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Aminergic control of aggressive behavior in social insects

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With 3 figures and 1 table

Abstract: Aggression is a common trait in almost all animals and one of the bases of animal sociality. It is closely linked to intraspecific conflicts, hunting, and defending offspring, among others. Social insects establish integrated groups and show various aggressions that link to colony defense, predation, social rank, reproductive hierarchy and so on. Thus, they represent excellent experimental model systems to investigate the mechanisms underlying aggressive behavior. The biogenic amines function as neurotransmitters, neuromodulators, and neurohormones in the nervous systems, and have crucial roles in the diversification and modulation of behavior in social and solitary insects. Aggressive behaviors are mediated by aminergic systems. However, many issues about the roles of biogenic amines in social insects still deserve further study. In this scenario, the present review analyzed the roles of biogenic amines on aggressive behavior in social insects. We provided insights on the biosynthesis of monoamines, we summarized current knowledge on the serotonergic, dopaminergic, octopaminergic, and tyraminergetic control of aggressive behavior in social insects, with a special focus on ants, bees, and termites. In the last section, we provided an updated synthesis of the role of biogenic amines in controlling aggressive behavior in social insects.

Keywords: Apidae; *Apis mellifera*; ants; bees; Formicidae; serotonin; dopamine; octopamine; aggression; social behavior; termites; wasps

1 Introduction

Aggressive behavior is a common trait in virtually all animals. Animals fight for obtaining resources such as food, territory, and mating partners, and for defending themselves and their offspring from natural enemies (e.g., predators, parasitoids, and parasites) (Aonuma 2020; Benelli 2014, 2015; Killian & Allen 2008; Rillich & Stevenson 2019; Rittschof et al. 2015; Szczuka et al. 2013; Tanner & Adler 2009). In an intraspecific fight, the combat sometimes escalates to violence, and the retreat of the opponent settles the fight to establish a dominant-subordinate relationship (Benelli et al. 2015a, b; Stevenson & Schildberger 2013). Many species of animals, not only vertebrates but also invertebrates, have been used to understand neurophysiological mechanisms underlying aggressive behavior (Rillich & Stevenson 2019; Rittschof et al. 2015).

Social insects are one of the most successful groups of insects in terms of diversity and number on the Earth. Ants, bees, wasps, and termites establish a colony, caste, dominant hierarchy, etc., and show various aggressive behaviors during colony establishment, colony defense, social ranking, and predation, just to cite some examples. Each aggressive behavior appears to be controlled by different aminergic systems. For

example, the serotonergic system controls defensive aggression in the ant *Odontomachus kuroiwae* (Matsumura) (Aonuma 2020) and the dopaminergic system controls reproductive hierarchy in the ant *Diacamma* sp. (Shimaji et al. 2017).

It has been reported that the action of biogenic amines is closely linked to aggressive behavior in insects (e.g., solitary insects: Stevenson et al. 2000; social insects: Aonuma 2020), like other animals (e.g., crustaceans: Huber & Delago 1998; vertebrates: Narvaes & Martins de Almeida 2014; Popova 2008). Biogenic amines function as neurotransmitters, neuromodulators, and neurohormones to play principal roles in the diversification and modulation of behavior both in social and solitary insects (Evans 1980; Woodring & Hoffmann 1994; Roeder 2005; Scheiner et al. 2006). The aminergic systems in the brain closely link to a variety of behaviors such as motivation (Selcho & Pauls 2019), desensitization (Gatellier et al. 2004), individual recognition (Boulay et al. 2000; Robinson et al. 1999; Vander Meer et al. 2008; Wada-Katsumata et al. 2011), learning and memory (Hammer & Menzel 1998; Unoki et al. 2005), rhythmic behavior (Libersat & Pflueger 2004) and others.

