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Peptides in insect oogenesis Cynthia Lenaerts, Emilie Monjon, Joachim Van Lommel, Lina Verbakel and Jozef Vanden Broeck



The physiological control of reproduction in insects depends on a combination of environmental and internal cues. In the adult stage, insects become sexually mature and generate gametes. In females, the latter process is designated as oogenesis. Peptides are a versatile class of extracellular signalling molecules that regulate many processes, including oogenesis. At present, the best documented physiological control mechanism of insect oogenesis is the insulin-related peptide signalling pathway. It regulates different stages of the process and provides a functional link between nutritional status and reproduction. Several other peptides have been shown to exert gonadoregulatory activities, but in most cases their exact mode of action still has to be unravelled and their effects on oogenesis could be direct or indirect. Some regulatory peptides, such as the Drosophila sex peptide, are being transferred from the male to the female during the mating process.

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Introduction

Peptides constitute a highly diverse class of extracellular signalling molecules which are implicated in the physiological control of many important biological processes, including reproduction. In animals, sexual reproduction is the most common strategy to generate offspring and to allow for rejuvenation and growth of populations. In females, the gametes (eggs or ova) are produced in the ovary via a process that is generally designated as oogenesis. In vertebrates, several peptides and glycoprotein hormones play a crucial role in the neuroendocrine control of reproduction. However, based on the current knowledge, the situation in insects is less clear and seems less uniform, given the high diversity of species in this largest class of animals. Nevertheless, the success of insects is often ascribed to their high reproductive capacity, in combination with the occurrence of a metamorphosis process that (usually) results in winged adults, which in many cases have different dietary preferences than the larval stages. Insect eggs contain a lot of yolk materials, which serve as nutritional store to support growth and development in the embryonic stage. Therefore, reproduction in insects is dependent on their nutritional and energetic state, as well as on (other) environmental cues. Sexually maturing individuals not only need nutrients and energy to support gonad development and to produce gametes, but they also exhibit energydemanding activities, such as flight, for foraging, for partner search and for finding a suitable site to deposit their eggs. Therefore, although this review will mainly focus on the current knowledge regarding the control of the oogenesis process by signalling peptides, it is important to keep in mind that this is not a stand-alone process, but is actually situated in a much broader physiological and ecological context. A generalised overview of the known peptides involved in the direct or indirect regulation of oogenesis is given in Figure 1.

The insulin signalling pathway (ISP)

Reproductive processes are functionally linked to the insect's nutritional state. The insulin signalling pathway (ISP) acts as a systemic nutrient sensor, thereby regulating the insect's metabolism in accordance with its nutritional state. For an extensive review on the ISP and its role in reproduction in insects, the reader is referred to Badisco *et al.* [1^{••}].

In insects, the ISP agonists are designated as 'insulinrelated peptides' (IRPs) or 'insulin-like peptides' (ILP) and a different number of paralogs can be found in different taxa, ranging from 1 IRP in locusts [2], over 8 ILPs in the fruit fly [3^{••}], to 30 ILPs in the silk moth [4]. The insulin receptor (IR) is a transmembrane receptor tyrosine kinase, which is capable of activating both the Ras-MAPK (mitogen activated protein kinase) and the PI3K/PKB (phosphatidylinositol-3-kinase/protein kinase B) pathways [1^{••}].

The majority of the available literature on the role of the ISP in oogenesis comes from *Drosophila* research (Figure 2). For an overview of the oogenesis process in *D. melanogaster*, the reader is referred to Bellés and Piulachs





General overview of the peptidergic regulation of oogenesis. Different peptides are, directly or indirectly, involved in the regulation of insect oogenesis. This is discussed in more detail in the text. It should be noted that not all interactions are occurring in all insect species. For instance, the stimulation of ecdysteroid synthesis by OEH, and subsequent upregulation of vitellogenesis and therefore the stimulation of oocyte growth, refers to the situation in mosquitoes. Moreover, no neuroparsins have been found in D. melanogaster. A dashed line means that the exact mode of action is not known, thus stimulation or repression might result from direct or indirect actions. Juvenile hormones, ecdysteroids and vitellogenins are also involved in the regulation of oogenesis, which is indicated with grey arrows. However, this regulation falls out of the scope of this review. Abbreviations: AT, allatotropin; AST, allatostatin; ETH, ecdysis triggering hormone; JH, juvenile hormone; NPF, neuropeptide F; sNPF, short neuropeptide F; ISP, insulin signalling pathway; CRF-DH, corticotropin-releasing factorlike diuretic hormone; MAG, male accessory gland; OEH, ovary ecdysteroidogenic hormone; AKH, adipokinetic hormone.

