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Juvenile hormone signaling in insect oogenesis

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Juvenile hormone (JH) plays a crucial role in insect reproduction, but its molecular mode of action only became clear within the last decade. We here review recent findings revealing the intricate crosstalk between JH and ecdysone signaling with nutrient sensing pathways in *Drosophila melanogaster*, *Aedes aegypti*, *Tribolium castaneum* and *Locusta migratoria*. The finding for a critical role of ecdysis triggering hormone (ETH) in both molting and ooogenesis now also highlights the importance of an integrated view of development and reproduction. Furthermore, insights from non-model insects, especially so social Hymenoptera and termites, where JH function gradually becomes decoupled from reproduction and plays a role in division of labor, emphasize the need to consider life cycle and life history strategies when studying insect reproductive physiology.

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Introduction

Since the groundbreaking work of Sir Vincent Wigglesworth [1] juvenile hormone (JH) has become established as the principal hormone controlling reproduction in female insects. It induces vitellogenin synthesis in the fat body and promotes the opening of intercellular spaces in the follicle epithelium (patency), facilitating the selective uptake of vitellogenin protein from the hemolymph via receptor-mediated endocytosis. Most of what was known about the role of JH in adult insects until the mid-nineties has been compiled in a review by Gerard Wyatt and Ken Davey [2] and subsequently by Raikhel *et al.* [3]. These are very rich sources of information, and we refer interested readers to these.

The cornerstone for the JH-vitellogenesis paradigm in female insects was largely built on experimental evidence obtained from hemimetabolan insects, primarily Dictyoptera and Orthoptera. Their large body size was advantageous for collecting the hemolymph volumes required for JH analyses, allatectomy experiments, and for measuring JH release from corpora allata (CA) *in vitro* [4]. Furthermore, the clearly defined reproductive cycles permitted synchronized sampling.

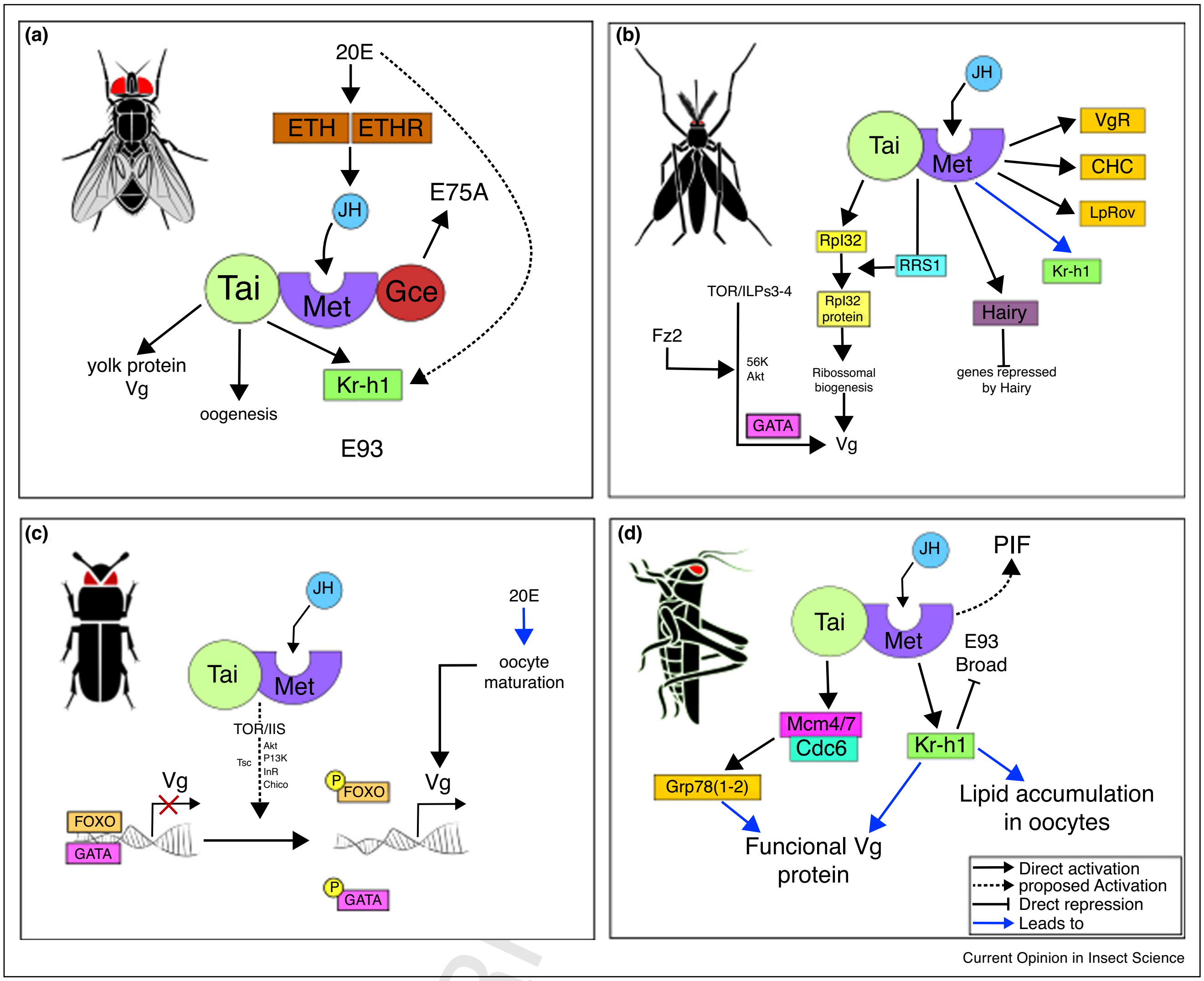
The emergent paradigm from these studies was that CA activity increases after the adult molt, leading to a first peak in adult JH hemolymph titers. This first peak, however, would not induce vitellogenin synthesis, but rather prime the transcription and translation machinery of the female fat body cells to react to a subsequent JH titer peak that would induce the first oogenic cycle (for review see [2]). This paradigm could, however, not be generalized to all insect orders, as, in the 1970s, it was shown that in the anautogenous mosquito *Aedes aegypti*, ovarian ecdysteroids, especially 20-hydroxyecdysone (20E), control vitellogenin synthesis in the fat body after a blood meal [5,6].

