et al.*, 1995; Ruan *et al.*, 1995; Yenush *et al.*, 1996), but this has been explicitly tested only for a few of the ILPs [see (Sajid *et al.*, 2011)]. There is typically one such receptor type (InR) in each species. The relaxin-like peptide, DILP8, in *Drosophila* activates a leucine-rich repeat-containing receptor (GPCR), Lgr3 (CG31096) (Colombani *et al.*, 2015; Garelli *et al.*, 2015; Vallejo *et al.*, 2015).

Distribution: In all studied insects one or more ILPs are produced by a set of median neurosecretory cells with axon terminations in the CC/CA and associated neurohemal areas. In *Drosophila* 14 such neurons are known, which produce DILP1, 2, 3 and 5, and are thus designated insulin-producing cells (IPCs) (Brogiolo *et al.*, 2001; Cao and Brown, 2001; Ikeya *et al.*, 2002; Liu *et al.*, 2016; Rulifson *et al.*, 2002). In *Drosophila*, a few of the DILPs are produced by other neuron types (DILP7), as well as intestinal muscle cells (DILP3), or cells of imaginal discs in larvae (DILP8), depending on developmental stage (Brogiolo *et al.*, 2001; Colombani *et al.*, 2012; Garelli *et al.*, 2012; Miguel-Aliaga *et al.*, 2008; Veenstra *et al.*, 2008; Yang *et al.*, 2008). The IGF-like peptides (DILP6 in *Drosophila*) are commonly produced by the adipocytes of the fat body, but also in glial cells of the CNS (Chell and Brand, 2010; Okamoto *et al.*, 2009; Slaidina *et al.*, 2009).

Functions: ILPs in general are multifunctional in insects, including regulation of development, growth, metabolism, reproduction, stress responses and lifespan [see (Antonova *et al.*, 2012; Broughton *et al.*, 2005; Géminard *et al.*, 2006; Grönke *et al.*, 2010; Nässel and Vanden Broeck, 2016)]. Also, food search and feeding are modulated by insulin signaling (Root *et al.*, 2011; Söderberg *et al.*, 2012; Tsao *et al.*, 2018). Some functions may be indirect by action on JH or other hormonal systems such as AKH [see (Nässel and Vanden Broeck, 2016; Post *et al.*, 2018)]. In *Drosophila,* the major different ILP gene products (insulin-like, IGF-like and relaxin-like) appear to have distinct functions [see (Nässel and Vanden Broeck, 2016)].

More details on the different DILPs and insulin signaling are available in section 8. 2. 1.

Related peptides: Bombyxin, insulin, insulin like growth factor (IGF), and relaxin.

5. 19. Ion-transport peptide (ITP)

First characterization: ITP was isolated and partially sequenced from the locust *Schistocerca gregaria* (Audsley *et al.*, 1992) and a full sequence obtained by cloning the precursor gene (Meredith *et al.*, 1996). Insect ITPs are ancestrally related to Crustacean Hyperglycemic Hormone (CHH) and Molt Inhibiting Hormone (MIH) (Dircksen, 2009). These peptides contain 6 highly conserved cysteine residues (Dircksen, 2009; Webster *et al.*, 2012). In several insect species, alternative gene splicing gives rise to several peptides. In *Drosophila,* three ITPs are predicted as detailed below.

Synonyms: -

Precursor gene: A partial sequence was used for cloning the gene encoding *S. gregaria* ITP (Meredith *et al.*, 1996). In *Drosophila* (CG13586) and *Manduca sexta,* the ITP gene encodes two types of peptides: a C-terminally amidated ITP (known as ITP) and C-terminally non-amidated peptides (known as ITP-like peptide, ITPL) (Dai *et al.*, 2007; Dircksen *et al.*, 2008). In *Drosophila,* ITP consists of 72 amino acids and there are two ITPL peptides consisting of 86 residues each (Dircksen *et al.*, 2008).

Isoforms: ITP, ITPL1, ITPL2 (Dircksen *et al.*, 2008).

Receptor: ITP and ITPL receptors were recently identified in the moth *Bombyx mori* (Nagai *et al.*, 2014; Nagai-Okatani *et al.*, 2016). BNGR-A2 (homologous to insect pyrokinin receptors) and BNGR-A34 (an orphan receptor) could be activated by ITP, whereas BNGR-A24 was activated by ITPL. BNGR-A24 is homologous to insect tachykinin receptors (such as *Drosophila* CG7887; DTKR), and is activated by both ITPL and tachykinin (Nagai-Okatani *et al.*, 2016). The *Drosophila* ITP/ITPL receptor(s) is/are not yet known.

Distribution: ITP and ITPL have been mapped in *Drosophila, Tribolium castaneum* and *Manduca sexta* by a combination of immunohistochemistry and *in situ* hybridization (Begum *et al.*, 2009; Dai *et al.*, 2007; Dircksen *et al.*, 2008; Drexler *et al.*, 2007). In these species, ITP is expressed in lateral neurosecretory cells of the brain, and it seems that ITP expression is confined to the CNS, whereas ITPL is predominantly expressed in peripheral tissues. In *Drosophila,* ITP is also produced by a subset of the clock neurons in the brain, one LNd and the 5th small LNv neurons (Johard *et al.*, 2009).

Functions: In the locust, ITP modulates ion transport across the hindgut (Audsley *et al.*, 1992; King *et al.*, 1999). ITP may therefore be an anti-diuretic hormone in insects. In *Drosophila,* ITP plays a role in the clock output pathway (Hermann-Luibl *et al.*, 2014). Recently it was also shown that in *Drosophila* ITP increases thirst and represses excretion, thereby promoting conservation of water, and in addition, it suppresses food intake (Galikova *et* *al.*, 2018). Knockdown of ITP by RNAi in *T. castaneum* increases mortality during larval development and reduces egg production by adults (Begum *et al.*, 2009).

Related peptides: ITP is only found in Ecdysozoa and no vertebrate orthologs have yet been identified.

5. 20. Leucokinin (LK) or kinins (insectakinins)

First characterization: Eight myostimulatory peptides were isolated from extract of the cockroach *Leucophaea maderae* and designated leucokinin I – VIII (LK-I – VIII) from the species name and their action on the gut (Holman et al., 1986, 1987) (Holman *et al.*, 1986a; Holman *et al.*, 1987). The active core of the leucokinins resides in the conserved carboxyterminus pentapeptide FXSWGa (Nachman and Pietrantonio, 2010), and the peptides can vary in length between 6 and 16 residues. This peptide is commonly referred to as leucokinin (LK) in *Drosophila*.

Synonyms: kinins, insectakinins, myokinins, drosokinins

Precursor gene: The first gene encoding a precursor containing three kinins was cloned from the mosquito *Aedes aegypti* (Veenstra *et al.*, 1997). In other insect species, kinin precursors encode varying numbers of kinin peptides, from one in *Drosophila* (*Lk*, CG13480) (Terhzaz *et al.*, 1999) to up to 12 copies in the blood-sucking bug *Rhodnius* (Te Brugge *et al.*, 2011a).

Isoforms: Not in *Drosophila*, but up to 12 in *Rhodnius*.

Receptor: A first LK receptor (CG10626) was identified from *Drosophila* (Radford *et al.*, 2002).

Distribution: In most studied insects, including *Drosophila*, LKs are produced in bilateral pairs of neurosecretory cells in the segmental abdominal ganglia (Cantera and Nässel, 1992; Chen *et al.*, 1994a; Nässel *et al.*, 1992; Te Brugge *et al.*, 2011a). In *Drosophila* and several other insect species, LK is colocalized with CRF-like diuretic hormone in these abdominal cells (Chen *et al.*, 1994b; Te Brugge *et al.*, 2011a; Thompson *et al.*, 1995; Zandawala *et al.*, 2018a). LKs are also expressed by varying numbers of interneurons in the brain and ventral nerve cord, depending on species (Cantera and Nässel, 1992; Chen *et al.*, 1994a; Nässel, 1993; Nässel *et al.*, 1992; Te Brugge *et al.*, 2011a).

