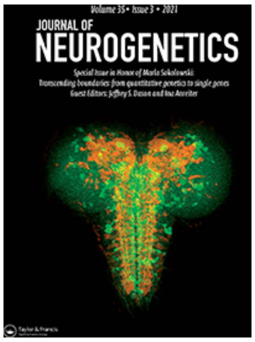

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REVIEW ARTICLE

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The *foraging* gene as a modulator of division of labour in social insects

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ABSTRACT

The social ants, bees, wasps, and termites include some of the most ecologically-successful groups of animal species. Their dominance in most terrestrial environments is attributed to their social lifestyle, which enable their colonies to exploit environmental resources with remarkable efficiency. One key attribute of social insect colonies is the division of labour that emerges among the sterile workers, which represent the majority of colony members. Studies of the mechanisms that drive division of labour systems across diverse social species have provided fundamental insights into the developmental, physiological, molecular, and genomic processes that regulate sociality, and the possible genetic routes that may have led to its evolution from a solitary ancestor. Here we specifically discuss the conserved role of the *foraging* gene, which encodes a cGMP-dependent protein kinase (PKG). Originally identified as a behaviourally polymorphic gene that drives alternative foraging strategies in the fruit fly *Drosophila melanogaster*, changes in *foraging* expression and kinase activity were later shown to play a key role in the division of labour in diverse social insect species as well. In particular, *foraging* appears to regulate worker transitions between behavioural tasks and specific behavioural traits associated with morphological castes. Although the specific neuroethological role of *foraging* in the insect brain remains mostly unknown, studies in genetically tractable insect species indicate that PKG signalling plays a conserved role in the neuronal plasticity of sensory, cognitive and motor functions, which underlie behaviours relevant to division of labour, including appetitive learning, aggression, stress response, phototaxis, and the response to pheromones.

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foraging gene; sociality; insects; behaviour; division of labour

Introduction

Animal social grouping is common because it increases the fitness of individuals by, for example, maximizing their access to resources and providing improved defences against predators (Wilson, 1987). Some of the most derived forms of sociality are exhibited by species of eusocial insects in the orders Hymenoptera (ants, bees, wasps) and Isoptera (termites), which together are estimated to represent more than 30% of the global animal biomass (Hölldobler & Wilson, 2009). All social insect colonies exhibit reproductive division of labour, in which majority of a colony is comprised of sterile female workers and just one or few reproductive individuals (the "queen" in social Hymenoptera and the "royal couple" in termites) (Oster & Wilson, 1978). The sterile workers, in turn, self-organize to become specialized in different tasks that are necessary for the growth and maintenance of the colony such as foraging, brood care and colony defence (Corona, Libbrecht, & Wheeler, 2016; Gordon, 2016; Leitner & Dornhaus, 2019). Although division of labour among workers is common across many different social insect taxa, different species show varying levels of individual specializations. At one extreme, workers might exhibit almost no task specialization, while at the other extreme workers might differentiate into developmentally-determined morphological castes (Oster & Wilson, 1978) (Figure 1).

Despite the overwhelming complexity associated with insect sociality and the regulation of division of labour, the evolutionary emergence of division of labour systems across different social insect species most likely depended on the co-option of existing sensory pathways, and associated modulatory neural circuits, to generate differential behavioural syndromes across individuals that share a common social and physical environment. Subsequently, although sensory stimuli for all tasks are simultaneously present in the colony, division of labour systems maintain differential behavioural response thresholds to task specific cues in different individuals (Figure 1). The highly-tuned network of semi-autonomous individuals provides a robust, systems-level modulation of task allocation across time and space based on the overall needs of the colony (Buttstedt, Ihling, Pietzsch, & Moritz, 2016; Haydak, 1970; Ingram, 2002; Kamakura, 2011; Libbrecht & Keller, 2013; Nygaard et al., 2011; Patel, Haydak, & Gochnauer, 1960; Schwander & Keller, 2008; Schwander, Lo, Beekman, Oldroyd, & Keller, 2010; Wheeler, 1991).