[5^{••}]. The ISP is involved in different stages of oogenesis. For instance, both germinal stem cell (GSC) proliferation and maintenance are controlled by dILPs via extension of the G2 and or G1 phase of the GSC cell cycle [6,7[•],8,9[•],10]. The extension of the G2 phase goes via the PI3K/PKB pathway, while that of the G1 phase is independent of this pathway [7[•],8]. The ISP also controls germline growth via the TOR (target of rapamycin) signalling pathway [6,11]. Furthermore, by acting on the cap cells, dILPs promote Notch signalling via FOXO. This Notch signalling is required for cap cell maintenance and as such GSC maintenance [9,10]. A recent study also discovered a FOXO-independent role of the ISP in GSC maintenance, namely via the adipocytes. Activation of the InR in these adipocytes results in the activation of Akt/ PKB and the subsequent inhibition of glycogen synthase kinase 3 (GSK3), which eventually results in the maintenance of the GSC [12[•]]. In addition, the ISP is also involved in the control of follicle growth. For instance, dILPs promote changes in the processing body and microtubules of the germ line cells via the TOR signalling pathway in the follicle cells [13]. The ISP is also involved in the regulation of lipid droplet accumulation in the nutrient-storing germline nurse cells during the final stages of oogenesis. Loss-of-function studies of the tumor suppressor Pten, resulted in the activation of Akt (PKB). which led to the accumulation of lipid droplets in the nurse cells [14]. Later research has shown that this effect was mediated via the TOR pathway [15]. The ISP is also important during late oogenesis, when the mitochondria in mature oocytes enter a low-activity state of respiration quiescence. Sieber et al. [17] have shown that a decrease in insulin signalling at the end of the last stage of oogenesis (stage 14) results in respiratory quiescence by remodelling the electron transport chain (ETC). This respiratory quiescence is mediated via GSK3 and results in the accumulation of glycogen, which is required for the developmental competence of the oocyte [16].

The role of the ISP in other insects is less documented. For instance, in the red flour beetle, Tribolium castaneum, loss-of-function studies of several components of the ISP have confirmed the crucial role of this pathway in oogenesis. An RNA interference (RNAi) mediated knockdown of InR, TOR or FOXO resulted in impairment of the maturation of the primary oocyte, as well as defective oocyte growth, right after the primary oocytes move to the neck region of the ovariole. RNAi-mediated knockdown of Akt, PI3K, Chico (an insulin receptor substrate) or the serine kinase S6K2 affected only the oocyte growth and not the maturation of the primary oocyte [17]. Also in the desert locust, Schistocerca gregaria, the ISP seems to play a role in oogenesis. The RNAi mediated knockdown of the IRP resulted in smaller oocytes, while no significant differences were observed for the vitellogenin transcript levels [18]. Moreover, in the German cockroach, Blattella germanica, RNAi-mediated silencing of InR and TOR resulted in reduced juvenile hormone (JH) biosynthesis by the corpora allata and vitellogenin production by the fat body, which in turn affected the oocyte growth [19,20]. On the other hand, RNAi-mediated knockdown of FOXO in starved females resulted in increased JH biosynthesis and vitellogenin production [21]. As such, it can be concluded that nutritional signals activate IH biosynthesis and vitellogenin production via the InR and TOR, thereby indirectly affecting oocyte growth. Furthermore, in the green lacewing, Chrysopa septempunctata, injections of bovine insulin promoted the ovarian growth, increased the vitellogenin abundance and improved the reproductive performance [22]. In addition, in the queenless ponerine ant *Diacamma* sp. InR and Akt are expressed in the nurse cells, oocytes and upper germinal regions of reproductiveness females (comparable to the queen in other ants), but not of worker females. This suggests that the ISP is involved in the differentiation between workers and reproductiveness [23]. Eventually, in the yellow





