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Ties between Aging Plasticity and Reproductive Physiology in Honey Bees (*Apis mellifera*) Reveal a Positive Relation between Fecundity and Longevity as Consequence of Advanced Social Evolution

Olav Rueppell^a, Denise Aumer^b, and Robin F.A. Moritz^b

^aUniversity of North Carolina at Greensboro, Department of Biology, Greensboro, NC, USA

^bInstitut für Biologie, Martin Luther Universität Halle-Wittenberg, Halle/Saale, Germany

Abstract

Honey bees (*Apis mellifera*) are the best studied model of aging among the social insects. As in other social insects, the reproductive queen far outlives her non-reproductive workers despite developing from the same genome in the same colony environment. Thus, the different social roles of the two female castes are critical for the profound phenotypic plasticity. In several special cases, such as the reproductive workers of *Apis mellifera capensis*, within-caste plasticity enables further studies of the fecundity – longevity syndrome in honey bees. At present, molecular evidence suggests that a reorganization of physiological control pathways may facilitate longevity of reproductive individuals. However, the social role and social environment of the different colony members are also very important and one of the key future questions is how much social facilitation versus internal regulation is responsible for the positive association between fecundity and longevity in honey bees.

Introduction

Among social insects, the Western Honey Bee *Apis mellifera* (L) has been studied in most detail due to its long affiliation with humans and contemporary ecological and economic importance. Honey bees live in large, perennial colonies headed by a single queen that produces all other colony members. Males (=drones) exclusively serve reproductive functions and are usually produced only in the mating season. The remaining colony members are female workers that fulfil all non-reproductive tasks in the colony, ranging from nursing and nest maintenance to food processing and foraging [1]. Workers exhibit a typical age-based behavioural progression from tasks in the nest centre to outside activities but remain behaviourally plastic and fulfil sets of different tasks at all ages [2]. Colony reproduction occurs via swarming when the mother queen departs her nest with a part of the

Corresponding Author: Olav Rueppell, olav_rueppell@uncg.edu.

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existing workers to establish a new colony before the next generation queen has emerged to take over the existing nest [1]. Mating occurs at the beginning of the queen's life with multiple males to give rise to genetically diverse colonies despite the strict monogyny of the species.

Female eggs are bi-potent and early larval nutrition triggers alternative queen or worker development via DNA methylation changes [3]. A queen develops 25% faster and grows about 25% heavier than typical workers [1]. The most significant distinction is the functional reduction of the reproductive tract in workers compared to queens: worker ovaries are usually less than 10% of the queen ovary in size and they lack the capability to mate and lay fertilized eggs. Similar to many other social hymenoptera, the workers of honey bees are restricted to laying haploid male eggs and do so only under exceptional circumstances [4]. Importantly, honey bee queens have been recorded to live for several years, much longer than the normally non-reproductive workers of their colony [5].

Long-lived, Reproductive Specialists

Although there are some costs of mating for queens [6], the reproductive role coincides with a longer life span. Honey bee queens mature and can lay up to 2000 eggs per day, which corresponds roughly to the body weight of the queen herself. The functional role of the queen is largely restricted to this reproductive function. The queen signals her fertility status with a set of glandular secretions, the queen pheromones [7] and workers may replace her if the pheromone profile is compromised. Studies indicate that queens can live several years but it is unclear how many actually do [5], especially in recent years of declining honey bee health. The development, maintenance, and physiological activity of the large queen ovary is either not costly or is overcompensated by other factors. Ovary grafts to increase ovary size of workers did not increase acute mortality but led to an earlier onset of foraging [8], which indicates that role-dependent mortality costs of large ovaries may exist. One compensatory factor that prolongs queen life may be the lack of foraging activity in honey bee queens. The metabolic rates during foraging flights are energetically much more demanding than the oxidative stress generated by egg laying [9,10]. Workers suffer the metabolic costs of foraging flights as well as predation risks. Queens only participate in flights for mating and in subsequent years for brief swarming events. In addition, queens are fed with royal jelly, a special diet with high protein content, throughout their life time [11]. In contrast, workers feed on pollen, which is difficult to digest [12] and requires repeated defecation flights, whereas the queen can stay protected in the nest.

