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Juvenile hormone and hemimetabolan eusociality: a comparison of cockroaches with termites Judith Korb¹ and Xavier Belles²



Termites are social Dictyoptera that evolved eusociality independently from social Hymenoptera. They are characterized by unique developmental plasticity that is the basis of caste differentiation and social organization. As developmental plasticity is a result of endocrine regulation, in order to understand the evolution of termite sociality it is helpful to compare the endocrine underpinning of development between termites and cockroaches. Niihout and Wheeler (1982) proposed that varying JH titers determine caste differentiation in termites. Based on current results, we extend this model by adding the importance of social interactions. High JH titers in the presence of soldiers lead to regressive development (decrease in body size, apparent regression in development), while an absence of soldiers induces (pre-) soldier differentiation. On the opposite side, low JH titers in colonies headed by reproductives result in progressive molts toward adults, while an absence of reproductives induces development of replacement reproductives. In cockroaches, transcription factors involved in JH signaling, including the adult specifier E93 (the co-called MEKRE93 pathway) regulate the morphogenetic transition between the nymph and the adult. In termites, we speculate that castes might be determined by social effects playing a modulatory action of JH in the MEKRE93 pathway.

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Introduction

How did eusociality evolve in termites? This is an intriguing question that has fascinated entomologists for decades. Especially remarkable is the fact that this

evolution proceeded in the context of a hemimetabolan mode of development, which is apparently simpler and morphogenetically more constrained in comparison with the holometabolan context, in which the social hymenopterans, ants, wasps and bees, evolved. Two recent developments can help to approach the above question with a new light. One is the robust phylogenetic analyses that definitively place termites as sister group of cockroaches [1,2[•]]. Thus cockroaches are the best non-eusocial insect clade to be compared with termites in order to obtain information about the evolution of sociality in the latter group. The other is the recent elucidation of the main players of the molecular action of juvenile hormone (JH) [3[•]], as JH appears to be an important factor in the determination of the different termite castes [4^{••},5,6].

Recent robust phylogenetic reconstructions of Dictyoptera give the topology: (mantises, (other cockroaches, (cryptocercid cockroaches, termites)) [1]. This indicates that while the classic suborders Mantodea (mantises) and Isoptera (termites) are monophyletic, Blattodea (cockroaches) is polyphyletic. Indeed, termites have been considered an infraorder of Blattodea [7]. Thus, the reference non-social group to study the evolution of eusociality in termites is cockroaches. In this group there are relevant data on the development, reproduction and physiology of JH in species of Blattidae (Periplaneta americana, Blatta orientalis), Ectobiidae (Blattella germanica) and Blaberidae (Diploptera punctata, Nauphoeta cinerea, Leucophaea maderae) [8-11]. Unfortunately, there are no data available on Cryptocercus spp. (wood-eating and subsocial cockroaches), which is the sister group of termites [1], and thus the phylogenetically more appropriate reference group. Concerning termites, relevant information is mainly available for lower termites: Zootermopsis nevadensis, Hodotermopsis sjostedti, Kalotermes flavicollis, Cryptotermes secundus, Reticulitermes speratus, and Reticulitermes flavipes [5,12–19]

The gradual postembryonic development of cockroaches: life cycle and JH

As typical in hemimetabolan species, the first nymphal instar of cockroaches already has an adult body plan. Thus, successive molts essentially promote increase in size (Figure 1a). The number and duration of nymphal instars are variable, from 4 or 5 to 11 or 12 instars, depending on the species [20]. However, some species have a very fixed number of nymphal instars, as in the case of *Blattella germanica*, that always has five or six, depending on the strain [21]. Quantitative differences in





Archetypal developmental pathways of (a) cockroaches, (b) wood-dwelling termites (here Kalotermitidae), and higher termites. (a) In cockroaches, winged reproductives develop from eggs after they have passed through 4–6 nymphal instars. These instars can molt progressively, stationarily and saltatorily (12). (b) In wood-dwelling Kalotermitidae, individuals follow a linear development that results in totipotent 'workers' which develop into one of three terminal castes: winged reproductives, neotenic reproductives and soldiers. The 'workers' comprise generally two larval (without wing buds) and 1–5 nymphal (with wing buds) which can molt progressively, stationarily, saltatorily, and *regressively* (12)). Worker instars develop progressively (13) from two dependent larval instars which do not function as workers. (c) Higher termites (Termitidae) are characterized by a bifurcated development: Winged reproductives develop progressively, generally via 5 nymphal instars, along the nymphal pathways. Workers and soldiers develop progressively via larval instars along the apterous pathway. Which pathway an individual follows is determined already in the egg or the 1. larval instar.

