

Advances in Nonapeptides for Eco-friendly Insect Control

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ABSTRACT

Nonapeptides have gained attention as environmentally sustainable scaffold systems for insecticide development due to their inherent receptor selectivity and their suitability for structural modification to overcome the instability associated with natural neuropeptides. This review discusses recent progress in designing metabolically stable nonapeptide analogs through strategies such as backbone cyclization, incorporation of peptidomimetic side chains, and the development of antagonist scaffolds to improve binding affinity, target selectivity, and biological persistence. Advances in delivery systems (including plant-based and recombinant expression platforms, nanoencapsulation techniques, and amphiphilic formulations) are also examined as potential solutions to key challenges such as cuticle penetration, degradation in the hemolymph, and limited field stability. Within the framework of integrated pest management, nonapeptide-based approaches offer significant ecological and resistance-management advantages compared with conventional chemical insecticides. Nevertheless, several challenges remain, including optimizing the balance between biological potency and environmental safety, minimizing off-target interactions, and achieving scalable production for agricultural deployment. Future research should prioritize receptor-guided molecular design, detailed structure–activity relationship analysis, and improved formulation strategies to translate molecular insights into practical and environmentally responsible pest control tools.

Keywords: Insect pests, Management, Nonapeptides, Neuropeptides, Sustainability

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Introduction

Nonapeptides are an established class of bioactive molecules that can be utilized as a form of insect control in a more environmentally friendly way, combining receptor selectivity with readily manipulable chemical modification pathways to address the peptide stability issue [1]. The insect neuropeptides regulate highly important biological processes (development, osmoregulation, feeding) and therefore their receptors represent promising targets for species-selective control agents that would reduce adverse effects and harm the target environment. The approaches based on neuropeptides focus on receptor selectivity and environmental friendliness that are not present in traditional chemistries (Scherkenbeck [2]). However, native peptides suffer from metabolic instability and unfavorable physicochemical properties for agricultural deployment. Nevertheless, their short sequences and defined structure–activity relationships, particularly within small families such as myokins and helicokins, render them suitable starting points for peptidomimetic engineering and antagonist design [1, 2]. The shift towards sustainable pest management and the push towards the development of environmentally conscious pesticides provide a favorable context for peptide-based solutions offering reduced amounts of chemical load at comparable efficacy [3, 4]. The main challenge lies in transforming short-sequence leads to stable, deliverable molecules with retained target specificity and useful field behaviour without the rapid development of resistance. Overcoming issues such as metabolic degradation, membrane permeation, and stability in formulations will be among the priorities of the application of the nonapeptides leads to scalable pest-control agents to the laboratory [1, 5].

The paper is based on nonapeptides as a discrete category of insect neuropeptides involves molecular design approaches (backbone cyclization, peptidomimetics, antagonist scaffolds) that enhance the receptor affinity, metabolic stability and selectivity [2]. It scans the delivery and production strategies, such as recombinant expression, plant-based expression systems, and nano-encapsulation of drug release and tissue penetration, comparing trade-offs between biosynthetic scalability and regulatory/environmental challenges [6]. Nonapeptide methodology into the context of integrated pest management systems, comparative ecological risk profile and resistance potential when compared to current technologies. It gives a final list of what needs to be studied and guidance on how to get to the point of converting these findings into sustainable crop protection solutions [5].

Neuropeptide-based insect control strategies represent a promising frontier in developing environmentally sustainable pest management solutions, with significant advances in peptidomimetics, RNA interference approaches, and delivery systems overcoming traditional limitations of peptide instability and poor cuticle penetration. This study provides a synthesis of recent

strategies in nonapeptide design, delivery, and target validation and outlines the strategy based on current molecular knowledge to develop novel environmentally friendly methods of insect control such molecules.