Phylogenetic studies indicate that division of labour systems likely evolved multiple times across, and within,

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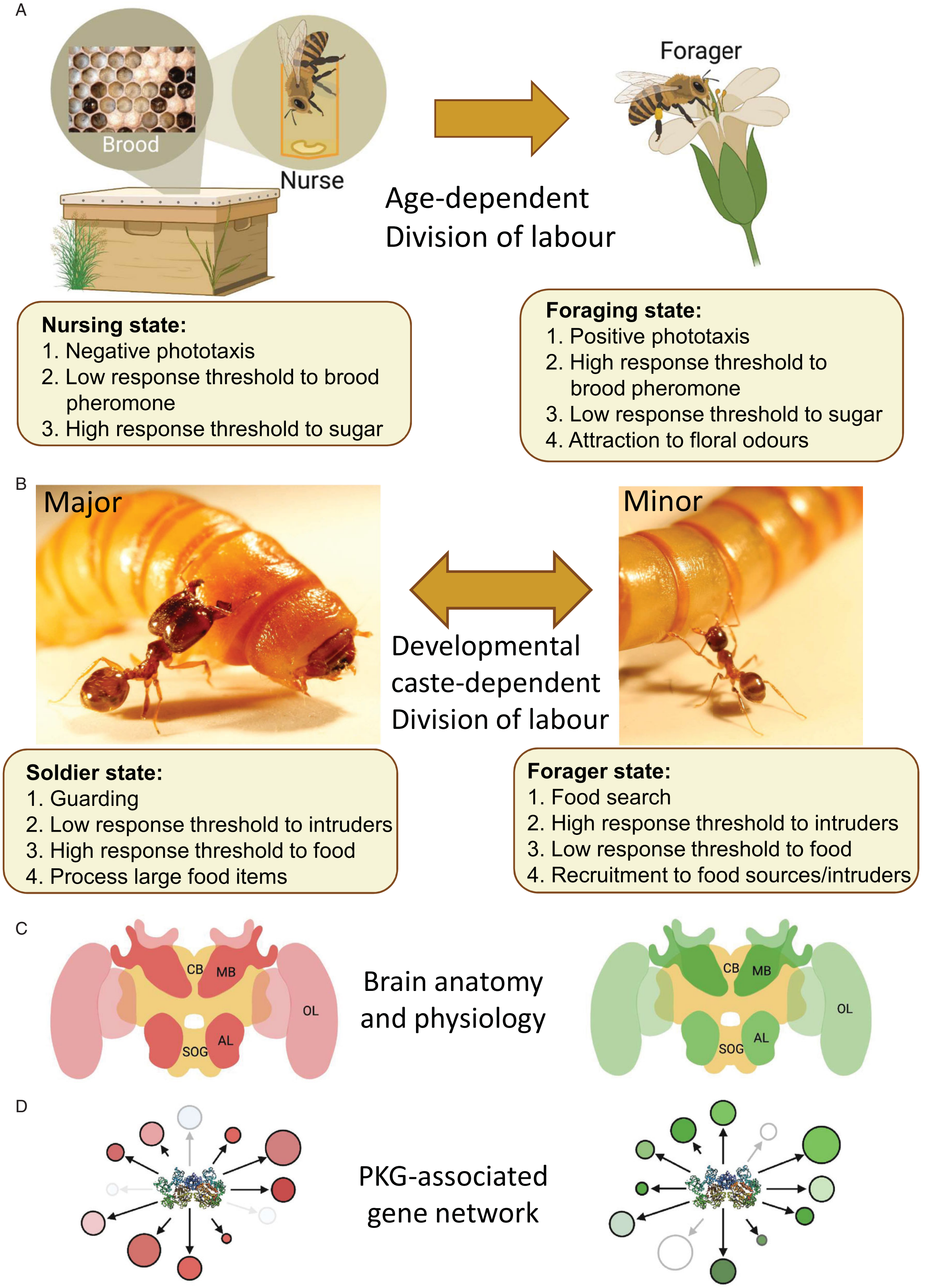