Functions: *In vitro* assays revealed that LKs stimulate contractions in visceral and reproductive muscle, and induce fluid secretion in renal tubules (Coast *et al.*, 1990; Holman *et al.*, 1987; Schoofs *et al.*, 1993; Terhzaz *et al.*, 1999). In *Drosophila,* genetic studies have inferred additional functions such as regulation of sleep, clock output, feeding and a role in desiccation and ionic stress resistance in adult flies (Al-Anzi *et al.*, 2010; Cannell *et al.*, 2016; Cavey *et al.*, 2016; Cognigni *et al.*, 2011; Liu *et al.*, 2015; Murphy *et al.*, 2016; Yurgel *et al.*, 2018; Zandawala *et al.*, 2018a; Zandawala *et al.*, 2018c). In larvae, LKs modulate locomotor behavior and are part of a multi-peptide cascade triggering ecdysis behavior and tracheal clearing during molts (Kim *et al.*, 2015; Kim *et al.*, 2018a; Kim *et al.*, 2006b; Okusawa *et al.*, 2014).

Related peptides: Leucokinin orthologs are not found in vertebrates (Mirabeau and Joly, 2013).

5. 21. Limostatin

First characterization: Limostatin (Lst) was identified in *Drosophila* in a screen for genes suppressing production and release of insulin-like peptides, DILPs (Alfa *et al.*, 2015). Its presence has not been confirmed by mass spectrometry.

Synonyms: -

Precursor gene: Lst is encoded on the gene CG8317 and the peptide consists of 15 residues and was proposed to be C-terminally amidated in spite of the lack of a Gly-signal in the precursor (Alfa *et al.*, 2015). *Lst* encoding genes were also identified in a number of other *Drosophila* species and in the mosquitos *Anopheles gambiae* and *Aedes aegypti* (Alfa *et al.*, 2015).

Isoforms: -

Receptor: The *Lst* receptor is encoded by CG9918, and is related to the neuromedin U receptor in vertebrates (Alfa *et al.*, 2015). Curiously, this receptor was originally characterized as a pyrokinin (Capa-PK) receptor (PK1-R) in *Drosophila* (Cazzamali *et al.*, 2005).

Distribution: *Lst* is expressed in the *Drosophila* fat body and in the adipokinetic hormone (AKH) producing endocrine cells of the corpora cardiaca (Alfa *et al.*, 2015). The Lst receptor is expressed by the insulin-producing cells (IPCs) in the brain (Alfa *et al.*, 2015).

Functions: The Lst expression can be regulated by carbohydrate diet after a period of starvation (Alfa *et al.*, 2015). Application of synthetic Lst to the brain attenuated Ca^{2+} levels in IPCs and thereby inhibited release of DILPs (Alfa *et al.*, 2015). Hence, Lst is one of several *Drosophila* peptides that act on IPCs to regulate production and/or release of DILPs (Alfa and Kim, 2016; Nässel and Vanden Broeck, 2016).

Related peptides: -

5. 22. Myosuppressin (Dromyosuppressin, DMS)

First characterization: Myosuppressin was discovered in the cockroach *Leucophaea maderae* and designated leucomyosuppressin (LMS) because of its inhibition of gut contractions (Holman *et al.*, 1986). A *Drosophila* myosuppressin (Dromyosuppressin, DMS) was biochemically isolated later (Nichols, 1992). Due to the common C-terminal FLRFamide the myosuppressins are also known as FLRFamides.

Synonyms: FLRFamides, Dromyosuppressin (DMS)

Precursor gene: The first precursor gene, encoding a single copy of myosuppressin, was cloned from the cockroach *Diploptera punctata* (Bendena *et al.*, 1997). The *Drosophila* DMS precursor gene (CG6440) was identified from the sequenced genome (Hewes and Taghert, 2001; Vanden Broeck, 2001).

Isoforms: -

Receptor: In *Drosophila* two DMS receptors have been identified, CG8985 and CG13803 (Egerod *et al.*, 2003a).

Distribution: DMS is produced by a small number of neurons in the pars intercerebralis (PI) and other parts of the *Drosophila* brain, including the optic lobes (Nichols, 2003; Park *et al.*, 2008). Axon terminations from DMS neurons innervate the crop, anterior gut and dorsal vessel (Dickerson *et al.*, 2012).

Functions: Myosuppressins inhibit spontaneous contractions in heart and visceral muscle in locusts (Orchard *et al.*, 2001) and *Drosophila* (Dickerson *et al.*, 2012) and inhibit ecdysone production in silkworm larvae (Yamanaka *et* *al.*, 2005). In *Drosophila*, optogenetic activation of myosuppressin neurons results in precocious eclosion (Ruf *et al.*, 2017).

Related peptides: -

5. 23. Natalisin

First characterization: Natalisin was identified and characterized in three different insects: *Drosophila*, *Tribolium castaneum*, and *Bombyx mori* (Jiang *et al.*, 2013). The C-terminus of natalisin displays some similarities to insect tachykinin-related peptides (also known as DTKs, TRPs or TKRPs) by sharing the common C-terminal sequence FxxxRamide.

Synonyms:

Precursor gene: The *Drosophila* precursor (CG34388) encodes 5 natalisins (NTL1-5) (Jiang *et al.*, 2013).

Isoforms: 5 in *Drosophila* and 11 in *Bombyx mori* (Jiang *et al.*, 2013). .

Receptor: The *Drosophila* natalisin receptor (CG6515) was previously known as NKD (neurokinin receptor *Drosophila*) or TakR86C (Monnier *et al.*, 1992) and considered a receptor for tachykinin-related peptide 6 (DTK6) (Poels *et al.*, 2009), which has the C-terminal sequence FVxxRa in common with some of the natalisins and thus activate CG6515 at higher concentrations (Jiang *et al.*, 2013).

Distribution: In the three insects investigated, natalisin is produced in 3–4 pairs of interneurons in the brain (Jiang et al., 2013).

Functions: Knockdown of natalisin or its receptor results in defects in reproductive behavior of male and female *Drosophila* (Jiang et al., 2013) and mating frequency in the oriental fruitfly *Bactrocera dorsalis* (Gui *et al.*, 2017).

Related peptides: Natalisin signaling system is paralogous to the tachykinin signaling system and originated in the arthropod lineage (Jiang *et al.*, 2013).

5. 24. Neuropeptide F (NPF)

First characterization: The first bona fide insect neuropeptide F (NPF, dNPF) was identified in *Drosophila* (Brown *et al.*, 1999) and was named after similarities to neuropeptide Y of vertebrates and NPFs from other invertebrates, such as tapeworm and snails (Maule *et al.*, 1996; Maule *et al.*, 1991). The *Drosophila* NPF consists of 36 amino acids and has an RVRFamide C-terminus (Brown *et al.*, 1999).

Synonyms: Long NPF, dNPF

Precursor gene: NPF is encoded on CG10342, and contains one peptide (Hewes and Taghert, 2001; Vanden Broeck, 2001). In *Drosophila,* a peptide with an RYamide C-terminus, like neuropeptide Y, is encoded on a separate gene (CG40733) and this peptide and its receptor (NepYr, or RYa-R; CG5811) thus exist in parallel with the NPF-NPFR system (see separate entry).

Isoforms: -

Receptor: The first NPF receptor in insects was identified in *Drosophila* (NPFR1; CG1147) and was found to be related to the neuropeptide Y receptors (Garczynski *et al.*, 2002).

Distribution: In *Drosophila,* NPF is produced by a small number of neurons in the brain of larvae and adults, and in enteroendocrine cells of the midgut (Brown *et al.*, 1999).

Functions: Multiple functional roles have been suggested for NPF in insects [summarized in (Nässel and Wegener, 2011)]. Genetic evidence indicates roles for *Drosophila* NPF in foraging, food odor perception and feeding (Beshel and Zhong, 2013; Chung *et al.*, 2017; Guevara *et al.*, 2018; Lee *et al.*, 2017a; Pu *et al.*, 2018; Shao *et al.*, 2017; Slade and Staveley, 2016; Tsao *et al.*, 2018; Wang *et al.*, 2016; Wang *et al.*, 2013), alcohol sensitivity and preference (Guevara *et al.*, 2018; Shohat-Ophir *et al.*, 2012; Wen *et al.*, 2005), stress (Xu *et al.*, 2010), aggression (Dierick and Greenspan, 2007), Malpighian tubule function (Chintapalli *et al.*, 2012), mating and reproduction (Kim *et al.*, 2013; Zer-Krispil *et al.*, 2018), learning (Krashes *et al.*, 2009), as well as circadian clock function (Erion *et al.*, 2016; He *et al.*, 2017; Hermann *et al.*, 2012) and sleep (Chung *et al.*, 2017).