Worker Life History Plasticity

The regular age-based division of labour of honey bee workers may have evolved in response to aging and mortality patterns [13]: Proximately, external mortality and internal physiological re-organization lead to higher mortality [14] and faster functional senescence [15] in foragers, although inside tasks, such as brood care, also have mortality costs [16]. Honey bee workers display a wide range of life expectancies, dependent on the rate of their behavioural ontogeny, which in turn is influenced by social environment, such as colony age composition [17] and size [18], and external environment, such as season [19,20]. Recent

life expectancy estimates of honey bee workers can vary from 18 to 30 days in one experiment [21], but earlier studies report higher life expectancies, ranging from 20 to 50 days [9] or even 28 to 154 days across multiple seasons [20]. Low food reserves and other forms of stress can accelerate the behavioural progression towards foraging through physiological control circuits (see below), and pheromone signals emitted by brood [22] and the queen [23] also influence the onset of foraging. Despite intensive functional genomic studies that reveal large shifts in neuronal state [24], it is not quite clear how these factors interact. Under special circumstances, the transition from in-hive tasks to foraging can also be reversed [25], which results in physiological rejuvenation [26,27] and presumably an extension of life, although the latter has never been directly shown.

Reproductive Workers

Although worker sterility is the rule, workers can activate their ovaries to produce offspring. This usually happens whenever the queen is lost and cannot be replaced (Bourke 1988). Reproductive workers experience lower mortality rates [21], although they do not live the degree of queens, and functional genomic studies suggest that the differences between normal and reproductive workers are much smaller than between workers and queens [28]. Rarely worker reproduction can be observed in the presence of the queen, which is known as the ‘anarchic syndrome’ [29]. In the extreme, laying workers can turn into pseudoqueens [30]. These pseudoqueens do no longer engage in worker tasks, but instead they behave and are treated like a queen [30]. However, their reproductive success is limited because they usually only reproduce up to ten days [31].

The pseudoqueen phenotype is most extreme in the Cape honey bee, *A. m. capensis*, where laying workers can develop into individuals living up to five months whereas foraging workers have a normal lifespan of a few weeks only [31]. These pseudoqueens can even act as social parasites by invading foreign colonies, killing the resident queen, and establishing themselves as reproductives [32]. In the first days after invasion there is a high risk of being killed by the host workers but once established, the host workers treat these workers as a fully functional queen with no phenotypic indications of senescence [31]. Due to an incomplete meiosis, workers of *A. m. capensis* produce diploid female offspring [= thelytoky, 33,34]. This trait has been repeatedly suggested to be controlled by a single recessive locus [35–38]. More recently the transcription factor *gemin*i was suggested to be the controlling gene [36]. But although *gemin*i controls ovary activation and queen pheromone production (Jarosch et al. submitted) it does not cause thelytoky [39, Aumer et al. submitted]. The simple mode of inheritance based on a single gene with two allelic forms, one for fecundity and one for sterility, in combination with the evolution of social parasitism can be used as an exceptional test system for studying the trade-off between fecundity and longevity by comparing individuals of the same caste with the same physiological constraints: the ones short-lived sterile altruistic workers, the others long-lived highly fecund social parasites. Both longevity comparisons and reproduction manipulations by using queen pheromones that can inhibit pseudoqueen reproduction at various stages [40] can experimentally be implemented.

Physiological Regulation of Longevity

The alternative developmental trajectories of queen- and worker-destined larvae are proximally caused by large scale gene expression differences [41]. In addition, the faster queen development is fuelled by higher mitochondrial activity [42], which may provide a cellular mechanism for the longevity of queens: In the light of similar mass-specific metabolic rates [43], more mitochondria may make queens less susceptible to the toxic by-products of the oxidative phosphorylation pathway because a higher mitochondrial redundancy reduces oxidative stress and makes cells more resistant to it. This reduced stress hypothesis is compatible with findings that the upregulation of classic antioxidant defence genes seems not to be responsible for the increased life expectancy of honey bee queens [44]. However, in honey bees the egg yolk protein vitellogenin serves an important antioxidant function [45] and might be partly responsible for the concomitant longevity and reproductive specialization in queens [46,47].

