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Review

Diversity of peptide toxins from stinging ant venoms

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ABSTRACT

Ants (Hymenoptera: Formicidae) represent a taxonomically diverse group of arthropods comprising nearly 13,000 extant species. Sixteen ant subfamilies have individuals that possess a stinger and use their venom for purposes such as a defence against predators, competitors and microbial pathogens, for predation, as well as for social communication. They exhibit a range of activities including antimicrobial, haemolytic, cytolytic, paralytic, insecticidal and pain-producing pharmacologies. While ant venoms are known to be rich in alkaloids and hydrocarbons, ant venoms rich in peptides are becoming more common, yet remain understudied. Recent advances in mass spectrometry techniques have begun to reveal the true complexity of ant venom peptide composition. In the few venoms explored thus far, most peptide toxins appear to occur as small polycationic linear toxins, with antibacterial properties and insecticidal activity. Unlike other venomous animals, a number of ant venoms also contain a range of homodimeric and heterodimeric peptides with one or two interchain disulfide bonds possessing pore-forming, allergenic and paralytic actions. However, ant venoms seem to have only a small number of monomeric disulfide-linked peptides. The present review details the structure and pharmacology of known ant venom peptide toxins and their potential as a source of novel bioinsecticides and therapeutic agents.

1. Stinging ant biodiversity

Hymenopterans are among the most speciose group of venomous animals. With approximately 120,000 currently described species (van Emden, 2013), they are significantly more diverse than the major venomous phyla including spiders (44,906 species), snakes (3496 species), cone snails (3253 species), sea anemones (3248 species) and scorpions (1454 species) (Fautin, 2014; Hallan, 2005; Kohn and Anderson, 2009; Platnick, 2014; Uetz and Hošek, 2014). Among the stinging aculeate Hymenoptera, ants and wasps (superfamily Vespoidea) and bees together with sphecoid wasps (superfamily Apoidea) are sister groups (Johnson et al., 2013). Ants (family Formicidae) evolved from wasp-like ancestors between 115 and 135 million years ago (Brady et al., 2006) and became a diverse taxonomical group with ~13,000 extant species belonging to 21 subfamilies (Agosti and Johnson, 2005; AntWeb, 2014). Due to their ubiquitous nature in terrestrial environments, and the fact that they constitute 15–20% of the animal biomass in tropical rainforests (Hölldobler and Wilson, 1990; Wilson, 1990), ants are arguably amongst the most abundant venomous animals.

Ants that belong to the subfamilies Formicinae, Dolichoderinae, Aneuretinae and Dorylinae lost their ability to sting during evolution (Fig. 1). Instead, they usually spray their venoms or have a residual, but non-functional, abdominal stinger. Also, it is unclear if the recently discovered subfamily Aenictogitoninae is venomous or not, as only male castes have been seen and females (workers and queens) are yet to be described (Brady et al., 2006). The remaining 16 subfamilies are all stinging ants (Fig. 1) and comprise of ~9100 extant species. This makes ants taxonomically more diverse than scorpions, snakes and cone snails. However, this biodiversity is not equally distributed within stinging ant subfamilies (Figs. 1 and 2). For example, Myrmicinae is the most speciose ant subfamily, with

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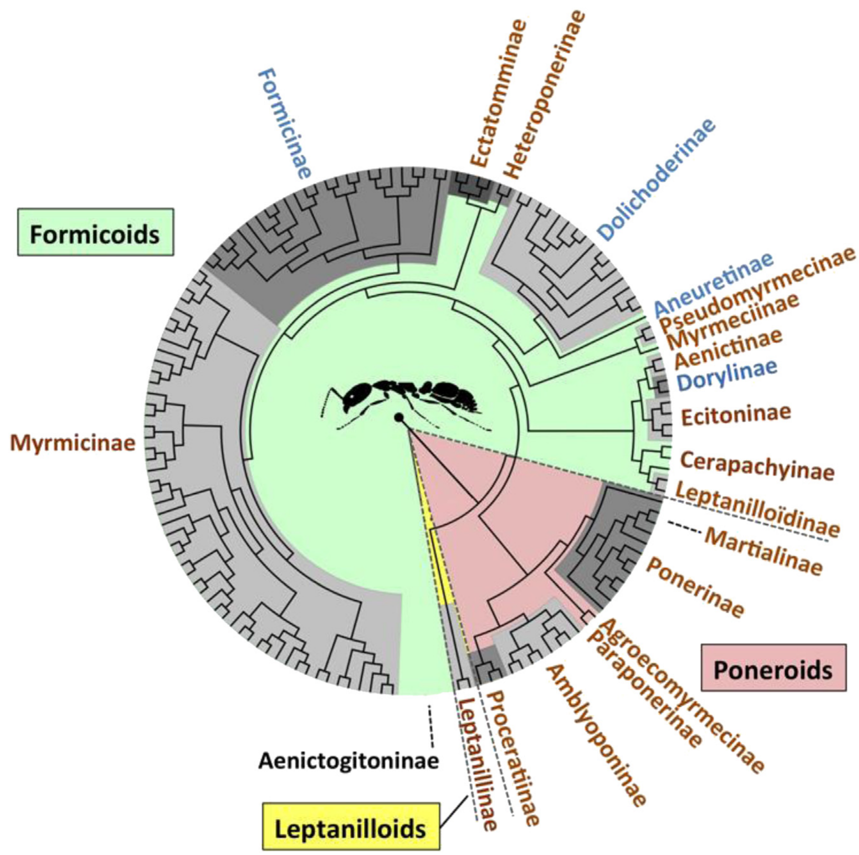