Related peptides: Neuropeptide Y, pancreatic polypeptide

5. 25. Neuropeptide-like precursors

In a quest to identify novel neuropeptides in *Drosophila* liquid chromatography and tandem mass spectrometry was employed on larval extracts (Baggerman *et al.*, 2005; Baggerman *et al.*, 2002). Bioinformatics revealed that several of the newly identified peptides were derived from four novel precursors, that were named neuropeptide-like precursors 1-4 (NPLP1-4) and to be found encoded by the genes CG3441, CG11051, CG13061 and CG15361 (Baggerman *et al.*, 2005; Baggerman *et al.*, 2002). Here we first describe NPLP1, and the others are presented next under separate headings.

5.25.1. Neuropeptide-like precursor 1 (NPLP1)

First characterization: see above (5.25)

Synonyms: -

Precursor gene: The NPLP1 precursor (CG3441) produces four peptides: IPNamide (NVGTLARDFQLPIPNamide), MTYamide (YIGSLARAGGLMTYamide), NAP peptide (SVAALAAQGLLNAP) and VQQ (NLGALKSSPVHGVQQ), which were confirmed by mass spectrometry (Baggerman *et al.*, 2002). Another peptide could possibly be cleaved from the same precursor: NIATMARLQSAPSTHRDP [see (Overend *et al.*, 2012)]. The NPLP1 precursor can also be found in insects such as *Apis mellifera* (Hummon *et al.*, 2006), *Tribolium castaneum* (Li *et al.*, 2008), and *Anopheles gambiae* (Riehle *et al.*, 2002).

Isoforms: Four (or five) totally different peptides encoded on the precursor.

Receptor: The receptor(s) of the NPLP1 peptides has not been identified, although one of the peptides, VQQ, was shown to activate the membrane receptor guanylate cyclase Gyc76c (CG42636) *in vitro* and stimulates cGMP production (Overend *et al.*, 2012).

Distribution: The NPLP1-derived peptide IPNamide has been localized to 28 neurons in the larval ventral nerve cord of the flies *Neobellieria (Sarcophaga) bullata* and *Drosophila* (Verleyen *et al.*, 2004; Verleyen *et al.*, 2009a). A few IPNamide expressing neurons were also detected in the brain. Some of the neurons of the ventral nerve cord may be neurosecretory cells that release peptides into the circulation [see (Overend *et al.*, 2012)]. In the *Drosophila* brain IPNamide is expressed by a subset of the clock neurons, the anterior dorsal DN1 neurons ($DN1_a$) (Shafer *et al.*, 2006).

Functions: Of all the NPLP1-derived peptides, only the action of the VQQ peptide on the renal tubules of *Drosophila* has been investigated (Overend *et al.*, 2012). The expression of IPNamide in a subset of clock neurons indicates a role in circadian clock function and/or sleep (Shafer *et al.*, 2006).

Related peptides: -

5. 25. 2. Neuropeptide-like precursor 2 (NPLP2)

First characterization: see above (5.25)

Synonyms: -

Precursor gene: The NPLP2 precursor gene (CG11051) encodes the peptide TKAQGDFNEF, designated NEF peptide (Baggerman *et al.*, 2002). A later study suggested that further peptides/fragments could be generated from the precursor in infected *Drosophila* larvae (Verleyen *et al.*, 2006). The NPLP2 precursor has not been identified outside of *Drosophila,* except in the honeybee *Apis mellifera* (Hummon *et al.*, 2006).

Isoforms: -

Receptor: No receptor has been identified.

Distribution: The transcript of the NPLP2 precursor is broadly expressed in the adult fly. It is expressed at high levels in most tissues except midgut, renal tubules, trachea, ovary and testes (FlyAtlas)(Chintapalli *et al.*, 2007). In the larva, the hindgut, trachea, fat body, salivary glands and carcass are enriched in *nplp2* transcript (FlyAtlas). RNA sequencing analysis of wing imaginal discs in *Drosophila* identified *nplp2* transcript in flies mutant in *Pacman*, a gene encoding an exoribonuclease (Jones *et al.*, 2016).

Functions: Upon bacterial infection of *Drosophila* larvae a number of peptides are released into the hemolymph and among these are peptides derived from the NPLP2 precursor (Verleyen *et al.*, 2006). Thus, NPLP2 peptides could be part of a humeral antimicrobial defense. The presence of *nplp2* in imaginal discs, together with insulin-like peptide 8, may indicate a role in developmental growth control (Jones *et al.*, 2016).

Related peptides: -

5. 25. 3. Neuropeptide-like precursor 3 (NPLP3)

First characterization: see above (5.25)

Synonyms: -

Precursor gene: The NPLP3 precursor (CG13061) gives rise to the peptides VVSVVPGAISHA (SHA peptide) and SVHGLGPVVIamide (VVIamide)

(Baggerman *et al.*, 2002). This precursor has only been identified in *Drosophila* species.

Isoforms: -

Receptor: No receptor has been identified.

Distribution: The NPLP3 precursor transcript is enriched in the eye and carcass of adult *Drosophila* according to FlyAtlas (Chintapalli *et al.*, 2007).

Functions: No functions are known

Related peptides: -

5. 25. 4. Neuropeptide-like precursor 4 (NPLP4)

First characterization: see above (5.25)

Synonyms: -

Precursor gene: The NPLP4 precursor (CG15361) gives rise to the peptide pQYYYGASPYAYSGGYYDSPYSY (YSYpeptide) (Baggerman *et al.*, 2002). This precursor is not known outside *Drosophila* species.

Isoforms: -

Receptor: No receptor has been identified.

Distribution: According to FlyAtlas (Chintapalli *et al.*, 2007) the NPLP4 precursor transcript is enriched in the eye, heart and hindgut of adult *Drosophila*; in the larva *nplp4* is enriched in the CNS, midgut, hindgut, salivary gland, carcass and especially trachea.

Functions: No functions are known

Related peptides: -

5. 26. Orcokinin (OK)

First characterization: Orcokinin, was isolated as a myostimulatory peptide from the crayfish *Orconectes limosus* (Stangier *et al.*, 1992). Later it was identified in the cockroach *Blattella germanica* (Pascual *et al.*, 2004) and has thereafter been detected in the genomes of *Bombyx, Anopheles* and *Apis* [see (Roller *et al.*, 2008)] and in *Drosophila* (Liu *et al.*, 2006).

Synonyms: Pedal peptide identified in the slug *Aplysia* (Lloyd and Connolly, 1989)

Precursor gene: In insect species studied so far the orcokinin precursor gene gives rise to at least two splice forms of the transcript, each producing distinct peptides (Chen *et al.*, 2015; Yamanaka *et al.*, 2011). In *Drosophila* the precursor gene CG13565 also results in two splice forms generating one peptide each, orcokinin A and B (Chen *et al.*, 2015). In other insects multiple peptides are produced from each transcript. For instance, in *Locusta migratoria,* where orcokinin A can give rise to 8 peptides, and orcokinin B gives rise to 6 peptides (Hou *et al.*, 2015).

Isoforms: Two splice forms, resulting in two isoforms, orcokinin A and B. In *Rhodnius prolixus*, a third splice form, orcokinin C, has been identified (Wulff *et al.*, 2017)

Receptor: No orcokinin receptor has been identified in insects or crustaceans.

Distribution: Peptides derived from orcokinin A are predominantly expressed in neurons of the CNS, whereas those from the B form are expressed in both CNS and the midgut (Chen *et al.*, 2015; Sterkel *et al.*, 2012; Yamanaka *et al.*, 2011). The distribution of orcokinin A and B has been described in detail for *Drosophila* (Chen *et al.*, 2015), and more generally in several other insect species (Hofer *et al.*, 2005). In *Drosophila,* orcokinin A is expressed by a small number of neurons in the brain, including the pars intercerebralis, and in a region near the medulla of the optic lobe where clock neurons are located (but not in bona fide clock neurons) (Chen *et al.*, 2015). In the abdominal ganglia orcokinin A produced by segmental abdominal neurons, adjacent to neurons producing leucokinin. Orcokinin B was detected in a single neuron in the abdominal ganglion, and in enteroendocrine cells of the anterior midgut (Chen *et al.*, 2015; Veenstra and Ida, 2014). In *Rhodnius,* orcokinin C transcript is only expressed in the anterior midgut (Wulff *et al.*, 2017).