Varying roles for JH and ecdysteroids have since been identified across insect order and even among genera, so a unifying model for the hormonal regulation of reproduction in female insects can no longer be upheld. But this is just the charm of this puzzle, and it made us, in this review, include a discussion on the importance of reproductive timing in the life cycle of adult female insects. Nonetheless, here we will focus on the JH–vitellogenin–ovary axis, especially so since up to 2011 the JH receptor had remained enigmatic. It was only once the Methoprene-tolerant (Met) protein became established as the genuine JH receptor [7,8] that the JH response cascade became accepted as consensus among insect endocrinologists [8]. The downstream members of this cascade include Krüppel homolog 1 (Kr-h1) and E93, constituting the so called MEKRE93 pathway [9]. Hence, much of what was known about the role of JH in insect reproduction needs now to be seen under this new perspective of the molecular mode of JH action.

The JH response — vitellogenesis connection in model organisms

In Figure 1 we present an overview on recent insights on the role of JH and its integration with other signaling

Figure 1



Insights on the integration of JH mode of action with other conserved signaling pathways regulating vitellogenesis in different insects models. **(a)** In *Drosophila melanogaster*, 20E is critical for the expression of ETH and ETHR in the maintenance of high JH levels. The JH receptor (Met or Gce) forms a transcription complex with Taiman (Tai), coordinating yolk protein synthesis and its uptake by the ovary. The expression of Kr-h1 also leads to the inhibition of E93. In a unique mode of action, the Gce/Tai complex (but not Met/Tai) can activate the ecdysone response gene E75A. **(b)** In *Aedes aegypti*, vitellogenin (Vg) synthesis is activated by nutrient sensing pathways (TOR/ILPs), acting in parallel with the Wnt signaling factor Fz. This leads to the phosphorylation of downstream kinases (S6K, Akt). And subsequent activation of GATA. Vg synthesis also requires ribosomal biogenesis induced by JH trough activation of RRS1 and Rpl32. In addition to Vg expression. JH also regulates the expression of genes involved in Vg uptake (VgR, LpRov and CHC), and ovary maturation, via Hairy. **(c)** In *Tribolium castaneum*, Vg synthesis is regulated by both JH and 20E, with the latter playing a role in oocyte maturation. And in concert with TOR/IIS, JH affects the regulation of Vg expression via the phosphorylation status of FOXO and GATA, **(d)** In *Locusta migratoria*, the JH-Met/Tai complex drives the polyploidization of fat body cells via Mcm 4/7 and Cdc6, and correct folding of Vg protein via Grp78(1–2). In parallel, this complex also enhances Kr-h1 expression, resulting in lipid accumulation and enhanced Vg synthesis, while inhibiting Broad and E93. Activation of the patency factor PIF facilitates Vg uptake.

pathways, especially nutrient sensing, in *Drosophila melanogaster*, *Ae. aegypti*, *Tribolium castaneum* and *Locusta migratoria*, as the currently best-studied organisms in this context. With respect to the role of ecdysteroids, especially in mosquito reproduction, we refer the reader to the recent review by Roy *et al.* [10].

Drosophila melanogaster

The JH response cascade was first established in *D. melanogaster*, showing that JH is a high-affinity ligand for two proteins of the bHLH-PAS family of transcription factors, Methoprene-tolerant (Met) and Germ-cell-expressed (Gce) [11]. The two are very similar in amino acid sequence, and both are capable of mediating JH-

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