The roles of biogenic amines in controlling various aggressive behaviors in invertebrate animals have been

reported (Kravitz & Huber 2003). Dopamine, serotonin, octopamine, and tyramine are major biogenic amines that control aggressive behavior. However, the modulatory effects of these amines on aggressive behavior appear to be different from animal to animal, e.g., dopamine modulates intraspecific aggression in crickets (Rillich & Stevenson 2014), serotonin modulates intraspecific aggression in the stalk-eyed flies (Bubak et al. 2014), and octopamine modulates intraspecific aggression in *Drosophila* (Hoyer et al. 2008). In social insects, the effects of biogenic amines on aggressive behavior are also different among species, e.g., dopamine modulates cast-dependent aggression in honeybees (Sasaki & Harada 2020), serotonin modulates defensive aggression in trap-jaw ants (Aonuma 2020), octopamine modulates predatory aggression in ants (Yakovlev 2018) and tyramine modulates colony defensive aggression in termites (Ishikawa et al. 2016). One possible explanation could be that each report addresses various types of aggressive behavior in distinct animal species. It is rather easy to separate the types of aggressive behaviors that link to colony defense (Nouvian et al. 2018), predation (Szczyka et al. 2013), social rank (Muscedere et al. 2016), reproductive hierarchy (Shimoji et al. 2017), etc., in social insects. This review aims to sort out aggressive behaviors to link to the roles of biogenic amines and provide an updated synthesis of the role of biogenic amines in controlling aggressive behavior in social insects.

2 Biosynthesis of monoamines

Biogenic amines are derived from amino acids by the activation of enzymes (Fig. 1). Serotonin (5-HT) is derived from

tryptophan through two catalytic steps. Tryptophan hydroxylase first catalyzes to synthesize 5-hydroxy-L-tryptophan (5-HTP) from tryptophan, and then the aromatic L-amino acid decarboxylase catalyzes to synthesize serotonin in the insect (Neckameyer et al. 2007; Watanabe et al. 2011). Tyrosine is the precursor of tyramine, octopamine, and dopamine. It was believed that tyramine is the intermediate product to synthesize octopamine from tyrosine. However, several studies demonstrated that tyramine itself functions as a neuromodulator (Farooqui 2012). Octopamine (OA) is synthesized from tyrosine through two steps. Tyrosine decarboxylase first catalyzes to synthesize tyramine (TA) from tyrosine, and then tyramine is hydroxylated to octopamine by the catalyzation of tyramine β -hydroxylase (Lehman et al. 2006; Roeder et al. 2003). Dopamine (DA) is derived from tyrosine via different catalyzation (Sugumaran & Barek 2016). Tyrosine is first hydroxylated to 3,4-dihydroxyphenylalanine (L-DOPA) that is then converted to dopamine by aromatic amino acid decarboxylase (Watanabe et al. 2013; Sasaki et al. 2021; Verlinden 2018).

3 Serotonergic control of aggressive behavior

Many studies have focused on the roles of biogenic amines in aggressive behavior. Serotonin is one of the key molecules that mediate aggressiveness in invertebrates (Edwards & Kravitz 1997). There are some studies demonstrating the enhancing effect of serotonin on aggressiveness in ants. The elevation of brain serotonin closely links to enhancing aggressiveness against interspecific and intraspecific insects in the red wood ant, *Formica rufa* (L.) (Kostowski &