Functions: There are no indications for a myostimulatory actions of orcokinin in insects so far (Pascual *et al.*, 2004), but a role in central circuits of the brain is suggested from the peptide distribution in numerous interneurons of locusts and cockroaches (Hofer *et al.*, 2005). A role of orcokinin in the circadian clock is suggestive in the cockroach *Leucophaea maderae* (Hofer and Homberg, 2006). In the moth *Bombyx,* orcokinin is as a prothoracicotropic factor that stimulates ecdysteroid production in prothoracic glands (Yamanaka *et al.*, 2011). Orcokinin may also play a role in gut function or signaling from the gut (Veenstra and Ida, 2014). In *Rhodnius,* knockdown of all the orcokinin transcripts results in ecdysis defects (Wulff *et al.*, 2017).

Related peptides: Orcokinin is orthologous to pedal peptides found in lophotrochozoans and echinoderms (Lin *et al.*, 2017; Lloyd and Connolly, 1989; Semmens *et al.*, 2016).

5. 27. Pigment-dispersing factor (PDF)

First characterization: Pigment-dispersing hormone (PDH) was isolated from eyestalks of crustaceans as a factor that disperses dark pigment in chromatophores, and triggers light-induced movements of shielding pigment in the compound eye (Rao and Riehm, 1988, 1993; Rao *et al.*, 1985). A related octadecapeptide was identified from the grasshopper *Romalea microptera* and designated pigment-dispersing factor (PDF) (Rao *et al.*, 1987).

Synonyms: Pigment-dispersing hormone (PDH).

Precursor gene: The first PDH precursor gene was cloned from the blue crab *Callinectes sapidus* (Klein *et al.*, 1994) and later a PDF encoding gene (CG6496) was identified in *Drosophila* (Park and Hall, 1998). The *Drosophila* precursor gives rise to one copy of PDF and a putative PDF precursor associated peptide, whose function has not been established.

Isoforms: -

Receptor: The *Drosophila* PDF receptor (CG13758) was identified as a class B (class II) GPCR with a sequence distantly related to the PACAP/VIP receptors in mammals (Hyun *et al.*, 2005; Lear *et al.*, 2005; Mertens *et al.*, 2005).

Distribution: PDF is produced in small sets of brain neurons and abdominal neurosecretory cells in most insects studied (Homberg *et al.*, 1991; Nässel *et al.*, 1993; Nässel *et al.*, 1991; Persson *et al.*, 2001). A set of PDF-producing neurons in the brain of *Drosophila* was found to colocalize the clock gene *period* suggesting a role of PDF in circadian clock function (Helfrich-Förster, 1995). These neurons, designated small and large lateral ventral neurons (s-LN_v and l-LN_v) have indeed been shown to be important components of the circadian clock circuit of the brain, and PDF a major signal substance (Park and Hall, 1998; Renn *et al.*, 1999). A small set of neurons in the tritocerebrum (PDF-Tri) transiently expresses PDF at the time of eclosion of the adult flies (Selcho *et al.*, 2018). The abdominal neurosecretory cells have axons that terminate on the hindgut in flies and locusts (Nässel *et al.*, 1993; Persson *et al.*, 2001).

Functions: In the *Drosophila* brain, the PDF expressing s-LN$_v$s and l-LN$_v$s. are critical for setting the phase of rhythm patterns in the circadian clock network in the brain and have been extensively investigated for their roles in clock function and sleep (Liang *et al.*, 2017; Nitabach and Taghert, 2008; Potdar and Sheeba, 2013; Renn *et al.*, 1999; Shafer *et al.*, 2008; Shafer and Taghert, 2009; Taghert and Nitabach, 2012). Also in the cockroach *Leucophaea (Rhyparobia) maderae,* PDF is important in circadian clock function (Wei *et al.*, 2014). There are also other functions of PDF. For instance, PDF in the sLN$_v$ neurons, together with neuropeptide F neurons, controls rival-induced prolonged mating in *Drosophila* in a sex-dimorphic fashion (Kim *et al.*, 2013). Furthermore, PDF-expressing LN$_v$ neurons in the brain co-express the cytokine unpaired1 (Upd1) (Beshel *et al.*, 2017) and the inhibitory amino acid transmitter glycine (Frenkel *et al.*, 2017) and, thus, seem to be multifunctional neurons utilizing multiple signaling substances.

A hormonal role of PDF was proposed due since *Drosophila* and other insects have neurosecretory cells in the abdominal ganglia, and due to the presence of PDF in locust hemolymph (Nässel *et al.*, 1993; Persson *et al.*, 2001). In *Drosophila* PDF was shown to stimulate contractions in of the ureter of the renal tubules in a cyclic AMP dependent fashion (Talsma *et al.*, 2012). Since the ureter is not innervated by PDF neurons, the PDF action is likely to be hormonal. In *Drosophila*, the PDF neurons also signal to the oenocytes located in the body wall and thereby modulate the phase of the oenocyte clock, which affects male sex pheromone production (Krupp *et al.*, 2013). This finding suggests that CNS derived PDF can modulate peripheral clock function. The PDF receptor is expressed in subsets of brain clock neurons (Hyun *et al.*, 2005; Lear *et al.*, 2005; Liang *et al.*, 2017; Mertens *et al.*, 2005; Shafer *et al.*, 2008; Shafer and Yao, 2014). The receptor is also found in sets of neurons regulating flight in *Drosophila,* and PDF was proposed to act to integrate sensory inputs and modulate downstream motoneuron activity in flight generation (Agrawal *et al.*, 2013). Finally, in the moth *Bombyx mori* it was shown that PDF stimulates ecdysone biosynthesis via the PDF receptor BNGR-B2 together with PTTH (Iga *et al.*, 2014).

Related peptides: Arthropod PDFs are structurally related and perhaps homologous to the cerebrin peptides found in Lophotrochozoa (Li *et al.*, 2001; Veenstra, 2010).

5. 28. Proctolin

First characterization: Proctolin is of historical interest since it was the first peptide to be isolated and sequenced from an insect, the cockroach *Periplaneta americana* (Starratt and Brown, 1975). As the name indicates it is myostimulatory on the proctodeum and it was shown to be a pentapeptide with the sequence RYLPT. This sequence is conserved amongst most arthropods.

Synonyms: -

Precursor gene: The precursor gene (CG7105), which contains a single copy of proctolin, was identified in *Drosophila* almost 30 years after the original peptide discovery (Taylor *et al.*, 2004).

Isoforms: -

Receptor: The first proctolin receptor gene (CG6986) was cloned in *Drosophila* (Egerod *et al.*, 2003b; Johnson *et al.*, 2003).

Distribution: Proctolin is produced by sets of motor neurons and small sets of interneurons in the CNS of several insect species (Anderson *et al.*, 1988; Clark *et al.*, 2006a; Taylor *et al.*, 2004; Veenstra *et al.*, 1985). In locusts and *Drosophila,* some proctolinergic brain neurons are lateral neurosecretory cells that innervate the corpora cardiaca (Clark *et al.*, 2006b; Taylor *et al.*, 2004). In certain slow motor neurons of cockroach, proctolin is colocalized with glutamate and act as a neuromodulator at the neuromuscular junction (Adams and O'Shea, 1983).

Functions: Proctolin stimulates muscle contractions in the hindgut and several other muscle types, such as reproductive, skeletal and heart muscle (Adams and O'Shea, 1983; Orchard *et al.*, 1989; Ormerod *et al.*, 2016; Taylor *et al.*, 2004). In locusts, proctolin was reported to stimulate release of adipokinetic hormone and biosynthesis of juvenile hormone (Clark *et al.*, 2006b). In larvae of *Drosophila,* locomotor (crawling) behavior is modulated by proctolin, especially at higher temperatures (Ormerod *et al.*, 2016).

Related peptides: Proctolin has no orthologs in deuterostomes (Jekely, 2013).