Figure 1. cGMP-dependent protein kinase is a key node in the gene network that regulates behavioral states associated with division of labour. (A) Division of labour in the honey bee *Apis mellifera* is regulated solely by age-dependent processes. Young bees start their lives as nurses and typically start foraging when they are 3 weeks old. (B) Division of labour in the ant *Pheidole pallidula.* Tasks are regulated by developmental caste determination of "majors" and "minors," as well by age-dependent regulation of behaviours such as nursing and foraging. Division of labour is also associated with task-specific sensory thresholds (A–B); and changes in neuronal anatomy and physiology (C). (D) Current models stipulate that *for* is a conserved regulatory node in the gene networks that regulate behavioral states across diverse social insect species. Therefore, changes in PKG activity can lead to shifts in the activity of peripheral and central neuronal populations that drive task-specific behavioral repertoires.

different lineages of the social hymenopterans (Gordon, 2016; Rueffler, Hermisson, & Wagner, 2012). Therefore, division of labour in colonies of social insects has emerged as an excellent model for understanding how animal social systems have evolved and are regulated at the physiological, molecular, and cellular levels (Kapheim *et al.*, 2015; Robinson, Grozinger, & Whitfield, 2005; Smith, Toth, Suarez, & Robinson, 2008; Toth & Robinson, 2007; Toth *et al.*, 2010; Whitfield et al., 2006). Transcriptomic analyses of gene expression in the brains of workers that are engaged in specific tasks, for example, have indicated that division of labour depends on broad and complex changes in many different neuronal signalling pathways across different parts of the brain and other tissues (Figure 1). This appears to occur via differential promoter activity, regulatory non-coding miRNAs, and epigenetic processes (Cash, Whitfield, Ismail, & Robinson, 2005; Greenberg et al., 2012; Kapheim *et al.*, 2020; Lattorff & Moritz, 2013; Simola et al., 2016; Sinha, Ling, Whitfield, Zhai, & Robinson, 2006; Toth et al., 2007; Whitfield et al., 2006). To date, changes in the expression levels of several genes have been associated with division of labour across diverse social insect species. However, only a few have been studied in any depth. The highly conserved cGMP-dependent protein kinase gene *foraging* (*for*), in particular, has been well-studied for its role in regulating division of labour. Previous work has established a causal association between *for* and task specialization, which is conserved across multiple independently-evolved lineages. Here we review the role of *for*, first identified as a behaviourally polymorphic gene in *Drosophila* associated with larval and adult foraging decisions (de Belle, Hilliker, & Sokolowski, 1989; Osborne et al., 1997), as a conserved signalling pathway that has been co-opted for the regulation of division of labour across diverse social insect species.

The study of sociality in the era of molecular genetics

Over 50 years ago, the pioneering ethologist Niko Tinbergen published his seminal paper entitled “On aims and methods of ethology” (Burkhardt, 2014; Tinbergen, 1963). With brilliant simplicity, Tinbergen argued that if biologists want to really understand “behaviour” then they need to ask the following four questions (rephrased): (1) What is the studied trait good for (its impact on fitness)? (2) How does it develop during the lifetime of an individual (development/ontogeny)? (3) How did it evolve over the history of the species (trait phylogeny)? (4) How does it work (mechanism/causation)? The emergence of modern neuroscience and neurogenetics followed in the footsteps of ethology by providing a mechanistic framework as a powerful approach to the design of behavioural studies and their interpretation in the context of brain functions (Tinbergen question #4).

However, modern neuroscience research is now largely framed in the context of causation and mechanism (Tinbergen question #4). Consequently, the diversity of animal species used for basic neurogenetic research has, historically, been reduced to just a few genetically tractable species that have sequenced genomes, including the roundworm *Caenorhabditis elegans* (Bargmann, 1998), the fruit fly *Drosophila melanogaster* (Bellen, Tong, & Tsuda, 2010), the zebrafish *Danio rerio* (Stewart, Braubach, Spitsbergen, Gerlai, & Kalueff, 2014), and the laboratory mouse *Mus musculus* (Lehner, 2013). While there is no doubt that these models have been instrumental in the phenomenal progress made in cellular and molecular neuroscience over the past three decades, the decline in model diversity is clearly an unfortunate side effect, and has negatively impacted our ability to understand behaviour in ecologically and evolutionary relevant contexts (Fitzpatrick et al., 2005; Walton, Sheehan, & Toth, 2020).