Fig. 1. Ant subfamily relationships as inferred from molecular phylogenetic studies. Phylogenetic relationships were generated from the S1573 TreeBASE data file (Moreau et al., 2006) using the FigTree v1.4.2 software package (http://tree.bio.ed.ac.uk/software/figtree/). Phylogenetic relationships for the subfamilies Aenictogitononae and Martialinae are currently unavailable. During evolution, four subfamilies lost their capacity to sting (blue text). Remaining subfamilies represent stinging ants (brown text). Ant clades are shaded green (Formicoids), red (Poneroids) and yellow (Leptanilloids). Females of subfamily Aenictogitoninae (black text) remain undiscovered and so this subfamily cannot be classified as either stinging or non-stinging. For clarification of colours in this figure, refer to the web version of this article. Note added in proof: Recently, the ant subfamilies Leptanilloïdinae, Cerapachyinae, Ecitoninae, Dorylinae, Aenictinae and Aenictogitoninae have been regrouped into one subfamily; Dorylinae (Brady, S., Fisher, B., Schultz, T., Ward, P., 2014. The rise of army ants and their relatives: diversification of specialized predatory doryline ants. BMC Evol. Biol. 14, 93–106.).

~6500 extant species, with a widespread distribution throughout the world. However, ponerine ants that belong to the subfamily with the second highest number of ants, Ponerinae (~1200 species), are mainly confined to tropical rainforests (AntWeb, 2014; Johnson et al., 2013). Furthermore, the subfamilies Paraponerinae and Martialinae only contain a single ant species both of which are found in Neotropical areas. Thus, taxonomic diversity varies within each ant subfamily however there is little doubt that ant venoms likely constitute a vast source of unique bioactive toxins.

2. Ant venom functions

Ant venom is composed of a complex mixture of chemicals such as proteins, enzymes, biogenic amines, peptides, hydrocarbons, formic acid and alkaloids (Davies et al., 2004; Kem et al., 2004; Yi et al., 2003). All these compounds are produced by the venom gland, which consists of two free cylindrical elongated and convoluted tubes, linked to a venom reservoir (Ortiz and Mathias, 2006). The venom secreted by the tubular glands is stored in the reservoir, linked to the delivery apparatus and, for example, can deliver up to 130 μg of venom after each sting (Schmidt, 1990). The stinger itself is a modified ovipositor located at the distal base of the abdomen. Ants use their venom for several purposes such as a defence against predators/competitors and microbial pathogens, for predation, as well as for social communication (Orivel et al., 2001; Schmidt, 1982). Hence, ant venoms have evolved to carry out many different functions.

2.1. Offensivevenoms

Ants are one of the leading predators of invertebrates in most ecosystems (Brady et al., 2006). They have developed, through natural selection, a vast arsenal of behavioural adaptations and weapons to subdue their prey including trap-mandibles and potent venoms (Casewell et al., 2013). Ant venom has paralytic and lethal effects on many arthropods (Maschwitz et al., 1979; Orivel and Dejean, 2001) and many ants are generalist predators, preying on numerous classes of invertebrates. Nevertheless, many ants are specialised predators and only feed on a restricted group of species. Such specialized hunters prey exclusively on earthworms, isopods, centipedes, millipedes, polyxena, collembolan, termites, other ants or even spider eggs (Cerdá and Dejean, 2011). Solitary hunting is the most common hunting behaviour employed by primitive ants such as ponerines. However, many ants have also developed a cooperative hunting behaviour such as army ants exhibiting extreme group hunting behaviour.

The ecological diversity of ants is also revealed in their preference for various nesting habitats. Predatory ants are primarily ground, or litter-dwelling, predators. However, some ants have evolved predatory behaviours adapted to foraging in trees (arboreal ants) and exhibit adaptions to prevent their prey from escaping by flying away, jumping or dropping. Accordingly, venoms of solitary-foraging, arboreal predatory ants are believed to be more efficient than ground-dwelling species at rapidly immobilising prey (Orivel and Dejean, 2001). Thus, the use of venom as an offensive weapon