5. 29. Prothoracicotropic hormone (PTTH)

First characterization: Prothoracicotropic hormone (PTTH) was first discovered in the silk moth *Bombyx mori* where it regulates production of ecdysone (Ecd) in the prothoracic gland (Kataoka *et al.*, 1991). The *Bombyx* PTTH is a homodimer consisting of two 109 amino acid monomers. Each monomer has seven cysteines. Six of these cysteines form three internal disulfide bridges within each monomer, and the seventh produces an intermolecular bridge to the other monomer (Kataoka *et al.*, 1991). The positions of the seven cysteines, and therefore the folding structure of the dimeric PTTH peptide, are well conserved among insects [see (Marchal *et al.*, 2010; Rybczynski, 2005)].

Synonyms: -

Precursor gene: The *Drosophila* PTTH precursor gene (CG13687) can give rise to a PTTH dimer very similar to that identified in lepidopterans (McBrayer *et al.*, 2007).

Isoforms: -

Receptor: In *Drosophila,* the PTTH receptor was identified as a receptor tyrosine kinase encoded by the gene *torso* (CG1389) (Rewitz *et al.*, 2009).

Distribution: In all studied insects, PTTH seems to be distributed exclusively in 2 pairs of large lateral neurosecretory cells (LNCs) of the brain (Marchal *et al.*, 2010; McBrayer *et al.*, 2007; Nagasawa *et al.*, 1986; Sauman and Reppert, 1996). These neurons have axon terminations in the prothoracic glands. In *Drosophila,* torso is expressed in the cells of the prothoracic gland and activation of torso phosphorylates extracellular signal regulated kinase, ERK (Rewitz *et al.*, 2009). A few days into adult life, the PTTH expressing neurons are no longer detectable in *Drosophila*.

Functions: The timing of molts and metamorphosis in insects is coordinated by the steroid hormone ecdysone (Gilbert *et al.*, 2002). PTTH regulates biosynthesis of ecdysone in the prothoracic gland during development. In *Drosophila,* genetic ablation of the PTTH neurons causes a delayed development and adult eclosion, resulting in bigger larvae, pupae and adults

(Rewitz *et al.*, 2009). This suggests that the role of PTTH is to regulate developmental timing via ecdysone production, but the peptide is not required for normal ecdysis. The PTTH neurons are regulated by a set of brain interneurons that respond to DILP8 released from the imaginal discs if these are damaged (Colombani *et al.*, 2015; Vallejo *et al.*, 2015). This signal to the PTTH neurons affects ecdysone production and thus developmental timing can be correlated with growth of tissues. It was recently shown that cells of the prothoracic gland release vesicular bound ecdysone in a calcium dependent manner, in addition to the previously proposed diffusion through membranes (Yamanaka *et al.*, 2015). Thus, there may be additional signals regulating calcium-dependent ecdysone release. Timing of PTTH release is regulated by an endogenous clock in prothoracic gland cells that in turn is synchronized with the master clock in the brain by means of signaling from s-LN_v clock neurons with sNPF (Selcho *et al.*, 2017). Finally, PTTH regulates light avoidance in *Drosophila* larvae (Yamanaka *et al.*, 2013).

Related peptides: -

5. 30. Pyrokinins (PK), Capa-PK (tryptopyrokinin) and Hugin-PK

First characterization: Pyrokinin was identified from the cockroach *Leucophaea maderae* and named leucopyrokinin (LPK) due to its N-terminal pyroglutamate and because it stimulates contractions of the cockroach hindgut (Holman *et al.*, 1986b). Several related peptides were identified in moths with the characteristic C-terminus FXPRLamide. Since no PK precursor gene had been identified these peptides were named after their actions/functions: Pheromone Biosynthesis Activating Neuropeptides (PBAN), Diapause Hormone (DH), Melanization and Reddish Coloration Hormone (MRCH) and so on [see (Ma *et al.*, 1994; Sato *et al.*, 1994)]. After identification of PK precursor genes in many insects it became clear that many of these peptides with slightly different sequences are derived from the same precursor. However, in some species, such as *Drosophila* and *Rhodnius*, more than one PK encoding gene is present; in *Drosophila* the *hugin* and *Capa* genes (Kean *et al.*, 2002; Meng *et al.*, 2002; Paluzzi and Orchard, 2010). Pheromone biosynthesis activating neuropeptide (PBAN) and diapause hormone (DH) are N-terminally extended pyrokinins that are found primarily in Lepidoptera.

Recent sequencing of the *Locusta migratoria* and *Zootermopsis nevadensis* genomes led to the identification of a novel gene that codes for tryptopyrokinins, peptides that have a characteristic WFGPRXamide C-terminus (Veenstra, 2014). The transcripts and the mature peptides have also been discovered recently using transcriptome sequencing and mass spectrometry analysis, respectively (Redeker *et al.*, 2017). The C-terminal domain of these peptides is highly similar to that of diapause hormone. Hence, it is not yet clear whether this family of peptides activates diapause hormone receptors or if they activate a distinct receptor and thus represents a novel signaling system. In *Drosophila* the *Capa* gene encodes a tryptopyrokinin (Kean *et al.*, 2002).

Synonyms: PBAN, DH, MRCH (although sequence differences), hugin(-PK)

Precursor gene: In *Drosophila,* two genes encode PKs, the *hugin* (CG6371) and *Capa* (CG15520) genes (Kean *et al.*, 2002; Meng *et al.*, 2002). The *hugin* gene could give rise to hugin-PK (PK-2; SVPFKPRLamide) and hugin γ (pQLQSNGEPAYRVRTPRLamide), but only hugin-PK has been identified by mass spectrometry (Meng *et al.*, 2002; Neupert *et al.*, 2007). The *hugin* gene is related to genes encoding PK/PBANs (Bader *et al.*, 2007). The Capa gene is discussed under a separate heading, and gives rise to Capa-PK (PK-1, a tryptopyrokinin) as well as to two periviscerokinins (Capa1 and Capa2). As a comparison, the PBAN precursors of the moths *Bombyx mori* and *Helicoverpa zea* are more complex and each encodes five peptides with an FXPRLamide or FXPKLamide C-terminus, which are isoforms of pyrokinin/PBAN (Ma *et al.*, 1994; Sato *et al.*, 1994; Sato *et al.*, 1993). In each of these precursors, there is one DH and one PBAN; the remaining three are shorter pyrokinin-like peptides.

Isoforms: - [but in moths the PBAN gene encodes five sequence-related PK-type peptides (Ma *et al.*, 1994; Sato *et al.*, 1994)].

Receptor: Three PK receptors have been identified in *Drosophila*, the Capa-PK receptor (CG9918) and two Hugin-PK receptors (CG8795 and CG8784) (Cazzamali *et al.*, 2005; Hewes and Taghert, 2001; Rosenkilde *et al.*, 2003).

Distribution: In insects investigated, the pyrokinins (and PBAN, DH) are produced by a small group of neurons in the subesophageal ganglion (Choi *et al.*, 2001; Raina and Menn, 1993). A few of these neurons are neurosecretory cells supplying axon terminations to neurohemal release sites, suggesting hormonal release of PK-type peptides. In *Drosophila,* the Hugin-PK expressing neurons are well characterized anatomically and functionally (Bader *et al.*, 2007) and their connectomics in larvae have been revealed (Schlegel *et al.*, 2016). The Capa-PK is coexpressed with Capa-PVK peptides in six large neurosecretory cells in the first three abdominal neuromeres of the ventral nerve cord (Kean *et al.*, 2002). These cells (Va neurons) have axons that terminate in perisympathetic organs in the larva and the dorsal neural sheath of the abdominal ganglion in the adult (Santos *et al.*, 2006). Transcripts encoding tryptopyrokinin, as well as their mature peptides have been detected in subesophageal zone (SEZ) of *Locusta* (Redeker *et al.*, 2017). Immunocytochemistry suggests that this peptide is expressed in ventral posterior median neurons of the SEZ.