Yet, recent advances in genetic and genomic approaches have enabled investigators to adopt modern molecular approaches for understanding the behaviour of a wider assortment of animal species in the lab and in their natural environments. Some of the first non-drosophilid insects for which genomic and molecular tools for studying behaviour have made a tremendous impact are the social insects, particularly in the several independent social clades within the order Hymenoptera. One of the best established model species for sociogenomic and genetic studies is the European honey bee *Apis mellifera*. As the most dominant domesticated insect, the long tradition of beekeeping has provided investigators with a rich knowledge of its behaviour and physiology, including well-established techniques for manipulating colony demography and colony genetics via artificial inseminations (Page, Gadau, & Beye, 2002; Vanengelsdorp & Meixner, 2010). Not surprisingly, the economic importance of the honey bee has led to the development of diverse molecular and genetic resources, including a relatively well-annotated genome, high-resolution population genetics, and successful genome transformations (Ament, Wang, & Robinson, 2010; Ben-Shahar, 2014; Ben-Shahar, Dudek, & Robinson, 2004; Chen et al., 2021; Foret, Kucharski, Pittelkow, Lockett, & Maleszka, 2009; Sinha et al., 2006; Wang et al., 2006; Weinstock *et al.*, 2006; Whitfield et al., 2006; Whitfield, Cziko, & Robinson, 2003). Subsequently, the progress in analysing honey bee behaviour with molecular and genetic tools has paved the way for similar breakthroughs in many additional social insect species (Kapheim *et al.*, 2020; Kapheim *et al.*, 2015; Libbrecht, Oxley, Kronauer, & Keller, 2013; Sadd *et al.*, 2015; Toth *et al.*, 2010). Nevertheless, the genetic mechanisms by which specific genes and neuronal signalling pathways regulate the complex behaviour of social insects had remained mostly a mystery until the discovery of the gene *foraging* (*for*), a cGMP-dependent protein kinase (PKG), and its role in the regulation of behavioural plasticity in colonies of social insects (Figure 1D). Subsequent studies of this gene of in the context of division of labour have provided some important mechanistic insights into animal sociality.

The role of *foraging* in regulating division of labour in social insect colonies

The *foraging* (*for*) gene encodes a cGMP-dependent protein kinase (Osborne et al., 1997), a highly conserved enzyme present in all animal genomes sequenced to date (Anreiter & Sokolowski, 2019; Lucas, Kornfein, et al., 2010). The *for* gene was first identified as a naturally polymorphic locus that regulates larval foraging behaviour in *Drosophila* (de Belle & Sokolowski, 1987; Sokolowski, 1980), and was later identified as a gene that encodes one of the two cGMP-dependent protein kinases (PKG) encoded by the *Drosophila* genome (Osborne et al., 1997). The highly conserved PKG family is broadly expressed in both neuronal and non-neuronal tissues, and has been implicated in numerous cellular and physiological functions via its kinase activity (Dason, Allen, Vasquez, & Sokolowski, 2019; Douglas, Dawson-Scully, & Sokolowski, 2005; Francis, Busch, Corbin, & Sibley, 2010; Lohmann, Vaandrager, Smolenski, Walter, & De Jonge, 1997; Wang & Robinson, 2002). In *Drosophila*, *for* is expressed in diverse tissues, including the peripheral (PNS) and central (CNS) nervous systems of both larvae and adults (Anreiter, Kramer, & Sokolowski, 2017). Several genetic studies have revealed that the natural polymorphism in *for* contributes to diverse sensory functions, including the visual, olfaction, and gustatory pathways (Lin, Nairn, & Guggino, 1992). In the CNS, *for* is expressed in the Kenyon cells of the mushroom bodies, the central complex, and the antennal lobes. It has been implicated in regulating neuronal and behavioural plasticity in diverse cognitive and motor functions such as neuronal sensitization and habituation, learning and memory, and sleep (Eddison, Belay, Sokolowski, & Heberlein, 2012; Engel, Xie, Sokolowski, & Wu, 2000; Scheiner, Sokolowski, & Erber, 2004). In addition to regulating behaviour via neuronal functions, *for* also indirectly contributes to feeding and foraging behaviours via its role in metabolic plasticity and the response to stress (Dason et al., 2020; Kaun, Chakaborty-Chatterjee, & Sokolowski, 2008; Kaun & Sokolowski, 2009; Kent, Daskalchuk, Cook, Sokolowski, & Greenspan, 2009).