development are associated with environmental conditions, like temperature, possible injuries, water or food availability or quality [22]. Interestingly, both stationary and saltatory molts have been reported in the woodfeeding cockroach *Panesthia cribrata* [23] and even in the anthropophilic and omnivorous *Periplaneta americana* [24], although the physiological or endocrinological basis of these molts is unknown. The transition from last nymphal instar to adult involves the morphogenesis of adult structures like external genitalia, tegmina (mesothoracic hardened wings with a protective role), membranous wings (metathoracic membranous wings with a flying role), and tergal glands in males. Hormonal patterns and functional genomic experiments show that JH represses adult morphogenesis, in pre-adult stages. At the beginning of the last

Patterns of Juvenile hormone concentration in the haemolymph in *Cryptotermes secundus* and *Blattella germanica*, and the MEKRE93 pathway. (a) JH titers measured in different nymphal instars (from N1 to N5) and in adult alates (not-yet reproducing winged reproductives) of *C. secundus*; data are from [38]. (b) JH titers measured in the two last nymphal instars (N5 and N6) and in adult females of *B. germanica* in the first reproductive cycle; data are from [57]. The inset shows the MEKRE93 pathway, which explains the molecular action of JH in metamorphosis [25**]. The high levels of JH in the adult female sustain vitellogenin production and promote patency in the first gonadotrophic cycle; 7c means 7-day-old adult female, with the basal oocyte chorionated [58].

nymphal instar, JH levels drop, which determines that the next molt will be the imaginal one (Figure 2). At molecular level, the regulatory axis of the action of JH in metamorphosis is very simple and based on the MEKRE93 pathway [25^{••}]. JH binds to *Methoprene-toler-ant (Met*, the JH receptor) and the complex induces the expression of *Kruppel-homolog 1 (Kr-h1)*, the transducer of the antimetamorphic signal of JH. Essentially, the antimetamorphic action is exerted by repressing the expression of *E93*, the master trigger of metamorphosis

[3°,25°,26] (Figure 2). If JH or JH signaling is depleted in penultimate or antepenultimate nymphal instars, then a precocious adult molt is triggered, respectively, after the next one or two molts [27–29]. As a central molecular regulator, IIS (insulin/insulin-like growth factor signaling) is involved in JH production and vitellogenic signaling in adults (see below). However, nothing is known about a possible interplay of IIS pathway and JH during nymphal development and metamorphosis of cockroaches.

The polymorphic postembryonic development of termites: life cycle and JH

In termites, juvenile postembryonic development proceeds through larval (without wingbuds) and nymphal (with wing buds) instars (Figure 1) [6,30]. During nymphal development, cockroaches have the wing forming tissue hidden in cuticle pockets in the latero-posterior side of the meso-notum and metanotum. The number of instars in termites varies between species. In lower termites (all termite families except Termitidae) the development is highly flexible (Figure 1b: linear pathway). Workers can comprise a number of larval and nymphal instars, and are able to develop into other castes. Especially in the wood-dwelling Archotermopsidae and Kalotermitidae, workers, which are also called pseudergates (sensu lato), comprise all stages after the third larval instar. They are totipotent immatures that differentiate into one of three terminal castes: Firstly, sterile soldiers, secondly, winged reproductives that disperse, and thirdly, neotenic replacement reproductives that develop within the natal nest, often when the current reproductives die or become unhealthy. Conversely, the development in higher termites (Termitidae) is relatively rigid and different castes often develop from defined instars. Workers and soldiers generally develop from a given larval instar (Figure 1c: apterous pathway) and are often arrested in further development. In some species, soldiers develop from workers. Winged sexuals, that disperse and found a new nest as primary reproductives, develop after a defined number of nymphal instars (normally 5) (Figure 1c: nymphal pathway).

The developmental plasticity of lower termites is realized through an unparalled diversity of molting types. In addition to the progressive, stationary and saltatory development that already occurs in cockroaches, termites have regressive molts during which body size decreases and, for instance, wing buds regress. Also the two synapomorphic castes that distinguish lower termites from cockroaches, the soldiers and neotenic reproductives, result from unique molting types. Soldiers develop via a presoldier instar [5]. Neotenic reproductives prematurely develop reproductive organs — generally after a single molt — without passing through all nymphal stages and after a shortened intermolt period [19,31].