Overview of the regulation of oogenesis by the insulin signalling pathway in *D. melanogaster*. For more details on the regulation of oogenesis by the ISP the reader is referred to the text. *Abbreviations*: ILP, insulin-like peptide; IRP, insulin-related peptide; InR, insulin receptor; Akt, protein kinase B; SGG, Shaggy; GSK3, glycogen synthase kinase 3; FOXO, forkhead box-related transcription factor; PI3K/PKB, phosphatidylinositol-3-kinase/protein kinase B pathway; TOR, target of rapamycin; Pten, phosphatase and tensin homologue.

fever mosquito, *Aedes aegypti*, ILP3 has been shown to stimulate egg formation after a blood meal [24].

Neuroparsins and ovary ecdysteroidogenic hormone

The family of the neuroparsins contains arthropod-specific neurohormones of ca. 80 amino acids long. In locusts, neuroparsins were discovered as anti-gonadotropic factors [18,25]. On the other hand, the NP-like ovary ecdysteroidogenic hormone (OEH) acts as a gonadotropic and ecdysteroidogenic factor in mosquitoes [26]. Recently, it has been shown that OEH exerts its role via a venus kinase receptor (VKR), a receptor tyrosine kinase, which was designated as the OEH receptor (OEHR) in mosquitoes. RNAi-mediated knockdown of this receptor resulted in significantly lower ecdysteroid and vitellogenin production, leading to disabled egg formation [27[•]]. In the locust *S. gregaria*, a VKR has been identified and shown to have a gonadotropic function, but it does not seem to be as crucial as in *A. aegypti* [28].

Allatoregulatory peptides

Allatoregulatory peptides, i.e. allatotropins (ATs) and allatostatins (ASTs) [29], were first discovered for their role in stimulating and inhibiting juvenile hormone (JH) synthesis [30,31]. Since JHs act as a major regulator of reproductive physiology, such as the induction of patency in the follicular cell layer, ATs and ASTs can indirectly regulate oogenesis [32,33°,34–36]. However, these peptides are pleiotropic and they do not show the same effects in all species. For an extensive review on their role in the female reproductive physiology, the reader is referred to Van Wielendaele *et al.* [37°•].

Recently, ecdysis triggering hormone (ETH), which is known for its role in the neuropeptidergic cascade

regulating the moulting process [38,39], has been found to regulate JH synthesis in adult *A. aegypti* [40[•]]. Moreover, ETH was reported to regulate the female reproductive physiology in *D. melanogaster*. Deficiency in ETH signalling reduced JH levels, which in turn resulted in reduction of ovary size, egg production, and yolk deposition in maturing oocytes [41]. Thus, ETH seems to work as an obligatory allatotropin in adult Diptera species.

Ecdysiotropic and ecdysiostatic peptides

In addition to JHs, ecdysteroids also play crucial roles in adult female physiology, but their exact action on oogenesis is dependent on the insect species, as reviewed by Bellés and Piulachs [5^{••}]. Similarly to the allatoregulatory peptides, some peptides will indirectly affect oogenesis via their regulatory actions on ecdysteroidogenesis. The brain neuropeptide prothoracicotropic hormone (PTTH) was originally identified to stimulate ecdysteroidogenesis in the prothoracic glands of juveniles. However, there is also some evidence for a steroidogenic role in adult female tobacco hornworm, Manduca sexta [42]. As discussed earlier, OEH also indirectly affects oogenesis in mosquitoes by regulating ecdysteroidogenesis [26,43]. Furthermore, Ovary Maturating Parsin (OMP) is also characterised as a gonadotropic peptide in insects. It has been shown that this peptide can stimulate oocyte growth in two locust species, L. migratoria and S. gregaria. It was therefore assumed that the gonadotropic role of OMP is probably due to its regulatory role in ecdysteroidogenesis [44,45].