Functions: In insects, PKs stimulate contractions in visceral muscle, including oviduct muscle (Holman *et al.*, 1986b). PKs have also been found to be a pupariation inducing factor in flies (Zdarek *et al.*, 1997; Zdarek *et al.*, 2004). The first analysis of the *hugin* gene suggested a role in the ecdysis process (Meng *et al.*, 2002). It was later found that the *hugin* expressing neurons receive gustatory inputs and regulate feeding (Melcher *et al.*, 2006; Melcher and Pankratz, 2005; Schoofs *et al.*, 2014). There are no studies on the specific function of the Capa-PK (PK1) or other tryptopyrokinins.

Related peptides: PK peptides are structurally related to Capa, tryptopyrokinin and ETH. The vertebrate ortholog of these peptides is neuromedin U.

5. 31. RYamides

First characterization: Bona fide RYamides were first identified in genome of the wasp *Nasonia vitripennis* (Hauser *et al.*, 2010). Subsequently, related peptides were also discovered in *Bombyx mori* and *Drosophila melanogaster*, as well as in crustaceans, annelids, mollusks and nematodes (Ida *et al.*, 2011a; Roller *et al.*, 2016; Veenstra, 2014). RYamides share an

FFXGSRYamide C-terminal consensus sequence (Hauser *et al.*, 2010; Roller *et al.*, 2016). It should be noted that insect peptides with an RYamide carboxyterminus (some sNPF isoforms) were known earlier from chemically identified peptides [see (Nässel and Wegener, 2011)], but only with the identification of the precursor genes it was clear that they constitute a distinct group derived from a separate gene

Synonyms: - [some were earlier designated sNPFs; see (Nässel and Wegener, 2011)]

Precursor gene: The insect RYamide encoding genes give rise to precursors containing multiple peptides with an RYamide C-terminus. Seven peptides are found in *Nasonia* and two in *Drosophila* (encoded on CG40733) and *Bombyx* (Hauser *et al.*, 2010; Ida *et al.*, 2011a; Roller *et al.*, 2016).

Isoforms: Two isoforms in *Drosophila,* dRYamide-1 and dRYamide-2.

Receptor: RYamide receptors have been identified in *Nasonia* and *Drosophila* (Collin *et al.*, 2011; Ida *et al.*, 2011a). The receptors in *Drosophila* (CG5811: NepYr or RYa-R) and *Nasonia* are related to luqin receptors in other invertebrates (Bauknecht and Jekely, 2015; Ohno *et al.*, 2017; Yanez-Guerra *et al.*, 2018). The *Drosophila* NepYr had been identified quite a while ago, but the endogenous ligand was not known at the time (Li *et al.*, 1992).

Distribution: The distribution of RYamide was investigated by *in situ* hybridization in *Bombyx mori*. It is present in 20 neurons in the brain and terminal abdominal ganglion, as well as in endocrine cells of the midgut (Roller *et al.*, 2016). In the *D. melanogaster* CNS only two neurons could be found in abdominal ganglia, and these send axons to the rectal papillae of the hindgut (Veenstra and Khammassi, 2017). These authors, however, found that in some other *Drosophila* species there are several more RYamide immunoreactive neurons in the CNS (Veenstra and Khammassi, 2017).

Functions: In *D. melanogaster,* injection of RYamide-1 increases the threshold of the proboscis extension reflex, suggesting that the peptide reduces the motivation to feed (Ida *et al.*, 2011a). The distribution of RYamide in gut endocrine cells also suggests a role in gut function or signaling from the gut (Roller *et al.*, 2016). The RYamide producing neurons that innervate the rectal papillae indicate that RYamides may regulate water homeostasis

(Veenstra and Khammassi, 2017).

Related peptides: Arthropod RYamides are orthologs of luqin peptides in other invertebrates. They do not have a vertebrate ortholog (Mirabeau and Joly, 2013; Yanez-Guerra *et al.*, 2018).

5. 32. Sex peptide (SP)

First characterization: Mating triggers a change in the female behavior in many insect species. Thus, they are no longer attractive to males, are not responsive to mating and they display an increased intake of protein-rich food and egg production [see (Chapman *et al.*, 2003; Chen *et al.*, 1988; Kubli, 2003)]. In *Drosophila* the trigger of this post-mating behavior is sex peptide (SP) that is transferred to the female along with the sperm and seminal fluid (Chen *et al.*, 1988; Liu and Kubli, 2003). Sex peptide is 36 amino acids long and has curiously not been found outside the genus *Drosophila*. Its action is confined to the female fly.

Synonyms: Acp70A

Precursor gene: SP is encoded on the precursor gene CG8982 and is produced exclusively in the male accessory glands.

Isoforms: -

Receptor: The *Drosophila* SP receptor (SPR; CG16752) is shared with myoinhibitory peptides (MIP1-5; also known as Allatostatin-B1-5) (Kim *et al.*, 2010; Poels *et al.*, 2010). This MIP receptor has been identified in most studied insects (see entry for Ast-B / myoinhibitory peptide, MIP), but SP is only found in the *Drosophila melanogaster* and *D. obscura* groups and no other insects (Kim *et al.*, 2010; Poels *et al.*, 2010; Tsuda and Aigaki, 2016).

Distribution: SP is only produced by the male accessory glands. While the SP/MIP receptor is widely distributed in the CNS of both sexes, only a small set of sensory neurons in the reproductive tract, with axons entering the CNS, is critical in mediating the response to SP via this receptor (Häsemeyer *et al.*, 2009; Yang *et al.*, 2009; Yapici *et al.*, 2008).

Functions: During mating, SP bound to the sperms is transferred with the semen, and acts on the SP receptor in sensory neurons of the female reproductive tract with axons terminating in the brain and thereby triggers a long-lasting alteration of the behavior and physiology (Aigaki *et al.*, 1991; Chapman *et al.*, 2003; Chen *et al.*, 1988; Kubli, 2003). This SP-mediated switch in behavior/physiology relies on a specific set of about 2000 neurons in the CNS that is characterized by expression of the transcription factor *fruitless* (*fru)* (Rezaval *et al.*, 2012; Yang *et al.*, 2009; Yapici *et al.*, 2008). After mating and SP action, the female flies are no longer receptive to courting males. Instead they increase protein ingestion and egg laying (Aigaki *et al.*, 1991; Kubli, 2003; Rezaval *et al.*, 2012). Interestingly, SP also changes sleep behavior of the mated females (Isaac *et al.*, 2010). Mated female flies sleep less than male flies, especially during midday, to increase foraging to ensure intake of nutrients for egg development and to search for egg-laying sites. In contrast, unmated females display a male-like sleep pattern with a midday siesta. This means that mating-transferred SP induces an 8-day-long reduction (by 70%) of the daytime rest (Isaac *et al.*, 2010). Furthermore, it is known that mated females develop a strong appetite for sodium. This salt appetite is generated by a SP-mediated modulation of taste processing (Walker *et al.*, 2015).

Related peptides: SP is structurally similar (no homology) to Ast-B/MIPs (Kim *et al.*, 2010).

5. 33. Short neuropeptide F (sNPF)

First characterization: Short neuropeptide F (sNPF) as a specific neuropeptide type was clearly identified after the sequencing of the *Drosophila* genome and annotation of its peptidome (Hewes and Taghert, 2001; Vanden Broeck, 2001). The *bona fide* sNPFs are characterized by a C-terminal sequence PxLRLRFamide and range in length between 8 and 19 amino acids (although there is a 6 amino acid sNPF in *Aedes aegypti*). Before the *Drosophila* peptidome annotation there was some confusion due to the existence of longer peptide forms designated neuropeptide F (NPF) and shorter forms that were given various names, including NPF, RYamides and head peptides [see (Hauser *et al.*, 2010; Nässel and Wegener, 2011)]. Therefore, the identification of separate genes encoding distinct precursors of NPF and sNPF, and later RYamides made it possible to go back and perform a classification of a number of peptides known earlier from biochemical isolation studies.

Synonyms: Head peptide

Precursor gene: The gene encoding *Drosophila* sNPF (CG13968) identified in the genome (Hewes and Taghert, 2001; Vanden Broeck, 2001) was cloned and the precursor found to contain 4 different sNPFs (Lee *et al.*, 2004) that were confirmed by mass spectrometry, together with further processed forms (Nässel *et al.*, 2008). In *Drosophila, A. aegypti* and *Anopheles gambiae* the precursor genes also encode sNPF peptides with an RLRWamide C-terminus [see (Hewes and Taghert, 2001; Lee *et al.*, 2004; Nässel and Wegener, 2011; Vanden Broeck, 2001)].