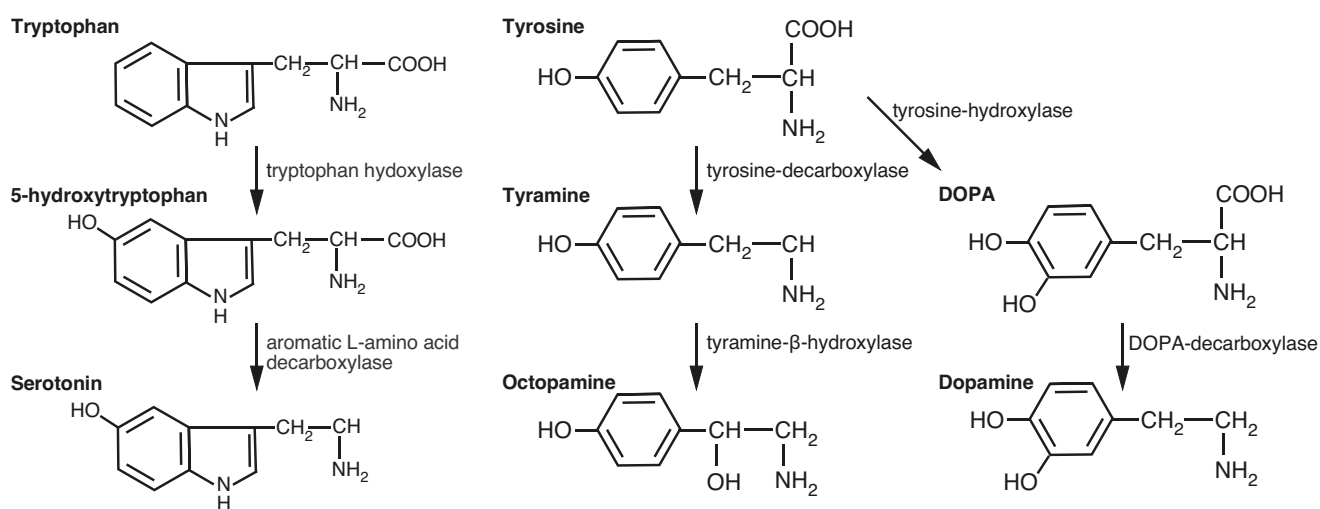


Fig. 1. Biosynthesis of monoamines in insects. Serotonin is derived from the amino acid tryptophan (Neckameyer et al. 2007; Watanabe et al. 2011). Both octopamine (Lehman et al. 2006; Roeder et al. 2003) and dopamine (Watanabe et al. 2013; Sasaki et al. 2021; Verlinden 2018) are derived from the amino acid tyrosine.

Tarchalska 1972; Tarchalska et al. 1975). The elevation of brain serotonin also links to enhancing aggressiveness to promote agonistic interaction among queens during colony establishment in the desert harvest ant *Veromessor pergandei* (Mayr) (Muscedere et al. 2016). In the trap-jaw ant, *Odontomachus kuroiwae* (Matsumura), defensive behavior against an unexpected threat (Fig. 2) is enhanced by the elevation of the brain serotonin (Aonuma 2020). In another social insect, i.e., the honeybee, serotonin is thought to regulate defensive behavior. The sting alarm pheromone, isoamyl acetate upregulates both serotonin and dopamine in the brain of workers, which elevates aggressiveness to enhance defensive behavior (Nouvian et al. 2018).

The action of serotonin in mediating aggressive behavior varies among insects. The elevation of brain serotonin enhances aggressive behavior in *Drosophila melanogaster* (Meigen) (Diptera: Drosophilidae) (Dierick & Greenspan 2007) and the stalk-eyed fly *Teleopsis dalmanni* (Wiedemann) (Diptera: Diopsidae) (Bubak et al. 2014; Bubak et al. 2020). Similar effects of serotonin on aggressiveness have been reported in other animals, for example, serotonin increases the aggressiveness of subordinates in crayfish (Edwards & Kravitz 1997; Huber et al. 1997; Kravitz 2000), and a tonic increase in 5-HT₂ receptor escalates aggression in mice (Shih et al. 1999; Takahashi et al. 2011). In the Japanese rotten wood termite, *Hodotermopsis sjostedti* (Holmgren) (Isoptera: Termitidae), the soldier is more aggressive than the pseudergate, and the brain serotonin level in the soldier is higher than that in the pseudergate (Ishikawa et al. 2016). However, a pharmacological treatment to increase brain serotonin did not increase aggressiveness. It has been demonstrated that serotonin suppresses the escape circuit of *Periplaneta americana* (L.) (Blattodea: Blattellidae) cockroaches, which is closely related to termites (Goldstein & Camhi 1991), suggesting that serotonin might link to modulating aggressiveness. On the other hand, serotonin has the opposite effect on aggressiveness in some insects. Serotonin has a suppressive effect on aggressiveness in crickets, *Gryllus bimaculatus* (De Geer) (Orthoptera: Gryllidae) (Rillich et al. 2019; Rillich & Stevenson 2018) and black widow spiders, *Latrodectus hesperus* (Chamberlin & Ivie) (Araneae: Theridiidae) (Schraft et al. 2023). The activating 5-HT₂ receptor is thought to suppress aggressiveness in *D. melanogaster* (Johnson et al. 2009). 5-HT₂ is G-protein-coupled receptor (GPCR) that accumulates IP₃, diacylglycerol (DAG), and activation of protein kinase C (PKC) in vertebrates. Of note, the intracellular action of 5-HT₂ in insects is still unclear. In crayfish, the protein kinase A (PKA)-cAMP pathway is involved in releasing aggression (Momohara et al. 2016). A dominant crayfish is less activated PKA than a subordinate one. To date, seven types of serotonin receptors have been identified in vertebrates (Nichols & Nichols 2008; Wacker et al. 2013). The activation of 5-HT₁, 5-HT₂, 5-HT₅, 5-HT₆, and 5-HT₇, which are GPCR, decreases intracellular cAMP (Fredriksson et al. 2003). Serotonin receptors in insects have been iden-