(Short) Neuropeptide F

The main role played by neuropeptide F (NPF) is the regulation of feeding and foraging behaviour. However, many other roles have been attributed to NPF, such as in reproduction, as reviewed by Van Wielendaele et al. [35]. Injection of a NPF-like peptide that had been identified in the Colorado potato beetle, Leptinotarsa decemlineata, into the haemocoel of locusts stimulated oocyte growth and maturation [46,47]. These findings were later corroborated by a study of Van Wielendaele and co-workers [48], where the opposite effect was observed upon RNAi mediated silencing of the locust NPF (NPF) precursor. Also in the kissing bug, *Rhodnius prolixus*, NPF was shown to increase egg production [49]. It is not known yet how NPF exerts these effects on oocyte development. Nevertheless, NPF was shown to have an influence on ecdysteroid titres in adult female desert locusts. In fact, RNAi mediated silencing of the NPF precursor led to a subsequent decrease in ecdysteroid levels in the haemolymph and ovaries, whereas peptide injection had the opposite effects [48]. It is possible that NPF influences oocyte development via an indirect way. Further studies are needed to analyse the mode of action.

Short neuropeptide F (sNPF) is phylogenetically distinct from NPF, despite its similar name. The first evidence

that sNPF might play a role in oogenesis in insects was the finding that the receptor is highly expressed during early stages of oogenesis in the red imported fire ant, *Solenopsis Invicta Buren*, mainly in the control of oocyte polarity and initial oocyte growth [50]. More recently, sNPF has been shown to stimulate egg production in *R. prolixus* [49].

CRF-like diuretic hormone

The CRF-like diuretic hormone (CRF-DH) is present in many insect species and plays a major role in water homeostasis by stimulating diuresis [51]. However, in *L. migratoria* and *R. prolixus* fewer and smaller eggs were observed upon injection of the peptide [$52^{\circ},53$]. The exact mode of action of CRF-DH in the latter process is still unknown, but it was suggested that this peptide might influence the nutritional state of the animal, which in turn influences reproduction [54].

Adipokinetic hormones

The adipokinetic hormones (AKHs) play an important role in carbohydrate and lipid mobilisation from the fat body during energy-demanding tasks, such as flight and reproduction [55]. There is some evidence that AKHs might be regulating the process of lipid incorporation during oogenesis in some insects, but not in D. melanogaster [56]. In G. bimaculatus, there was a substantial decrease in lipid content of the fat body which coincided with an increase in fat content of the eggs [57]. Moreover, injections of AKH in this cricket species resulted in reduction of ovary mass due to retarded oocyte maturation and a reduced number of terminal oocytes being produced. The authors concluded that egg production was indirectly inhibited by AKH via its action on energy stores in the fat body [58]. In addition, the AKH receptor was shown to be expressed in the ovaries of A. *aegypti* [59] and B. mori [60]. Moreover, in Spodoptera frugiperda, AKH II and AKH IV were localised in the germarium [61]. Nevertheless, AKH has an additional role during oocyte development in (some) insects, since it inhibits the synthesis of vitellogenins to be incorporated into the vitellogenic oocytes [62,63].

Male-derived peptides influencing oogenesis

Male accessory gland (MAG) secretions that are transferred during copulation have been shown to affect the female reproductive physiology. The best studied MAG derived factor is the sex peptide (SP) of *D. melanogaster*. It induces a range of post-mating effects in the female, such as its reproductive behaviour and the progression of oocytes through early vitellogenic stages [64[•]]. Also in *A. aegypti*, the bean weevil, *Acanthoscelides obtectucs*, and the cotton bollworm, *Helicoverpa armigera*, various MAG secretions have been shown to stimulate egg development [65–67].

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as

- of special interest
- •• of outstanding interest
- 1. Badisco L, Van Wielendaele P, Vanden Broeck J: Eat to
- reproduce: a key role for the insulin signaling pathway in adult insects. Front Physiol 2013, 4:1-16.

This paper was the last extensive review about the role of the ISP in insect reproductive physiology.

- Badisco L, Claeys I, Van Hiel M, Clynen E, Huybrechts J, Vandersmissen T, Van Soest S, Vanden Bosch L, Simonet G, Vanden Broeck J: Purification and characterization of an insulin-related peptide in the desert locust, *Schistocerca* gregaria: immunolocalization, cDNA cloning, transcript profiling and interaction with neuroparsin. J Mol Endocrinol 2008, 40:137-150.
- 3. Nässel DR, Vanden Broeck J: Insulin/IGF signaling in Drosophila
- and other insects: factors that regulate production, release and post-release action of the insulin-like peptides. *Cell Mol Life Sci* 2016, **73**:271-290.