In most insects, juvenile hormone triggers reproductive activation and expression of egg yolk precursor proteins [48], but this regulatory link is reversed in honey bees where juvenile hormone and vitellogenin have a mutually suppressive relationship that regulates social behaviour and life history [49,50]. As a key reproductive protein, vitellogenin is much more expressed in queens, where it may exert its protective effect against oxidative stress [47] in addition to serving its role in provisioning the maturing eggs. Interestingly, the relation between nutrition and insulin-like signalling, a major regulator of life expectancy throughout animals [51], might also be inversed in honey bees [47]. The abundant food supply that honey bee queens experience during development and adulthood may not lead to a down-regulation of longevity-assurance genes via JH and insulin-like signalling. Thus, molecular studies suggest some inversions in the regulatory circuits that control life history and aging in most other animal species in a conserved fashion [52]. The coincidence of these physiological differences and the unusual, positive association between reproduction and longevity supports the general hypothesis that internal, physiological mechanisms support the unique, long-lived stem cell function of honey bee queens and presumably other social insect reproductives [53].

Social Evolution of Individual Life Expectancy

Advanced social evolution in honey bees has shifted the focus of selection from the individual to the colony level and many traits can be understood as colony-level adaptations [54]. Colony resource allocation toward individuals influences their life expectancy but may not be selected to maximize the lifespan of all colony members [46]. Under specific circumstances, colony members even sacrifice their life in defence of their colony [55]. Such sacrificial behaviour is only observed by non-reproductive individuals of social insects and may be regarded as equivalent to the regular deaths of somatic cells of any multicellular organism in defence against environmental insults [56] or pathogens [57]. Just like somatic cells, the non-reproductive workers are disposable for the larger unit of selection, in contrast to the reproductive individuals.

The honey bee queen has been compared to the gonad of the colony super-organism [58] but it may be more analogous to a universal stem cell because the queen produces not only the next generation of sexual males and females, but also the non-reproductive workers to grow and replace the somatic portion of the colony. In multicellular organisms stem cells are particularly protected [59] and by analogy, we would also expect mechanisms that particularly protect the longevity of the honey bee queen. Such adaptations lie at the centre of the positive association between fecundity and longevity and their study may shed light on the evolution of aging more generally. The initial key question in our quest for understanding the high fecundity/longevity syndrome of social insect queens is how much of it can be attributed to reorganization of internal physiological mechanisms and how much is due to social facilitation comprised of external factors, such as behavioural interactions and environment [52].

As described above, the control circuits connecting reproduction with the major hormone and growth regulatory processes seem to have been fundamentally altered in honey bee social evolution [52, 60]. This rewiring may provide a proximate explanation for the positive relation between fertility and longevity and may be reflected more widely in age-related molecular changes, as recently described in the ant *Cardiocondyla obscurior* [61]. However, these intrinsic adaptations have presumably been enabled by the social environment during social evolution. Honey bee workers feed queens with glandular secretions that provide a direct resource transfer to the queen. Workers also protect the queen by physical defence and grooming behaviour. In addition, the society reduces mortality of its members by building a physical structure that provides a safe, homeostatic environment, which explains in part the difference in mortality of pre-foraging and foraging workers [14]. Although we do not exactly know which specific factors are important, these combined social effects enable the longevity of a few select individuals externally, in addition to internal changes but studies of the relative importance of this social facilitation of queen longevity are still needed in honey bees.

Conclusions

Due to the phenotypic plasticity and genotypic diversity, honey bees provide several interesting experimental opportunities to pursue the study of the relation between fecundity and longevity within and between castes (Figure 1). Molecular mechanisms of longevity regulation may be reversed or preserved [62]. In particular, the pseudoqueen phenomenon of *A. m. capensis* provides an exceptional test system to investigate the fecundity/longevity relation in honey bees by comparing long-lived reproductive workers with short-lived sterile workers. At present, it appears that a combination of social facilitation and internal reorganization of physiological pathways is responsible for the reversal of the concurrence of the high reproductive rate and exceptional longevity in honey bee queens but more studies are needed.

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Highlights

- Long-lived, reproductive honey bee queens outlive usually non-reproductive workers.
- Worker longevity in honey bees is primarily driven by age-dependent division of labour.
- Physiology and social facilitation contribute to longevity of honey bee queens
- Honey bees are excellent for studying the relation between fecundity and longevity.

Figure 1.

Depending on resources, development of a fertilized egg leads to a short-lived, sterile worker or a long-lived reproductive queen phenotype. In the absence of reproductive inhibition from a queen, adult workers can become reproductively active which have an intermediate life expectancy, although only workers of the Cape honey bee can produce diploid eggs. White arrows indicate benefits, such as behavioural interactions, resource transfers, or protection, that may explain a proximate “social facilitation” of the longevity of reproductive individuals.