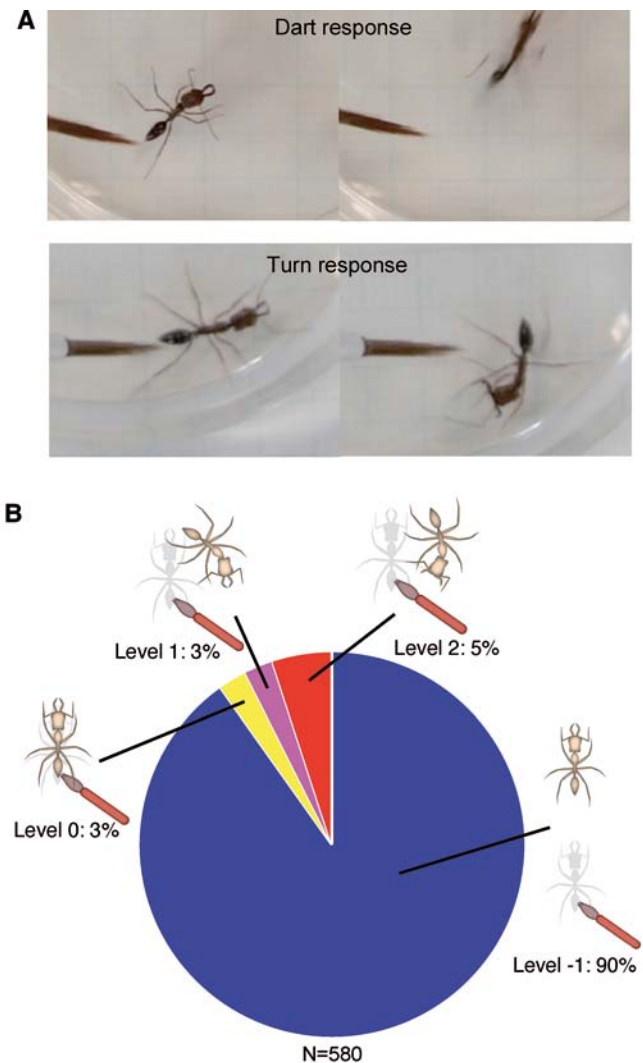


Fig. 2. Response to unexpected touch in the trap-jaw ant *Odontomachus kuroiwae*. **(A)** The ant responds with a dart or a turn to unexpected touch on their abdomen. **(B)** Most ants (90%) respond with a dart to unexpected touch to leave the potential threat. Less than 10% of ants respond with a defensive turn to the stimulus. The ants that show a turn response have more serotonin in the brain than the ants that show dart escape. Pharmacological treatment demonstrated brain serotonin could be the key to modulating defensive aggression. Level -1: dart, Level 0: no response, Level 1: turn without opening mandible, Level 2: turn with opening mandible (Fig. 2B redrawn using data in Aonuma 2020).

tified as functional homology (Tierney 2018), for example, 5-HT₁, 5-HT₂, and 5-HT₇ (fruit fly and honeybee: Blenau & Thamm 2011; cricket: Watanabe & Aonuma 2012; red flour beetle: Vleugels et al. 2013). Serotonin modulates neuronal activities in the brain. Indeed, the distribution of serotonergic neurons in the brain of honeybees and ants has been identified by immunohistochemistry (e.g., Schürmann & Klemm 1984; Tsuji et al. 2007) (Fig. 3). Serotonin could also affect the activity of corpora allata where juvenile hormone (JH) is