This recent review focused on the regulatory events that are situated upstream of ISP activation by insulin-like peptides in*D. melanogaster* and other insects.

- Aslam AFM, Kiya T, Mita K, Iwami M: Identification of novel bombyxin genes from the genome of the silkmoth Bombyx mori and analysis of their expression. Zool Sci 2011, 28:609-616.
- 5. Bellés X, Piulachs MD: Ecdysone signalling and ovarian
- development in insects: From stem cells to ovarian follicle formation. Biochim Biophys Acta – Gene Regul Mech 2015, 1849:181-186.

This review gives a nice overview of the different stages of oogenesis in *D. melanogaster*.

- LaFever L, Feoktistov A, Hsu H-J, Drummond-Barbosa D: Specific roles of target of rapamycin in the control of stem cells and their progeny in the Drosophila ovary. Development 2010, 137 2451–2451.
- LaFever L, Drummond-Barbosa D: Direct control of germline
 stem cell division and cyst growth by neural insulin in Drosophila. Science 2005, 309:1071-1073.

This was the first report on the direct regulation by *Drosophila* insulin-like peptides of germline stem cell division rate, germline cyst growth and vitellogenesis.

- Hsu HJ, LaFever L, Drummond-Barbosa D: Diet controls normal and tumorous germline stem cells via insulin-dependent and -independent mechanisms in Drosophila. Dev Biol 2008, 313:700-712.
- Hsu H-J, Drummond-Barbosa D: Insulin levels control female
 germline stem cell maintenance via the niche in Drosophila. Proc Natl Acad Sci 2009, 106:1117-1121.

This paper was the first to show that also systemic factors are involved in stem cell maintenance. The authors proved that insulin signalling integrates the effects of diet and age on germ stem cell maintenance by acting on the cap cells.

- Hsu H-J, Drummond-Barbosa D: Insulin signals control the competence of the Drosophila female germline stem cell niche to respond to Notch ligands. Dev Biol 2011, 350:290-300.
- 11. Grandison RC, Wong R, Bass TM, Partridge L, Piper MDW: Effect of a standardised dietary restriction protocol on multiple

laboratory strains of *Drosophila melanogaster*. *PLoS ONE* 2009, **4**:e4067.

 Armstrong AR, Drummond-Barbosa D: Insulin signaling acts in adult adipocytes via GSK-3beta and independently of FOXO to control Drosophila female germline stem cell numbers. Dev Biol 2018, 440:31-39.

This publication showed that adipocytes, known for their endocrine and nutrient-sensing roles, are also involved in the regulation of oogenesis via the ISP. The adipocytes use distinct axes of the ISP to regulate different stages of the germ stem cell lineage.