The role of the cGMP-PKG signalling axis in regulating feeding behaviours is conserved in other animal species. For example, cGMP-signalling has been shown to regulate the response threshold of insects to pheromones (Boekhoff et al., 1993; Ziegelberger, van den Berg, Kaissling, Klumpp, & Schultz, 1990), and to influence olfactory communication in rats (Kroner, Boekhoff, Lohmann, Genieser, & Breer, 1996; Moon et al., 1998). In the worm *Caenorhabditis elegans*, the PKG-ortholog *egl-4* plays a role in foraging, olfaction, sleep, body size and lifespan (Fujiwara, Sengupta, & McIntire, 2002; L'Etoile et al., 2002; Raizen et al., 2008). Yet, in spite of its broad role in regulating different forms of behavioural plasticity in diverse animal species, the identities of the specific neuronal substrates modulated by *for* in the context of foraging behaviour and social insect division of labour remain mostly unknown. However, studies in genetically tractable species provide some mechanistic insights into how PKG signalling might be regulating neuronal processes associated with division labour. For example, studies in the mouse, indicate that PKG activity can have broad effects on long-term neuronal processes and behavioural plasticity via diverse downstream effectors. Neuronal PKG activity can modulate long-term potentiation (LTP) in the mammalian brain via a direct modulation of cAMP-phosphodiesterases, which regulate cAMP levels and synaptic plasticity (Bollen et al., 2014). In addition, studies of *Egl-4*, the ortholog of *for* in the worm *C. elegans*, has shown that sensory-induced neuronal plasticity within the chemosensory system depends on the transition of activated PKG to the nucleus, which leads to changes in neuronal gene expression via the modulation of heterochromatin binding proteins (Lee et al., 2010). Together, these examples illustrate the broad role *for* and related kinase genes play in regulating neuronal plasticity and organismal behaviour via diverse molecular and cellular mechanisms in the peripheral and central nervous systems of invertebrates and vertebrates.

The *foraging* gene in social bees

The realization that *for* plays a key role in regulating feeding-related behavioural plasticity in *Drosophila* suggested that the phylogenetically conserved PKG signalling pathway is also likely to be driving similar foraging-related decisions in other insect species, including in the regulation of foraging vs. brood care behaviour in social insect division of labour. Recently, *for* has also been implicated in the regulation of social networks in *Drosophila* (Alwash et al., 2021). By using transcriptomics and gene candidate approaches (Fitzpatrick et al., 2005), multiple studies have identified several key genes that play a role in regulating division of labour in honey bees including the acetylcholine esterase (*AchE*) gene (Shapira, Thompson, Soreq, & Robinson, 2001), the *foraging* (*for*) gene (Ben-Shahar, Leung, Pak, Sokolowski, & Robinson, 2003; Ben-Shahar, Robichon, Sokolowski, & Robinson, 2002), and the manganese transporter *malvolio* (Ben-Shahar et al., 2004). In terms of how *for* exerts its action in honey bees, follow-up studies have identified an increase in brain expression levels of *for* just prior to the initiation of foraging, which suggests that its activity may serve as a trigger for the transition from in-hive behaviours to foraging outside (Heylen et al., 2008). Furthermore, QTL analysis of foraging-related traits in honey bee populations has identified an association with QTLs in the *for* locus, suggesting that in addition to its role at the developmental and physiological timescales, *for* may play a role in shaping division of labour at the evolutionary timescale as well (Ruppell, Pankiw, & Page, 2004).