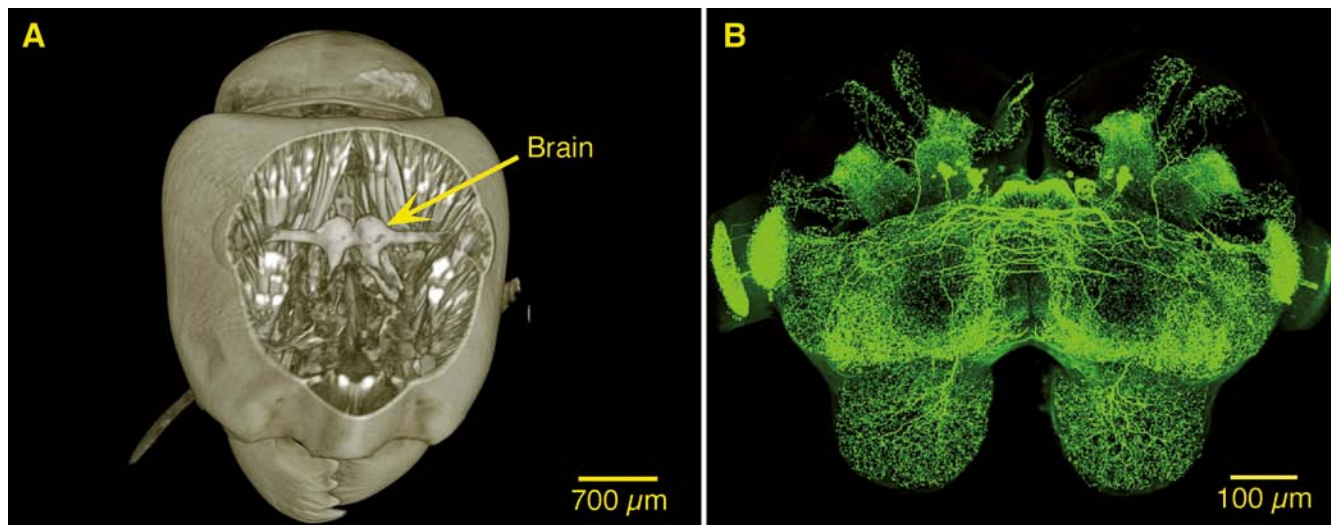


Fig. 3. Serotonergic neurons in the brain of the ant *Camponotus japonicus*. **(A)** X-ray micro-CT scanning image of the head showing the brain (yellow arrow). **(B)** Confocal microscopic image of the distribution of the serotonergic neurons in the brain. The neuronal branches of the serotonergic neurons are expanded all over the brain suggesting serotonin modulates neuronal actions at each neuropil in the brain.

synthesized in honeybees (Rachinsky 1994). Notably, there is not enough evidence demonstrating the action of serotonin on modulating JH production in corpora allata of ants. Pharmacological experiments have contributed to investigating the roles of serotonin in insects so far. However, it has not been well identified yet which types of serotonin receptors are activated to modulate aggressive behavior in insects. It will be necessary to find and use receptor-specific antagonists, which provide us with a better understanding of the role of serotonin in aggressive behavior.

4 Dopaminergic control of aggressive behavior

Like serotonin in insects, dopamine has both enhancing and reducing effects on aggressiveness in animals (Narvaez & Martins de Almeida 2014). However, dopamine mainly enhances aggressiveness in insects. Many studies about the roles of dopamine on aggressive behavior have been performed on solitary insects and demonstrated that dopamine enhances aggressiveness to promote fighting behavior in crickets (Rillich & Stevenson 2014) and in *Drosophila* (Alekseyenko et al. 2013).

In social insects, dopamine also enhances aggressiveness towards intraspecific and interspecific individuals. *Formica polyctena* (Förster) ants showed higher aggressiveness towards prey, enemies, and rivals after a pharmacological treatment to increase dopamine (Szczuka et al. 2013). *Diacamma* sp. ants establish a social hierarchy among workers after agonistic interactions, where the dominant workers have more dopamine in the brain than subordinates (Shimoji et al. 2017). Similarly, more aggressive workers have more

dopamine in the brain, and the pharmacological elevation of dopamine enhances defensive aggression in the trap-jaw ant *O. kuroiwae* (Aonuma 2020). In the termite *H. sjostedti*, the brain dopamine level in the soldier is higher than that in the pseudergate, although dopamine appears not to increase aggressiveness (Ishikawa et al. 2016). Interestingly, symbiotic *Macrosiphoniella yomogicola* (Matsumura) (Homoptera: Aphidae) aphids provide honeydew containing dopamine to *Lasius japonicus* (Santschi) ants to enhance their aggressiveness, thus receiving stronger protection by them (Kudo et al. 2021). Dopamine production in the brain is also closely linked to enhancing aggressiveness in the honeybee (Sasaki & Harada 2020). Dopamine receptors have been identified in ants and honeybees (Calkins et al. 2019), however, it remains unclear which types of receptors act to motivate aggressive behavior in social insects.