- Burn KM, Shimada Y, Ayers K, Lu F, Hudson AM, Cooley L: Somatic insulin signaling regulates a germline starvation response in *Drosophila* egg chambers. *Dev Biol* 2015, 398:206-217.
- 14. Vereshchagina N, Wilson C: Cytoplasmic activated protein kinase Akt regulates lipid-droplet accumulation in *Drosophila* nurse cells. *Development* 2006, **133**:4731-4735.
- Gulia-Nuss M, Elliot A, Brown MR, Strand MR: Multiple factors contribute to anautogenous reproduction by the mosquito Aedes aegypti. J Insect Physiol 2015, 82:8-16.
- Sieber MH, Thomsen MB, Spradling AC: Electron transport chain remodeling by GSK3 during oogenesis connects nutrient state to reproduction. Cell 2016, 164:420-432.
- Parthasarathy R, Palli SR: Molecular analysis of nutritional and hormonal regulation of female reproduction in the red flour beetle, *Tribolium castaneum*. Insect Biochem Mol Biol 2011, 41:294-305.
- Badisco L, Marchal E, Van Wielendaele P, Verlinden H, Vleugels R, Vanden Broeck J: RNA interference of insulin-related peptide and neuroparsins affects vitellogenesis in the desert locust Schistocerca gregaria. Peptides 2011, 32:573-580.
- Maestro JL, Cobo J, Bellés X: Target of rapamycin (TOR) mediates the transduction of nutritional signals into juvenile hormone production. J Biol Chem 2009, 284:5506-5513.
- Abrisqueta M, Süren-Castillo S, Maestro JL: Insulin receptormediated nutritional signalling regulates juvenile hormone biosynthesis and vitellogenin production in the German cockroach. Insect Biochem Mol Biol 2014, 49:14-23.
- Süren-Castillo S, Abrisqueta M, Maestro JL: FoxO inhibits juvenile hormone biosynthesis and vitellogenin production in the German cockroach. Insect Biochem Mol Biol 2012, 42:491-498.
- Zhang TT, Zhang GC, Zeng FF, Liu CY, Mao JJ: Insulin-like peptides regulate vitellogenesis and oviposition in the green lacewing, *Chrysopa septempunctata*. Bull Entomol Res 2017, 107:148-154.
- Okada Y, Miyazaki S, Miyakawa H, Ishikawa A, Tsuji K, Miura T: Ovarian development and insulin-signaling pathways during reproductive differentiation in the queenless ponerine ant Diacamma sp. J Insect Physiol 2010, 56:288-295.
- 24. Gulia-Nuss M, Robertson AE, Brown MR, Strand MR: Insulin-like peptides and the target of rapamycin pathway coordinately regulate blood digestion and egg maturation in the mosquito Aedes aegypti. PLoS One 2011, 6:e20401.
- 25. Girardie J, Boureme D, Couillaud F, Tamarelle M, Girardie A: Antijuvenile effect of neuroparsin A, a neuroprotein isolated from locust corpora cardiaca. *Insect Biochem* 1987, **17**:977-983.
- Brown MR, Graf R, Swiderek KM, Fendley D, Stracker TH, Champagne DE, Lea AO: Identification of a steroidogenic neurohormone in female mosquitoes. J Biol Chem 1998, 273:3967-3971.
- Vogel KJ, Brown MR, Strand MR: Ovary ecdysteroidogenic
 hormone requires a receptor tyrosine kinase to activate egg formation in the mosquito Aedes aegypti. Proc Natl Acad Sci U S A 2015, 112:9-10.

This study showed that RNAi-mediated knockdown of the ovary ecdysteroidogenic hormone receptor in mosquitoes disables egg formation due to reduced ecdysteroid and vitellogenin production.

- 28. Lenaerts C, Palmans J, Marchal E, Verdonck R, Vanden Broeck J: Role of the venus kinase receptor in the female reproductive physiology of the desert locust, Schistocerca gregaria. Sci Rep 2017, **7**:11730.
- 29. Verlinden H, Vleugels R, Zels S, Dillen S, Lenaerts C, Crabbé K, Spit J, Vanden Broeck J: Receptors for neuronal or endocrine signalling molecules as potential targets for the control of insect pests. Adv Insect Physiol 2014, 46:167-303.
- 30. Kataoka H, Toschi A, Li JP, Carney RL, Schooley DA, Kramer SJ: Identification of an allatotropin from adult Manduca sexta. Science 1989, 243:1481-1483
- 31. Rankin SM. Stav B: Distribution of allatostatin in the adult in vitro. J Insect Physiol 1987, **33**:551-558.
- Griebler M, Westerlund SA, Hoffmann KH, Meyering-Vos M: **RNA** interference with the allatoregulating neuropeptide genes from the fall armyworm *Spodoptera frugiperda* and its effects on the JH titer in the hemolymph. *J Insect Physiol* 2008, **54**:997-32 1007
- 33. Noriega FG: Nutritional regulation of JH synthesis: a mechanism to control reproductive maturation in

mosquitoes? Insect Biochem Mol Biol 2004, 34:687-693. This review summarised the link between the nutritional status of A. aegypti and JH synthesis, via allatostatins and allatotropins. The link with reproduction was also discussed.

- Gadot M, Applebaum SW: Farnesoic acid and allatotropin 34. stimulation in relation to locust allatal maturation. Mol Cell Endocrinol 1986, 48:69-76.
- 35. Rachinsky A, Srinivasan A, Ramaswamy SB: Regulation of juvenile hormone biosynthesis in Heliothis virescens by Manduca sexta allatotropin. Arch Insect Biochem Physiol 2003, 54:121-133
- Ulrich GM, Schlagintweit B, Eder J, Rembold H: Elimination of the 36. allatotropic activity in locusts by microsurgical and immunological methods: evidence for humoral control of the Corpora allata, hemolymph proteins, and ovary development. Gen Comp Endocrinol 1985, **59**:120-129.
- 37. Van Wielendaele P, Badisco L, Vanden Broeck J:
 Neuropeptidergic regulation of reproduction in insects. Gen Comp Endocrinol 2013, 188:23-34.