Isoforms: Four isoforms in *Drosophila* (sNPF1-4), two of which can be processed to also give rise to shorter forms (sNPF-$1^{4\text{-}11}$ and sNPF-$2^{12\text{-}19}$)

Receptor: A receptor for sNPFs (NPFR76F or sNPFR1; CG7395) was first identified in *Drosophila* (Garczynski *et al.*, 2006; Mertens *et al.*, 2002), and later in the fire ant *Solenopsis invicta* and the mosquito *Anopheles gambiae* [see (Chen and Pietrantonio, 2006; Garczynski *et al.*, 2007; Nässel and Wegener, 2011)].

Distribution: Due to the RFamide C-terminus being in common with several other unrelated neuropeptides, *Drosophila* sNPF distribution was mapped by immuonolocalizing with an antiserum to a sequence of the sNPF precursor, and *in situ* hybridization, in *Drosophila* (Johard *et al.*, 2008; Nässel *et al.*, 2008). In *Drosophila* sNPF is expressed in numerous small interneurons in the CNS, chemosensory cells in the antennae and labial palps as well as a set of large neurosecretory cells in the brain (Nässel *et al.*, 2008). Specifically, a large subpopulation of the intrinsic Kenyon cells of the mushroom bodies express sNPF (Johard *et al.*, 2008). There are no sNPF producing gut endocrine cells, but in larval *Drosophila* a set of 4 sNPF expressing neurons in the hypocerebral ganglion send axons over the proventriculus and anterior midgut, suggesting a role in gut function (Veenstra, 2009b). In *Bombyx mori*, sNPF is also expressed in neurons of the frontal ganglion and endocrine cells of the corpora cardiaca (Yamanaka *et al.*, 2008).

Functions: Correlated with the widespread distribution of sNPF, quite a wide range of functions has been proposed in *Drosophila* and other insects [reviewed in (Nässel and Wegener, 2011)]. These include roles in food search, feeding (Lee *et al.*, 2004; Martelli *et al.*, 2017; Slade and Staveley, 2016; Tsao *et al.*, 2018), growth (Lee *et al.*, 2008b; Lee *et al.*, 2004), regulation of osmotic and metabolic stress (Kahsai *et al.*, 2010a; Kapan *et al.*, 2012), modulation of complex explorative walking behavior (Kahsai *et al.*, 2010b), modulation of olfactory inputs and olfaction guided behavior (Ko *et al.*, 2015; Root *et al.*, 2011; Tsao *et al.*, 2018), including pheromone responses (Kim *et al.*, 2016), modulation of taste responses and feeding decisions (Inagaki *et al.*, 2014), facilatory feedback in mechanosensory/nociceptive pathway (Hu *et al.*, 2017), circadian clock function (Liang *et al.*, 2017; Selcho *et al.*, 2017), sleep induction (Chen *et al.*, 2013; Kucherenko *et al.*, 2016; Shang *et al.*, 2013), olfactory reward learning (Barnstedt *et al.*, 2016; Knapek *et al.*, 2013), control of hormone release (Kapan *et al.*, 2012; Lee *et al.*, 2008b; Selcho *et al.*, 2017), regulation of juvenile hormone biosynthesis (Kaneko and Hiruma, 2014) and intestinal immune response (Shen *et al.*, 2016). It was also found that sNPF producing clock neurons (LNvs) mediate timing signals from the central clock to PTTH producing neurosecretory cells that in turn trigger production/release of ecdysone from the prothoracic glands (PG) (Selcho *et al.*, 2017). Thus, this sNPF signal mediates a coupling between the central clock in the brain and peripheral clocks in the PG cells that generates a daily steroid hormone rhythm.

Related peptides: Receptor similarity suggests that sNPF and prolactin-releasing peptide in vertebrates could be orthologs (Jekely, 2013).

5. 34. SIFamide

First characterization: SIFamide was isolated from the fleshfly *Sarcophaga bullata* (*Neobellieria bullata*) as a myostimulatory peptide (Janssen *et al.*, 1996). The sequence of SIFamides is well conserved among arthropods with the consensus C-terminus X_1X_2RKPPFNGSIFamide (Verleyen *et al.*, 2009b). In the locust *Schistocerca gregaria,* the sequence of SIFamide differs somewhat with an N-terminal extension, AAATFRRPPFNGSIFamide (Gellerer *et al.*, 2015).

Synonyms: IFamide

Precursor gene: The *Drosophila* SIFamide precursor is encoded by CG4681 (Hewes and Taghert, 2001; Vanden Broeck, 2001).

Isoforms: -

Receptor: A receptor for SIFamide (CG10823) was characterized in *Drosophila* (Jorgensen *et al.*, 2006) and in several other insects (Hauser *et al.*, 2006; Verleyen *et al.*, 2009b).

Distribution: The SIFamide distribution in the CNS of insects studied so far is well conserved. Two pairs of SIFamide expressing neurons in the pars intercerebralis (PI) can be found in all insects [see (Janssen *et al.*, 1996; Ons *et al.*, 2011; Terhzaz *et al.*, 2007; Verleyen *et al.*, 2009b)]. These neurons have extensive branches spreading throughout the brain. Their branches innervate most brain neuropils, except the *bona fide* mushroom bodies, and also invade widespread areas in the ventral nerve cord (Carlsson *et al.*, 2010; Martelli *et al.*, 2017; Terhzaz *et al.*, 2007). In cockroaches and the locust *Schistocerca gregaria,* the same types of PI neurons were detected together with several groups of smaller neurons (Arendt *et al.*, 2016; Gellerer *et al.*, 2015). In *S. gregaria* the PI neurons colocalize SIFamide and leucokinin (Gellerer *et al.*, 2015; Ludwig *et al.*, 2001). In insects studied so far, SIFamide seems to be restricted to interneurons within the CNS, and, thus, it is not likely that the peptide has hormonal or intestinal functions in those species.

Functions: In *Drosophila*, knockdown of SIFamide by targeted RNAi or ablation of the neurons producing the peptide results in male flies that are promiscuous and mate females and males with equal vigor, whereas females become much more receptive to mating (Terhzaz *et al.*, 2007). Thus, SIFamide neurons and their peptide are involved in control of sexual behavior (see below). The SIFamide receptor is expressed by a large population of neurons that also express the transcription factor fruitless and are known to be part of neuronal circuitry that control sexual behavior (Sellami and Veenstra, 2015). Thus, in *Drosophila,* SIFamide acts on neuronal circuitry that organizes mating behavior. SIFamide has also been found to promote sleep in *Drosophila* (Park *et al.*, 2014). More recently, it was shown that SIFamide neurons also are part of an extensive neuronal network that regulates feeding (Martelli *et al.*, 2017). The SIFamide neurons integrate orexigenic and anorexigenic signals to facilitate signals in chemosensory pathways, promote appetitive behavior and increase food ingestion (Martelli *et al.*, 2017). This action to increase feeding-related behavior represses reproductive behavior, suggesting that SIFamide acts as a switch between feeding and reproduction (Martelli *et al.*, 2017). The SIFamide neurons (together with DH44 expressing MNCs) have also been reported to be involved in rest-activity rhythms and sleep in *Drosophila* (Bai *et al.*, 2018; Cavanaugh *et al.*, 2014). The SIFamide neuron activity is affected by the *Neurofibromatosis 1* (*Nf1*) protein, neurofibromin, and mediates an output pathway from the clock (Bai *et al.*, 2018).

Related peptides: SIFamide is orthologous to the vertebrate Neuropeptide FF (NPFF) and Gonadotropin-inhibitory hormone (GnIH) (Jekely, 2013; Mirabeau and Joly, 2013).

5. 35. Sulfakinins (SK)

First characterization: Sulfakinins (leucosulfakinin-I and II) were first purified from the cockroach *Leucophaea maderae* and found myostimulatory on the cockroach hindgut (Nachman *et al.*, 1986). The name of the peptide is due to its sequence similarity to the mammalian peptide cholecystokinin (CCK) and its sulfated tyrosine residue (Nachman *et al.*, 1986). The sulfakinins are characterized by their C-terminal sequence YGHMRFamide. The Y residue is commonly sulfated.