Dopamine-related aggression sometimes links to reproduction. The ant queen's contact with the workers inhibits synthesizing of dopamine in the workers' brains, which in turn suppresses their aggressiveness toward their nest mates (Shimoji et al. 2017). The absence of the queen introduces the agonistic interaction among the nests to establish the reproductive hierarchy, which in turn initiates the development of the ovary in the dominant (Penick et al. 2014). In the social parasite ant *Vollenhovia nipponica* (Kinomura & Yamauchi), mated queens become more aggressive than virgin queens, and mated queens have more dopamine than virgins (Ohkawara & Aonuma 2016). In the honeybee, brain dopamine action in the workers is modulated by the queen mandibular gland pheromone (Beggs et al. 2007; Beggs & Mercer 2009). The increase in brain dopamine promotes ovary development in honeybee workers (Harris & Woodring 1995; Sasaki & Nagao 2001). Similar phenomena

were reported for the workers of paper wasps and bumblebees (Sasaki et al. 2021).

The dopaminergic system closely links to the endocrine system in social insects (Sasaki et al. 2021). JH and ecdysteroids are the key molecules to determine caste and division of labor in social insects (ant, Wilson 1983; honeybee, Robinson 1987). In the honeybee, JH affects caste determination during the larval stage (Robinson & Vargo 1997). It promotes foraging behavior in the workers in the honeybee and in the ant (Penick et al. 2011). Although JH does not promote ovarian development during the adult stage in queens and egg-laying workers (Robinson & Vargo 1997), it promotes ovarian development during an adult stage, and egg-laying behavior in primitively eusocial species including paper wasps, bumble bees, and fire ants (Shpigler et al. 2014; Tibbetts et al. 2011). Ovarian activity links to establishing caste and social status in social insects. JH enhanced the brain dopamine levels and JH titer was correlated with the ovarian activation in the females of the paper wasp *Polistes chinensis* (Fabricius) (Hymenoptera: Vespidae) (Tsuchida et al. 2020). Therefore, aggressive behavior among nestmates closely links to ovarian activities that are regulated by JH (Sasaki et al. 2021). The dopaminergic system appears to activate the reproduction in females and to control conflicts among nestmates in the colonies of primitively and advanced eusocial species.

Dopamine and octopamine are stress-sensitive amines. Physical stressors change the content of dopamine and octopamine in the brain (Chen et al. 2008). To face predator-induced stress, the insect increases its defensive aggressive behavior associated with an increase in brain dopamine. In the honeybee, workers use alarm pheromones to recruit nestmates to handle the predators (Nouvian et al. 2016). The sting alarm pheromone, isoamyl acetate, upregulates dopamine together with serotonin in the brain, which elevates the aggressiveness of workers and, in turn, enhances defensive behavior (Nouvian et al. 2018). It is thought that an increase in the brain amines would enhance arousal, cognitive processes, and sensitivity to stimuli and then activates corpora cardiac to release some hormones into the hemolymph in insects (Even et al. 2012). For a full understanding of defensive behavior in social insects, it would be important to consider the physiological responses to the stressors in the brain.

5 Octopaminergic and tyraminerpic controls of aggressive behavior

Octopamine is another biogenic amine that enhances aggressiveness in insects. Tyramine used to be believed as an intermediate product of octopamine, but it is now believed that tyramine itself functions as a neuromodulator. The physiological functions of tyramine and octopamine in invertebrates are similar to those of adrenalin and noradrenalin in vertebrates, respectively (Roeder 2003, 2005). There are few reports demonstrating the effects of tyramine on the

aggressive behavior of insects including ants and bees. It was reported that the pharmacological treatment of tyramine increases defensive behavior in the termite *H. sjostedti*, but octopamine does not (Ishikawa et al. 2016). In crustaceans, tyramine has been demonstrated to associate with aggressive behavior (Momohara et al. 2018).