This extensive review summarised the available knowledge regarding the neuropeptides involved in female and/or male reproductive physiology. For a more detailed review on some of the peptides described in the current review paper, the reader is referred to this publication

- Lenaerts C, Cools D, Verdonck R, Verbakel L, Vanden Broeck J, 38. Marchal E: The ecdysis triggering hormone system is essential for successful moulting of a major hemimetabolous pest insect, Schistocerca gregaria. Sci Rep 2017, 7:46502.
- 39. Adams ME, itňan D: Identification of ecdysis-triggering hormone in the silkworm Bombyx mori. Biochem Biophys Res Commun 1997, 230:188-191.
- Areiza M, Nouzova M, Rivera-Perez C, Noriega FG: Ecdysis 40.
- triggering hormone ensures proper timing of juvenile hormone biosynthesis in pharate adult mosquitoes. Insect Biochem Mol Biol 2014, 54:98-105.

This study identified the allatotropic role of ETH to ensure the proper timing of JH synthesis in pharate adult mosquitoes, thereby having an indirect role in female reproductive physipology.

- Meiselman M, Lee SS, Tran R-T, Dai H, Ding Y, Rivera-Perez C, 41. Wijesekera TP, Dauwalder B, Noriega FG, Adams ME: Endocrine network essential for reproductive success in Drosophila melanogaster. Proc Natl Acad Sci U S A 2017, 114:E3849-E3858.
- 42. Rybczynski R, Snyder CA, Hartmann J, Sakurai S, Gilbert LI: Manduca sexta prothoracicotropic hormone: evidence for a role beyond steroidogenesis. Arch Insect Biochem Physiol 2009, 70:217-229
- Dhara A, Eum J-H, Robertson A, Gulia-Nuss M, Vogel KJ, Clark KD, Graf R, Brown MR, Strand MR: Ovary ecdysteroidogenic hormone functions independently of the insulin receptor in the yellow fever mosquito, Aedes aegypti. Insect Biochem Mol Biol 2013, 43:1100-1108.

- 44. Van Wielendaele P, Dillen S, Marchal E, Badisco L, Vanden Broeck J: CRF-like diuretic hormone negatively affects both feeding and reproduction in the desert locust, Schistocerca gregaria. PLoS ONE 2012, 7:e31425.
- 45. Girardie J, Huet JC, Atay-Kadiri Z, Ettaouil S, Delbecque JP, Fournier B, Pernollet JC, Girardie A: Isolation, sequence determination, physical and physiological characterization of the neuroparsins and ovary maturing parsins of Schistocerca gregaria. Insect Biochem Mol Biol 1998, 28:641-650.
- Cerstiaens A, Benfekih L, Zouiten H, Verhaert P, De Loof A, Schoofs L: Led-NPF-1 stimulates ovarian development in locusts. Peptides 1999, 20:39-44.
- Schoofs L, Clynen E, Cerstiaens A, Baggerman G, Wei Z, Vercammen T, Nachman R, De Loof A, Tanaka S: Newly discovered functions for some myotropic neuropeptides in locusts. Peptides 2001, 22:219-227.
- 48. Van Wielendaele P, Wynant N, Dillen S, Badisco L, Marchal E, Vanden Broeck J: In vivo effect of Neuropeptide F on ecdysteroidogenesis in adult female desert locusts (Schistocerca gregaria). J Insect Physiol 2013, 59:624-630.
- 49. Sedra L, Lange AB: Cloning and expression of long neuropeptide F and the role of FMRFamide-like peptides in regulating egg production in the Chagas vector, Rhodnius prolixus. Peptides 2016, 82:1-11.
- 50. Lu H-L, Pietrantonio PV: Immunolocalization of the short neuropeptide F receptor in gueen brains and ovaries of the red imported fire ant (Solenopsis invicta Buren). BMC Neurosci 2011, 12:57.
- 51. Gäde G: Regulation of intermediary metabolism and water balance of insects by neuropeptides. Annu Rev Entomol 2004, **49**:93-113.
- 52. Mollayeva S, Orchard I, Lange AB: The involvement of Rhopr-CRF/DH in feeding and reproduction in the blood-gorging insect Rhodnius prolixus. Gen Comp Endocrinol 2018, 258:79-90

This paper reported on the role of CRF-DH in another insect than locusts. It demonstrated that the peptide is also involved in the control of feeding and reproduction in*Rhodnius prolixus*. The authors have demonstrated a role for CRF-DH in egg production, oviduct contraction and egg laying.