The discovery of *for* as a putative key regulator of division of labour in the honey bee was followed by studies investigating its role in regulating division of labour across the social hymenopteran phylogeny. It was shown that changes in *for* expression are also associated with division of labour in other species of social bees, including the Asian honey bee *A. cerana* (Ma et al., 2018), as well as different bumblebee species (Kodaira, Ohtsuki, Yokoyama, & Kawata, 2009; Tobback, Mommaerts, Vandersmissen, Smagghe, & Huybrechts, 2011). Interestingly, in contrast to the reported increased *for* expression in the brains of honey bee foragers, the expression of *for* in association with the size-dependent regulation of division of labour in bumblebees was variable, indicating higher *for* expression in *Bombus terrestris* foragers but lower in brains of *B. ignitus* foragers (Couvillon, Jandt, Duong, & Dornhaus, 2010; Kodaira et al., 2009; Shpigler et al., 2013). Together, these studies suggest that the functional relationship between *for* activity in the brain and the behavioural states that define the probability of performing specific tasks by individual bees is complex and likely involve both central and peripheral neuronal pathways.

The *foraging* gene in ants

In ants, *for* has been shown to be involved in age-related division of labour, as in honey bees (Ingram et al., 2016; Ingram, Oefner, & Gordon, 2005; Lucas, Nicolas, & Keller, 2015; Manfredini et al., 2014; Oettler, Nachtigal, & Schrader, 2015). However, in contrast to social bees, which primarily regulate division of labour on a physiological timescale, studies of *for* in ants revealed its role in regulating polyethisms in association with both age-dependent and developmentally-regulated morphological castes. For example, colonies of the ant *Pheidole pallidula* have two morphologically-distinct workers (Passera, 1985), each associated with specific behavioural repertoires. The majors have a large head with large mandibles and are mainly involved in the defence of the colony and processing of large food items, while the minors are smaller and are mainly involved in brood care and foraging. This morphological and behavioural division of labour was associated with changes in brain activity; minors had lower brain PKG activity than majors (Lucas & Sokolowski, 2009). In addition, although minors and majors typically perform distinct roles in the colony, when confronted with changing needs of the colony, majors may assist minors in foraging activities and minors may help with defence tasks (Aarab, 1991). Accordingly, experimental manipulations showed that majors that respond to foraging stimuli show minor-like, low brain PKG activity. Similarly, when participating in colony defence, minors showed a significant increase in brain PKG activity to major-like levels (Lucas & Sokolowski, 2009). Moreover, pharmacological treatment of minors with the PKG activator 8-Br-cGMP induced brain PKG activity, and led to an increase in defence and decrease in foraging behaviours (Lucas & Sokolowski, 2009), thus establishing a causal association between PKG activity and worker behavioural plasticity. The *foraging* gene in *P. pallidula* therefore appears to modulate both foraging behaviour and defence behaviour (Anreiter & Sokolowski, 2019; Lucas, Hughson, & Sokolowski, 2010; Lucas & Sokolowski, 2009) and, under conditions that require plastic task reallocation, can drive neuronal plasticity even in species with a robust morphological division of labour system (Anreiter & Sokolowski, 2019; Lucas, Hughson, et al., 2010). These findings suggest that *for* exerts at least two levels of control over worker behaviour in ants: (1) Differences in baseline brain PKG activity are associated with caste polyethism at the developmental timescale; and (2) Plasticity in PKG activity allows colony-level responses to environmental changes at the physiological timescale. This link between defence and PKG activity has also been demonstrated in a field study, where feeding the ant *Allomerus octoarticulatus* with a PKG activator, increased defence behaviour of the ant-plant *Cordia nodosa* against herbivores, suggesting a molecular basis for ant-plant mutualism (Malé et al., 2017).

In another ant species, *Solenopsis invicta*, *foraging* gene expression in workers was influenced by colony demography, in particular whether the colony had one queen (monogynous) or multiple queens (polygynous) (Lucas et al., 2015). Workers from monogynous colonies of *S. invicta*, which are very territorial and aggressive (Chirino, Gilbert, & Folgarait, 2012; Tschinkel, 2006), had higher brain expression levels of *for* relative to workers from the more docile polygynous colonies (Lucas et al., 2015). Altogether, these results suggest that the *for* gene might be involved in regulating differential levels of aggression associated with territorial foraging or caste polyethisms. Recently, *for* has been shown to regulate aggression in flies as well, providing further support to the idea that the role of *for* in regulating behavioural plasticity across distant species is conserved not only for foraging behaviour but may be also for defence behaviour (Wang & Sokolowski, 2017).