In insects, postembryonic development is largely regulated by JH. In cockroaches, JH has a simple repressive role of adult morphogenesis [9,25^{••}]. In termites, seminal work in the 1950s and 1960s (summarized in [19]) lead to the model of Nijhout and Wheeler [32], who proposed that different JH titers during an intermolt period could trigger different molting types (Figure 3). Accordingly, there are three JH sensitive periods between two consecutive molts. Continuously high JH titers result in soldier development, while continuously low JH titers result in imaginal development. Varying JH titers trigger neotenic

Figure 3

JH and development in termites. Model proposed by Nijhout and Wheeler (1982) to account for the developmental plasticity of lower termites [adapted [38]]. They hypothesized that varying JH titers during three sensitive periods between two molts determine the subsequent molting type of a worker. Continuously high or low titers result, respectively, in pre-soldier/soldier differentiation or development into winged imagoes. Titers that vary during the inter-molt period account for neotenic and continued worker development.

and worker development. However, this model is incomplete as it does not distinguish the different worker molting types such as progressive or regressive development. It also still remains largely untested, as we generally lack period-specific JH data, and only slowly are we beginning to understand how JH regulates molting types and caste development in termites [4**,5] (Figure 3).

Concerning lower termites, in the case of soldiers, high JH titers indeed trigger soldier development [33] (Figure 4). Challenging the Nijhout and Wheeler model, JH may not be constantly high but only at the end of the intermolt period [13]. High JH titers have been linked to low expression of hexamerin genes [34–36] and high expression of a cytochrome P450 gene in the CYP15 family [37]. In cockroaches and locusts, CYP15A1 orthologs encode a JH epoxidase that catalyzes the final step in JH biosynthesis [38]. This implies that the termite CYP15 gene is involved JH synthesis that leads to soldier differentiation.

Similarly, regressive molts have been linked to high JH titers, along with an extended intermolt period [12,39] (Figure 4). One possible explanation to differentiate between (pre)soldier and regressive development is social effects. It has been repeatedly shown that the presence of soldiers inhibits further soldier development [5,19]. Accordingly, as long as enough soldiers are present, individuals with high JH titers develop regressively, while without soldiers they proceed along the soldier pathway. JH-induced soldier differentiation seems to

 $JH \times$ social interaction model. Based on current data, which are limited in that they do not address period-specificity and mainly cover the period directly before a molt, we propose an extension of the Nijhout/Wheeler model that includes social interactions. It addresses only the period before a molt. (a) JH titers and terminal caste differentiation. In the absence of soldiers and reproductives (indicated by the lightning bolts), high and low JH titers, respectively, result in the differentiation of soldiers and neotenic reproductives. (b) JH titers and postembryonic development. In the presence of soldiers and reproductives, high and low JH titers, respectively, lead to regressive and progressive molts.

be connected to the IIS pathway [40[•]]. JH-analoginduced soldier differentiation leads to an upregulation of several central IIS genes (*InR*, *FOXO* and *PKB/Akt*) during soldier-specific mandible elongation. As the IIS pathway is generally acting upstream of JH in insects, the results imply that a feedback loop between IIS and JH may exist in termites.

The differentiation of neotenic reproductives from worker instars is generally associated with an absence of same-sex reproductives, a shortened intermolt period and may be linked with low JH titers (Figure 4) [19,31]. If JH titers are constantly low during neotenic development, this may challenge part of the Nijhout and Wheeler model. Although period-specific data are lacking (Figure 3), low JH titers in the presence of healthy reproductives can trigger progressive development [39]. Hence, as in soldier development, JH titers together with social effects seem to determine whether a terminal caste does or does not develop, and may thus explain molting type diversity in lower termites. We propose to extend the Nijhout and Wheeler model by including social interactions (Figure 4).