- Van Wielendaele P, Dillen S, Marchal E, Badisco L, Vanden 53. Broeck J: CRF-like diuretic hormone negatively affects both feeding and reproduction in the desert locust, Schistocerca gregaria. PLoS ONE 2012, 7:e31425.
- Van Huis A, Woldewahid G, Toleubayev K, Van Der Werf W: Relationships between food quality and fitness in the desert locust, Schistocerca gregaria, and its distribution over habitats on the Red Sea coastal plain of Sudan. Entomol Exp Appl 2008, 127:144-156.
- 55. Lorenz MW, Gäde G: Hormonal regulation of energy metabolism in insects as a driving force for performance. Integr Comp Biol 2009, 49:380-392.
- Gáliková M, Diesner M, Klepsatel P, Hehlert P, Xu Y, Bickmeyer I, Predel R, Kühnlein RP: Energy homeostasis control in Drosophila adipokinetic hormone mutants. Genetics 2015, 201:665-683
- 57. Lorenz MW, Anand AN: Changes in the biochemical composition of fat body stores during adult development of female crickets, Gryllus bimaculatus. Arch Insect Biochem Physiol 2004, 56:110-119.
- 58. Lorenz MW: Adipokinetic hormone inhibits the formation of energy stores and egg production in the cricket Gryllus bimaculatus. Comp Biochem Physiol Part B Biochem Mol Biol 2003, 136:197-206.
- Kaufmann C, Merzendorfer H, Gäde G: The adipokinetic hormone system in Culicinae (Diptera: Culicidae): molecular 59. identification and characterization of two adipokinetic hormone (AKH) precursors from Aedes aegypti and Culex aegypti. Insect Biochem Mol Biol 2009, 39:770-781.

- Shi Y, Huang H, Deng X, He X, Yang J, Yang H, Shi L, Mei L, Gao J, Zhou N: Identification and functional characterization of two orphan G-protein-coupled receptors for adipokinetic hormones from silkworm *Bombyx mori*. J Biol Chem 2011, 286:42390-42402.
- Abdel-latief M, Hoffmann KH: The adipokinetic hormones in the fall armyworm, Spodoptera frugiperda: cDNA cloning, quantitative real time RT-PCR analysis, and gene specific localization. Insect Biochem Mol Biol 2007, 37:999-1014.
- Glinka AV, Kleiman AM, Wyatt GR: Roles of juvenile hormone, a brain factor and adipokinetic hormone in regulation of vitellogenin biosynthesis in *Locusta migratoria*. *Biochem Mol Biol Int* 1995, 35:323-328.
- 63. Moshitzky P, Applebaum SW: The role of adipokinetic hormone in the control of vitellogenesis in locusts. Insect Biochem 1990, 20:319-323.

 64. Soller M, Bownes M, Kubli E: Control of oocyte maturation in
 sexually mature Drosophila females. Dev Biol 1999, 208:337-351.

This paper reported on the important discovery of the effect of a peptide derived from male accessory glands, more specifically the sex peptide (SP), which controls late oogenesis in*D. melanogaster*.

- 65. Klowden MJ, Chambers GM: Male accessory gland substances activate egg development in nutritionally stressed Aedes aegypti mosquitoes. J Insect Physiol 1991, **37**:721-726.
- 66. Huignard J, Quesneau-Thierry A, Barbier M: Isolement, action biologique et evolution des substances paragoniales contenues dans le spermatophore d'Acanthoscelides obtectus (Coleoptère). J Insect Physiol 1977, 23:351-357.
- 67. Jin Z-Y, Gong H: Male accessory gland derived factors can stimulate oogenesis and enhance oviposition in *Helicoverpa armigera* (Lepidoptera: Noctuidae). *Arch Insect Biochem Physiol* 2001, 46:175-185.