Moreover in the ant *S. invicta*, *for* expression level was shown to be associated with reproductive state (future queen vs. workers) and the number of future queens (monogynous vs. polygynous) (Lucas et al., 2015), suggesting that in addition to its role in regulating behavioural plasticity in workers, *for* also contributes to reproductive division of labour in *S. invicta*. Interestingly, variations in colony demography (monogynous vs. polygynous) exist in several ant species, and are thought to confer colony-level benefits by increasing genetic diversity, and therefore, amplifying worker behavioural differences that underlie division of labour (Cronin, Molet, Doums, Monnin, & Peeters, 2013; Krista K Ingram, 2002; Manfredini et al., 2014; Pearcy, Aron, Doums, & Keller, 2004; Ross & Keller, 1995).

The neuroethological context of the regulation of division of labour by *for*

Based on theoretical and empirical studies, one of the primary models for self-organized division of labour in social insect colonies is based on the idea that animals at different behavioural states exhibit different behavioural response thresholds to task-specific stimuli (Beshers & Fewell, 2001; Duarte, Pen, Keller, & Weissing, 2012). Consequently, although workers are exposed to many or all task-stimuli in the colony, the probability that an individual worker will respond to the stimulus for a particular task varies (Bonabeau, Theraulaz, & Deneubourg, 1998; Detrain, Deneubourg, & Pasteels, 1999; Duarte et al., 2012; Leitner & Dornhaus, 2019). Subsequently, molecular, genetic, and neuroethological studies have suggested that the PKG activity of *for* regulates division of labour, at least in part, via the modulation of task-specific sensory thresholds (Ben-Shahar et al., 2003; George, Bröger, Thamm, Brockmann, & Scheiner, 2020; Heylen et al., 2008; Thamm & Scheiner, 2014).

As a kinase, *for* is likely to have numerous protein targets in the insect brain (Wang & Robinson, 2002). To date, the specific protein targets that mediate its role in behavioural plasticity in general, and division of labour in particular, remain mostly elusive, however, studies in various species suggest that *for* may have targets within the sensory system. Studies in *Drosophila,* for example, have indicated that *for* contributes to sucrose responsiveness in adults (Scheiner et al., 2004) and the larval nociception threshold (Dason et al., 2020). Similar effects on sensory thresholds have also been identified in *C. elegans* and rodent models, further indicating a conserved role for cGMP-dependent signalling in modulating behavioural states via sensory functions (Gangadharan, Wang, & Luo, 2017; Jaumann et al., 2012; Levy & Bargmann, 2020). Subsequently, several studies in the honey bee have indicated that *for* activity plays a role in regulating the response threshold to light, indicating that increased PKG activity drives positive phototaxis in foragers (Ben-Shahar, 2005; Ben-Shahar et al., 2003). In addition, *for* has also been implicated in honey bee sucrose responsiveness and the response threshold to queen pheromones (Fussnecker, McKenzie, & Grozinger, 2011; Thamm & Scheiner, 2014). Together, these studies suggest that *for* is likely to regulate division of labour via multimodal modulation of sensory functions.

In addition to its role in regulating sensory functions, *for* has been shown to contribute to both simple forms of neuronal plasticity, such as the habituation in the giant fiber escape circuit responsiveness to sugar (Engel et al., 2000; Scheiner et al., 2004), as well as more complex processes such as visual memories (Kuntz, Poeck, & Strauss, 2017; Wang et al., 2008) and associative learning (Kaun, Hendel, Gerber, & Sokolowski, 2007; Mery, Belay, So, Sokolowski, & Kawecki, 2007) in flies. Because division of labour is often associated with differential learning and memory capacities (Ben-Shahar, Thompson, Hartz, Smith, & Robinson, 2000; Ben-Shahar & Robinson, 2001; Roussel, Carcaud, Sandoz, & Giurfa, 2009), it has been hypothesized that *for* is also likely to also modulate division of labour via its action in central neuronal circuits associated with higher level cognitive functions (Ben-Shahar, 2005; Menzel, Leboulle, & Eisenhardt, 2006). Interestingly, in *Pheidole* ants, the expression pattern of *for* in the brains of majors is specific to a subregion of the mushroom bodies, while both minor and major workers share its expression in several brain regions including the lobula, which plays a role in the integration of visual cues (Lucas & Sokolowski, 2009). Although it is still unknown how the action of *for* in this specific brain region is contributing to the behaviours exhibited by minors and majors, the well-established anatomical and physiological role of the mushroom bodies in regulating division of labour in diverse social insects suggest that *for*-dependent signalling in this brain region is important for cognitive processes associated with division of labour. This is further supported by the recent findings that *for* activity is associated with interindividual differences in the dance intensity of returning foragers (George et al., 2020), and the impact of cGMP pharmacological treatment on spatial learning in honey bee foragers (Tsvetkov, Madani, Krimus, MacDonald, & Zayed, 2019).