The gonadotrophic role of juvenile hormone in adult cockroaches

In adult female cockroaches, JH is produced at much higher amounts than in nymphs (Figure 2). This is related to two important JH roles: inducing vitellogenin production and promoting patency in the basal oocyte [10]. Patency is the process by which large intercellular spaces are formed between follicle cells [41]. Induction of vitellogenin expression in the fat body is very rapid (after 2 hours of treatment *in vitro*), which would suggest that it

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is direct [42]. However, it seems that the action is mediated by protein factors, given that treatment with cycloheximide, a protein synthesis inhibitor, impairs the hormonal effect [43]. Recent evidence obtained in B. germanica indicates that IIS signaling is needed for JH production, and that JH action on vitellogenin production in the fat body is mediated or potentiated by the IIS pathway [44]. These results are reminiscent of those observed in the beetle Tribolium castaneum [45]. In any case. Met. the IH receptor in the antimetamorphic action of JH, is also needed to transduce the gonadotrophic signal of JH, as has been shown in D. punctata [46] and B. germanica [47]. The high levels of JH observed (Figure 2) might be required to induce patency, given that only low amounts of JH are needed to trigger and sustain vitellogenin production [43]. Patency facilitates the access of vitellogenin to the oocyte membrane, where it is then internalized into the oocyte through a specific vitellogenin receptor [48]. Recent data obtained in locusts points to another still uncharacterized factor (Patency Inducing Factor or PIF) as the direct inducer of patency, although JH would still have the role of amplifying the effect of PIF [49].

The role of juvenile hormone in adult termites

The role of JH in adult termites seems to be similar to that in cockroaches, although less information is available. Reproducing queens have generally high JH titers (reviewed in [4^{••}]) and this has been linked to increased vitellogenin expression [14], also likely mediated via *Met* and the IIS pathway [50]. Interestingly, a doubling of DNA content through endoploidy in the fat body was recently found in one termite species [51]. This may contribute to the high fecundity of some termite species, although similar duplications also exist in some solitary insects [51].

In social Hymenoptera, vitellogenins (Vgs) have also been linked to social functions. For instance, in the honeybee, Vg is involved in division of labor among workers (nurse versus forager bees) and probably immune priming [52,53]. This may be linked to duplications of Vg genes in ants (but not in the honeybee, which has only one Vg gene) [54]. As termites also have several Vg genes which are differentially expressed between castes [55[•]] this may imply a convergent 'evolutionary exploitation' in both major social insect lineages [56].

Body conditions and development

In lower termites, even within species, the duration of the intermolt period is highly variable and lasts several weeks (in C. secundus: mean about 2 months; [39]) (Figure 2). In cockroaches, the intermolt period can be considerably long and variable, but in species of relatively small size, like B. germanica, its lasts between 3 and 8 days, in favorable conditions [21] (Figure 2). The long intermolt periods of termites may be due to their nitrogen-poor wood diet. At least in C. secundus, inter-individual variation in the length of intermolt periods correlates with molting type [39]. In Drosophila melanogaster molts are induced when individuals/cells reach a certain weight/ size [57]. Assuming that individuals in good body conditions (e.g. more storage proteins) develop and reach a size threshold faster, we additionally propose that such individuals develop progressively or into neotenics, as they have shorter intermolt periods. By contrast, individuals in poor body conditions follow regressive/soldier development, which is characterized by a long intermolt period. These two hypotheses are clearly testable.

Conclusions and prospects

The summarized data suggest that the role of JH in the adult female of (at least) lower termites and cockroaches is very similar and it is typical for insects, that is, high JH titers are linked to vitellogenin production and thus oocyte growth and embryo viability. The extreme diversity of molting types that underlies the differentiation of synapomorphic termite castes and hence build the molecular basis of termite social evolution, might be linked to a 'social exploitation' of endocrine signatures. Based on current results, we extend the Nijhout and Wheeler model [32] and propose that varying JH titers together with social effects determine postembryonic development and terminal differentation (Figures 3 and 4). High JH titers in the presence of soldiers lead to regressive development, while an absence of soldiers induces (pre-) soldier differentiation. On the opposite side, low JH titers in colonies headed by reproductives result in progressive molts while an absence of reproductives induces neotenic development. In turn, we speculate that social effects might modulate the expression of the transcription factors

involved in JH signaling (like Kr-h1or Broad Complex), as well as that of E93, an adult specifier in cockroaches [25^{••},26], thus contributing to caste determination. Practically nothing is known about the mechanisms transducing the JH signal, the MEKRE93 pathway [25^{••}], in the situations determining the different castes. Therefore, further studies addressed to cover this gap of information can provide new insights about the interplay of social effects and JH that appear to be crucial in termite polyphenism. Together with new-omics studies that reveal the genetic underpinning of termites' developmental plasticity, this will pave the way for understanding how termites became social cockroaches.

Conflict of interest statement

We declare that we have no conflict of interest.

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