Octopamine plays a major role in modulating aggressive behavior in solitary insects, such as crickets (Stevenson et al. 2000) and *D. melanogaster* flies (Dierick 2008; Potter & Luo 2008). However, the roles of octopamine in aggressive behavior in social insects are ambiguous. The effects of biogenic amines on intra- and interspecific aggression in *F. polyctena* workers have been examined relying on pharmacological experiments. It has been reported that serotonin, dopamine, and tyramine have enhancing effects on aggression, while octopamine has no effect on it (Szczuka et al. 2013). Similarly, *O. kuroiwae* workers do not show any change in terms of aggressiveness post-administration of octopamine (Aonuma 2020) as well as the queen of the ant *Polyrhachis moesta* (Emery) (Koyama et al. 2015). Further research reported that octopamine positively modulates ant's aggressive behavior. Indeed, it enhances aggressiveness in nest-mate recognition and territorial defense in the Australian weaver ant, *Oecophylla smaragdina* (Fabricius) (Kamhi et al. 2015). Japanese wood ants, *Formica japonica* (Motschoulsky), showing higher intraspecific aggression have more octopamine in their brain (Aonuma & Watanabe 2012a). Queen contact increases brain octopamine levels and enhances aggressiveness in the worker of the red wood ant, *Formica aquilonia* (Yarrow) (Yakovlev 2018). In the red fire ant, *Solenopsis invicta* (Buren), the absence of the queen induces a drastic decrease both in worker aggressiveness towards non-nestmates, and a decrease in brain octopamine in workers (Vander Meer et al. 2008). Although octopamine suppresses aggression in crustaceans (Edwards & Kravitz 1997), it has an enhancing effect or no effect on aggressiveness in social insects. Although octopamine receptors have been identified in insects (Evans & Robb 1993), it remains unclear which types of receptors act during aggressive behavior in social ones.

Octopamine, as well as dopamine, are associated with defensive behavior in insects. Being exposed to a predator activates a stress response increasing brain octopamine, thus inducing defensive behavior in insects (Adamo & Baker 2011; Adamo et al. 2017). Octopamine increases in the brain of stressor-exposed honeybees (Even et al. 2012). However, the octopamine level does not change in honeybees and ants during defensive behavior, while it increases in bumble bees (Abbot 2022). On the other hand, octopamine improved nest-mate recognition, which could decrease aggressiveness towards nest-mate, but increase non-nestmates (Gene et al. 1999). Overall, the action of octopamine in social insects differs significantly, according to the studied species and caste (see also Scheiner et al. 2006).

It has been reported that the production of JH is regulated by the octopaminergic system in insects, e.g., octopamine

stimulates JH production in corpora allata in honey bees (Kaatz et al. 1994) and locusts [*Locusta migratoria migratorioides* (Reiche & Fairmaire) (Orthoptera: Acrididae)] (Lafon-Cazal & Baehr 1988), but it suppresses JH production in cockroaches [*Diploptera punctata* (Eschscholtz) (Blattodea: Blaberidae)] (Thompson et al. 1990) and crickets (*G. bimaculatus*) (Woodring & Hoffmann 1994). In *Pogonomyrmex californicus* (Dole) harvester ants, JH and ecdysteroids act as primary regulators of behavior and ovarian activity (Dolezal et al. 2012). In social wasps [*Polistes canadensis* (L.) (Hymenoptera: Vespidae)], JH is involved in regulating the reproductive maturation in queen as well as in the behavioral maturation of worker tasks (Giray et al. 2005). In our opinion, ovarian activity is closely linked with aggressive behavior, thus octopaminergic aggression could also associate with reproductive behavior.

6 Conclusions and future research directions

Overall, aggressive behavior is one of the most complex behaviors to understand the neuronal mechanisms because it can be motivated by many kinds of reason and links to

many other behaviors. In social insects, aggressive behavior can occur at early colony establishment, territorial defense, predation, social rank, and reproductive hierarchy, among others. The motivation of behaviors is controlled by neurochemical systems in the nervous systems, where biogenic amines play key roles (Table 1). The major biogenic amines that regulate aggressive behavior are serotonin, dopamine, and octopamine in social insects as well as solitary insects. These amines are multifunctional and link to many kinds of behavioral and physiological events. For example, dopamine regulates not only aggressive behavior but also arousal level in the brain, which in turn initiates a variety of behaviors in insects, such as locomotion, grooming, courtship, learning, sleep, and others (Andreć et al. 2005; Mustard et al. 2010; Scheiner et al. 2002; Van Swinderen & Andreć 2011). Serotonin regulates aggressive behavior, feeding behavior, and locomotion, just to mention some (Falibene et al. 2012; Yellman et al. 1997), and octopamine regulates aggressive behavior, rhythmic behavior, locomotion, feeding behavior, learning behavior, and more (Roeder 1999; Selcho & Pauls 2019). These pieces of evidence suggested that plural biogenic amines regulate aggressive behavior. Indeed, more aggressive ants have more serotonin, dopamine and octopamine in the brain, although octopamine did not enhance