Significance of Neuropeptides in Insect Control

Neuropeptides as Prime Targets for Pest Management

Neuropeptides regulate virtually all key physiological processes in insects, including embryonic and post-embryonic development, homeostasis, osmoregulation, migration, oviposition, and mating, making them ideal targets for developing selective insect control agents. Unlike conventional neurotoxic insecticides, neuropeptide-based approaches offer the potential for species-specific action with minimal environmental impact, aligning with integrated pest management (IPM) programs [1]. The molecular diversity of insect neuropeptides (hundreds of primary structures have been identified across insect species) provides numerous biochemical targets for disrupting critical physiological functions [2]. In *Drosophila melanogaster* alone, genomic evidence indicates at least 30 genes encoding neuropeptide precursors and more than 40 neuropeptide receptors, highlighting the complexity and potential of this regulatory system [7].

Current Limitations of Conventional Pest Control

There are serious challenges to the pest control sector around the world when using the traditional form of insecticides which includes the development of resistance, pre-emption of the environment, and non-specificity on desirable species. The organosynthetic chemical insecticides are also efficient and have contributed to acquired resistance in many insects' pests and threat to human health and eco-balance [3]. Available bio-insecticides of about 2-3 percent of insecticides market are plagued by high cost of production and not being applicable throughout the wide spectrum, they thus cannot substitute the organo-chemicals as the mainstream compounds of pest control [1]. The necessity to regulate the use of toxic organo-chemical compounds, and increasing environmental concern, has increased interest in finding environmentally benign and species-specific agents [4].

Challenges in Neuropeptide-Based Pest Control

Physicochemical Limitations of Natural Peptides

Naturally occurring neuropeptides have serious limitations to practical use as insect control agonists because of their inherent physicochemical characteristics. The environment and the stomach system of insects cause rapid breakdown of peptides, which are metabolically unstable. Inorganic solubility and the failure to penetrate the insect cuticle (which has surface layers of a polar-soluble apolar lipid matrix and prevents the penetration of polar compounds such as peptides) are further disadvantageous factors [5]. To illustrate, *Manduca sexta*-AS can be inactivated rapidly in the gut of larvae of *Lacanobia oleracea* in soluble and/or membrane bound peptides

when it is orally ingested [8]. Such drawbacks require the formulation of improved analogs that have a high stability and delivery level.

Delivery and Targeting Challenges

Another significant challenge is that neuropeptide-based agents are sensitive to their delivery sites. With RNA interference (RNAi) strategies, the key concern is how to find appropriate delivery systems able to deliver the dsRNA across the midgut barrier to its target location in the central nervous system (CNS) or indeed in epithelial cells [9]. Plant-mediated herbivorous insect RNAi promise needs to bridge the hurdle of transfer of the target genes to target cells that are not in midgut epithelial [10]. Moreover, since neuropeptide action is highly specific (whereas its selectivity is beneficial to it), unless the target species poses a serious economic risk, commercial development can be restricted [5]. Human/animal health hazards should be taken into significant consideration in the development of amphiphilic analogs as the compounds developed to add holes in the insect cuticle would easily add holes in the skin of the vertebrate and even penetrate through the blood-brain barrier [11].

Advanced Strategies for Neuropeptide-Based Pest Control

Peptidomimetic Approaches

Peptidomimetics (non-peptide compounds that mimic the biological activity of neuropeptides) represent a breakthrough in overcoming the limitations of natural peptides. The first nonpeptide analog of an insect neuropeptide, Bztc, functions as a mimetic of the FLRFamide myosuppressin family, binding to and activating the same receptor sites as the natural peptide [5]. Remarkably, pseudohexapeptide His-Val-Phe-Cpa-Arg-Phe-NH₂ and pseudotetrapeptide Phe-Cpm-Arg-Phe-NH₂ containing conformationally restricted amino acid analogues completely antagonize locust oviduct myoinhibitory activity at micromolar concentrations. NMR studies reveal that these analogues adopt specific conformations (γ -turns) that explain their recognition by receptors without activation, providing critical insights for rational design [2].