The *foraging* gene in other social contexts

The complex role of *for* in regulating division of labour in bee and ant species indicates that this gene is highly pleiotropic, regulating not only foraging but also many other behavioural aspects of division of labour and other sociality-related traits. The study of *for* in other social species, such as wasps and termites, will yield important discoveries for understanding how *for* regulates social behaviours across diverse insect taxa. For example, a study on the comparisons of brain gene expression between the social wasp *Polistes metricus* and the honey bee *Apis mellifera* allowed to identify common molecular roots for division of labour, demonstrating the importance of *for* across lineages (Toth *et al*., 2010). In the termite *Reticulitermes flavipes*, a recent study showed differences in mRNA expression depending on caste, temperature and photoperiod (Merchant, Song, Yang, Li, & Zhou, 2019), suggesting the possibility that the differential expression of *for* may very well be important for this social insect group as well. Future comparisons between termites and social hymenopteran will likely shed even more light on how *for* regulates division of labour across phylogenetically distant social systems (Hymenoptera/Isoptera) with distinct developmental processes (e.g., holometabolism vs. hemimetabolism).

Although the precise origin of insect eusociality remains mostly unknown at the molecular level, it is clear that some key neuronal signalling pathways, such as *for*, contribute to social interactions between conspecifics in non-social insects as well. For example, flies with low *for* expression are more sensitive to social context in learning paradigms than those with high expression levels (Kohn et al., 2013). In addition, *for* has been shown to be associated with population density-dependent regulation of polyphenisms in some aphid species (Tarès, Arthaud, Amichot, & Robichon, 2013), and between solitary and gregarious forms in the locust *Schistocerca gregaria* (Lucas, Kornfein, et al., 2010; Rogers et al., 2003; Tobback et al., 2013).

Concluding remarks

The association between the PKG activity of the *foraging* gene and behavioural plasticity in response to changes in the social and biotic environments, especially in the context of feeding and foraging behaviours, is conserved across a broad range of animal species, from insects to humans (Anreiter & Sokolowski, 2019; Armstrong, López-Guerrero, Dawson-Scully, Peña, & Robertson, 2010; Chardonnet et al., 2014; Kohlmeier, Alleman, Libbrecht, Foitzik, & Feldmeyer, 2019; Lucas, Kornfein, et al., 2010; Malé et al., 2017; Merchant et al., 2020; Robertson & Sillar, 2009; Struk et al., 2019; Tarès et al., 2013; Tobback et al., 2013). Additionally, it remains unknown whether all or only some of the alternative transcripts transcribed by *for* in at least some social insect species play a role in regulating neuronal plasticity and behaviour in social insects (Lucas & Sokolowski, 2009; Merchant et al., 2020; NCBI, 2021). Furthermore, the specific molecular targets and neuronal signalling pathways modulated by *for* activity across the evolutionary, developmental, and physiological timescales remain a mystery. Nevertheless, recent developments in transposon-mediated transgenesis and *Cas9*/CRISPR-dependent genome editing in several social insect species (Ben-Shahar, 2014; Chen et al., 2021; Kohno, Suenami, Takeuchi, Sasaki, & Kubo, 2016; McAfee, Pettis, Tarpy, & Foster, 2019; Schulte, Theilenberg, Muller-Borg, Gempe, & Beye, 2014; Trible et al., 2017) will likely yield new insights into the molecular and cellular pathways that underlie the role of *for*, and other important signalling pathways, in the "social" brain.

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