Table 1. Current knowledge about the different roles of monoamines in ant, bee, and termite aggressive displays during predation, colony defense, and social ranking.

| Amine | Aggressive behavior | Species | References |
|-------|---|--------------------------------|---|
| 5HT | Territorial defense/ predation | <i>Formica rufa</i> | Kostowski & Tarchalska 1972; Tarchalska et al. 1975 |
| | Territorial defense/ predation | <i>Formica polyctena</i> | Szczuka et al. 2013 |
| | Defense against enemy | <i>Odontomachus kuroiwayae</i> | Aonuma 2020 |
| | Social rank/ reproductive hierarchy/ colony establishment | <i>Veromessor pergandei</i> | Muscedere et al. 2016 |
| | Colony defense | <i>Apis mellifera</i> | Nouvian et al. 2018 |
| DA | Territorial defense | <i>Lasius japonicus</i> | Kudo et al. 2021 |
| | Territorial defense/ predation/ defense against enemy | <i>Formica polyctena</i> | Szczuka et al. 2013 |
| | Defense against enemy | <i>Odontomachus kuroiwayae</i> | Aonuma 2020 |
| | Colony defense | <i>Apis mellifera</i> | Nouvian et al. 2018 |
| | Caste dependent | <i>Vollenhovia nipponica</i> | Ohkawara & Aonuma 2016 |
| | Social hierarchy/ reproductive hierarchy | <i>Diacamma</i> sp. | Shimoji et al. 2017 |
| | Caste dependent | <i>Apis mellifera</i> | Sasaki & Harada 2020 |
| TA | Colony defense | <i>Hodotermopsis sjostedti</i> | Ishikawa et al. 2016 |
| OA | Territorial defense/ nest-mate recognition | <i>Apis mellifera</i> | Gene et al. 1999 |
| | Territorial defense/ nest-mate recognition | <i>Oecophylla smaragdina</i> | Kamhi et al. 2015 |
| | Predation | <i>Formica japonica</i> | Aonuma & Watanabe 2012 |
| | Territorial defense/ nest-mate recognition | <i>Solenopsis invicta</i> | Vander Meer et al. 2008 |
| | Predation | <i>Formica aquilonia</i> | Yakovlev 2018 |

defensive aggression (Aonuma 2020; Ohkawara & Aonuma 2016). Similarly, a soldier termite that is more aggressive than pseudergate has more serotonin, dopamine, tyramine and octopamine in the brain, although serotonin, dopamine and octopamine did not enhance defensive aggression (Ishikawa et al. 2016). To the best of our knowledge, there are few studies examining the co-effect of biogenic amines on aggressive behavior in social insects. Experiments of the combination of pharmacological treatments and behavior observation have been performed to examine the effect of single biogenic amines on aggression (Aonuma 2020; Rillich & Stevenson 2019).

To better understand the mechanism leading to aggressive behavior in social insects, we now need to investigate how plural biogenic amines simultaneously or sequentially act in the brain to regulate aggressive behavior. High-performance liquid chromatography (HPLC) with electrochemical detection (ECD) allows us to investigate the contents of biogenic amines and their precursors and metabolites at the same time (e.g., Aonuma & Watanabe 2012b; Aonuma 2020). The simultaneous measurements of biogenic amines, their precursors, and metabolites can allow a full understanding of the putative combination of biogenic amines regulating various aggressive behaviors. We need to identify which biogenic amine or combination of biogenic amines routes aggressive behavior. Pharmacological experiments may help us to understand the role of biogenic amines (Aonuma 2020; Rillich & Stevenson 2019), and we need to examine the effects of the cocktail of agonists of the biogenic amines and/or their antagonists to investigate the functional roles of the combination of plural biogenic amines. We also need to carefully identify which biogenic amine or combination of them regulates aggression-related behaviors, and how subsequent aggressive experience may modulate their production. Mathematical models and simulation help us to predict the functional roles of biogenic amines (e.g., Yano et al. 2013) and robotics tools can be useful to understand shed light on insect behavioral displays routed by biogenic amines (e.g., Funato et al. 2011). These approaches could boost our knowledge at the interface of neurophysiology and the behavior of social insects. A broad combination of multidisciplinary approaches involving physiologists, neurobiologists, ethologists, and bio-robotics experts is warmly encouraged to break through the issue.

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