Synonyms: Drosulfakinin (DSK)

Precursor gene: In 1988, a *Drosophila* gene (CG18090) that encodes two sulfakinins (drosulfakinin-1 and 2; DSK-1 and 2) was cloned (Nichols *et al.*, 1988).

Isoforms: Two sequence-related peptides in *Drosophila*, and a third peptide (DSK0) can be liberated from the precursor.

Receptor: Two DSK receptors (CG6857 and CG6881) that display similarities to mammalian CCK receptors were identified and functionally characterized in *Drosophila* (Kubiak *et al.*, 2002).

Distribution: In *Drosophila,* four pairs of DSK producing neurons can be found in the larval CNS, including a subset of the insulin-producing median neurosecretory cells, and a few additional neurons can be seen in the adult brain (Nichols and Lim, 1996; Park *et al.*, 2008; Söderberg *et al.*, 2012). Also in other insects, SKs are present in a small number of neurons in the brain (Duve *et al.*, 1994; East *et al.*, 1997).

Functions: In *Drosophila* and other insect species, sulfakinins inhibit food ingestion (Söderberg *et al.*, 2012; Yu *et al.*, 2013; Zels *et al.*, 2015) and in locusts SK also affects digestive enzyme secretion from the gut (Zels *et al.*, 2015). Furthermore, in *Drosophila* elevated DSK signaling induces hyperactivity and aggression (Williams *et al.*, 2014).

Related peptides: Gastrin and CCK in vertebrates.

5. 36. Tachykinins (TKs)

First characterization: Four peptides related to vertebrate tachykinins were isolated from the locust *Locusta migratoria* and were, thus, designated locustatachykinins (LomTKs) (Schoofs *et al.*, 1990a; Schoofs *et al.*, 1990b). TKs were subsequently identified from other insects and crustaceans and are characterized by a conserved C-terminus FX_1GX_2Ramide (X_1 and X_2 are variable residues) and consist of between 7 and 19 amino acids [see (Nässel, 1999; Van Loy *et al.*, 2009)].

Synonyms: Tachykinin-related peptides (TRPs, TKRPs), insectatachykinins, invertebrate tachykinins (InvTKs), *Drosophila* tachykinins (DTKs).

Precursor gene: The *Drosophila* TK precursor encoded by CG14734 was the first to be identified (Siviter *et al.*, 2000). From this precursor, five TKs (DTK1-5) can be cleaved. There is a putative DTK6 which is N-terminally extended and has a G to A substitution in the C-terminus: FVAVRa; this peptide has not been detected by mass spectrometry. The TK precursors in the cockroaches *Leucophaea maderae* and *Periplaneta americana* each contain 13 copies of TKs (LemTRP1-13 and PeaTRP1-13), two of which are N-terminally extended and predominantly expressed in the intestine (Muren and Nassel, 1997; Muren and Nässel, 1996; Predel *et al.*, 2005).

Isoforms: 6 sequence related isoforms

Receptor: In the 1990s, two tachykinin receptors were proposed in *Drosophila*, DTKR (Takr99D; CG7887) and NKD (Takr86C; CG6515) (Li *et al.*, 1991; Monnier *et al.*, 1992). These were not tested with endogenous TK ligands at the time. Later on, one of these (Takr99D; CG7887) was confirmed as a receptor for DTK1-5 (Birse *et al.*, 2006), whereas the NKD was characterized as the receptor of the more recently discovered natalisins, peptides with structural similarity to tachykinins (Jiang *et al.*, 2013). In the interim, NKD was found to be activated by DTK6, a peptide that displays some sequence similarities to natalisins, but not by DTK1-5 (Poels *et al.*, 2009).

Distribution: In *Drosophila* and several other insects studied, TKs are widely distributed in numerous interneurons of the CNS, sets of brain neurosecretory cells, as well as enteroendocrine cells of the midgut (Johard *et al.*, 2003; Kahsai *et al.*, 2010a; Kwok *et al.*, 2005; Muren *et al.*, 1995; Nässel, 1993; Siviter *et al.*, 2000; Skaer *et al.*, 2002; Vitzthum and Homberg, 1998; Winther *et al.*, 2003; Zhao *et al.*, 2017). These studies show that interneurons producing TKs innervate a wide range of brain neuropils, including the central complex, antennal lobes, optic lobes, and in some species, the mushroom bodies. Also in the thoracic and abdominal ganglia numerous TK-expressing interneurons can be found (Muren *et al.*, 1995; Siviter *et al.*, 2000; Winther *et al.*, 2003). In cockroaches, the stomatogastric nervous system and intestine (foregut and hindgut) are innervated by TK expressing axons (Muren *et al.*, 1995; Nässel *et al.*, 1998). TKs are colocalized with other neurotransmitters and neuropeptides in some sets of neurons in *Drosophila*: with GABA in olfactory local interneurons (LNs) (Ignell *et al.*, 2009), with sNPF and ITP in large protocerebral neurosecretory cells (Kahsai *et al.*, 2010a) and with DH31 and NPF in gut endocrine cells (Veenstra and Ida, 2014).

Functions: TKs play roles in modulation of contractions in different visceral muscles in several insect species and stimulate release of adipokinetic hormone from the corpora cardiaca in locusts [see (Nässel, 1999; Nässel *et* *al.*, 1998; Nässel *et al.*, 1995; Schoofs *et al.*, 1990b; Van Loy *et al.*, 2009)]. Many additional TK functions have been discovered in *Drosophila* with the aid of genetic approaches: presynaptic modulation of olfactory inputs in the antennal lobe (Ignell *et al.*, 2009; Ko *et al.*, 2015), central modulation of explorative walking behavior (Kahsai *et al.*, 2010b), modulation of stress responses (Kahsai *et al.*, 2010a), regulation of brain insulin producing neurons (Birse *et al.*, 2011), control of aggression in male flies (Asahina *et al.*, 2014), regulation of pheromone detection (Shankar *et al.*, 2015), and mediation of thermal nociceptive signals (Im *et al.*, 2015). In addition, TKs from midgut endocrine cells regulate lipid production in the intestine (Song *et al.*, 2014). In summary, TKs appear to display multiple distributed functions, depending on their presence in specific neuronal circuits in different parts of the brain or in endocrine cells of the intestine.

Related peptides: In salivary glands of the mosquito *Aedes aegypti* and cephalopods peptides were identified that are more similar to vertebrate tachykinins; these peptides have been referred to as invertebrate tachykinins (InvTKs), in contrast to tachykinin-related peptides or TKs (Kanda *et al.*, 2003; Satake *et al.*, 2003). The mosquito sequence is SGNTGDKFYGLMa and that of mammalian substance P is RPKPQQFFGLMa. Other related peptides: Natalisins (see separate entry), vertebrate tachykinins (including substance P, neurokinin A and B).

5. 37. Trissin

First characterization: Trissin was isolated from a purified extract of *Drosophila* on basis of activating an orphan receptor, CG34381 (Ida *et al.*, 2011b). Trissin contains six highly conserved cysteine residues that form three disulfide bridges. The trissin neuropeptide and its receptor have been lost in some insects, including *Rhodnius prolixus*.

Synonyms: -

Precursor gene: From the partial amino acid sequence of the isolated peptide the gene encoding the trissin precursor (CG14871) was cloned (Ida *et al.*, 2011b). Additional genes encoding trissin have been identified in several arthropods, including the silk moth *Bombyx mori* (Roller *et al.*, 2016).

Isoforms: -

Receptor: The receptor encoded by CG34381 was utilized for identifying the peptide (Ida *et al.*, 2011b).

Distribution: No specific mapping of trissin has been performed in *Drosophila*. However, FlyAtlas expression data suggests that the peptide is highly expressed in the central nervous system (CNS), whereas its receptor is expressed in the CNS and crop. In *Bombyx mori,* the expression of trissin has been mapped in the CNS and gut (Roller *et al.*, 2016). It is produced in two pairs of brain interneurons and four to five neurons in the frontal ganglion that co-express other neuropeptides.

Functions: The functional role of trissin is not yet known, but the expression of the peptide in the moth frontal ganglion indicates a role in regulation of foregut-midgut contractions and food intake.

Related peptides: -

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These are also included in the reference list of the main paper

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