Amphiphilic Analogs for Cuticle Penetration

The development of amphiphilic analogs addresses the critical challenge of cuticle penetration while maintaining water solubility necessary for reaching target receptor sites. These analogs incorporate hydrophobic components that enable penetration through the insect's hydrophobic cuticle while retaining sufficient water solubility to function in the circulatory system [12]. For example, pyrokinin/PBAN family analogs with amphiphilic character have demonstrated topical activity, with some compounds showing effectiveness at picomole concentrations [13]. The amphiphilic design strategy has been successfully applied to various neuropeptide families, including myokinin, which are particularly promising due to their short chain lengths (6–13 residues) and potent diuretic activity with EC₅₀ values in the low nanomolar range [14]. However, careful selection of lipidic attachments is essential to avoid vertebrate toxicity concerns.

RNA Interference Approaches

Plant-mediated herbivorous insect RNAi represents a significant advancement in neuropeptide-based pest control. This strategy involves engineering crop plants to produce specific insect dsRNA that, when consumed by pests, suppresses critical insect genes [6]. Transgenic corn plants expressing dsRNAs against the V-type ATPase A gene showed significant reduction in feeding damage by western corn rootworm (*Diabrotica virgifera virgifera*) [15]. Similarly, tobacco and *Arabidopsis* plants engineered to produce dsRNAs against the cytochrome P450 gene *CYP6AE14* from cotton bollworm (*Helicoverpa armigera*) resulted in reduced transcript levels and increased sensitivity to plant metabolites [16]. This approach has been successfully applied to Lepidopteran, Coleopteran, and Hemipteran pests, demonstrating broad potential. Bursicon and its receptor show high potential as target genes for this approach, as dsRNA treatment can dramatically decrease bursicon activities and disrupt insect development [5].

Future Directions and Implementation Considerations

Molecular Biology and Genomic Advances

The recent progress in insect genomics has brought a large amount of knowledge about neuropeptides systems. Follow-ups of other insect genomes have shown that certain neuropeptide genes have been acquired or lost by some systems over evolution of a particular insect, and that in others they are more varied. This has been made possible by quantitative mass spectrometry measures whereby analysis of the peptide expression in insects can be done under various conditions indicating that peptide expression is not a static process in adult insects. The creation of methods

to identify the peptidome of preferred neuron types (single genetic labeling with GFP and mass sorting and mass spectrometry with fluorescence) makes it possible to map out neuropeptides in large neuron types [17]. Such developments offer unmatched possibilities to find new targets and develop very specific control agents.

Environmental and Safety Considerations

The realization of the neuropeptide-based pest control agents should put into consideration issues of safety and the environment. Even the amphiphilic analogs aiming at insect cuticle penetration may enter human skin, which requires very strict human/animal health risk evaluation [11]. Peptides derived using insects should be avoided due to unintended effects of having the same structure as that of vertebrates. Neuropeptides are highly specific and do not affect all organisms, which can be advantageous and also a limitation because of its uses, and also lets it be very much specific since it can be extremely selective in terms of action, however, not necessarily commercially viable if the target species is not of a major economic concern [14]. Global testing on different species will be necessary to identify the physiological impacts of the compounds on the target pest species as well as the undesired non-target species that may contact the compounds [4].

Conclusion

Neuropeptide-based methods offer the possibility of highly selective, environmentally friendly substitutes for traditional neurotoxic insecticides, marking a paradigm shift in insect pest management. Many of the conventional drawbacks of natural peptides, such as instability, poor cuticle penetration, and rapid degradation, have been addressed by notable developments in peptidomimetics, amphiphilic analogs, and RNA interference technologies. Particularly promising targets for species-specific control agents are the bursicon, myosuppressin/FLRFamide, and diuretic hormone systems. The development of environmentally safe delivery methods, thorough evaluation of non-target effects, and ongoing research into neuropeptide receptor structures will all be necessary for future success. The development of these next-generation control agents is becoming more and more critical as resistance to existing insecticides, such as neonicotinoids, continues to spread and endanger beneficial species, including pollinators. The integration of molecular biology, peptide chemistry, and delivery technology holds the key to realizing the full potential of neuropeptide-based pest management strategies that are both effective and environmentally responsible.

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