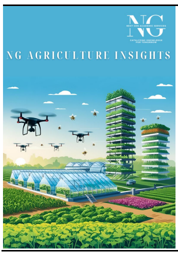

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GPCRs as Promising Molecular Targets for Next-Generation Pest Management

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A B S T R A C T

Traditional chemical insecticides have been used for crop protection for year's exhibit significant drawbacks. Pests may develop resistance to insecticides and the chemicals remain in the soil and water for long time. Furthermore, insecticides kill insects that are beneficial, such as bees and wasps. Scientists now explore more targeted approaches, focusing on the interference with G protein-coupled receptors (GPCRs), which are "molecular switches" within the insects controlling development, feeding, mating and behaviours. Due to the significance of these switches, targeting them is a promising way of eliminating pests without damaging effects on other organisms and the environment caused by traditional chemical insecticides. This article examines functioning of these receptors, including those involved in hormonal and neuropeptide signalling. Moreover, it describes recent methods developed for targeting GPCRs in insects, including RNA interference, CRISPR/Cas9-based genetic modification, computer-assisted drug design and virtual screening of molecules. While there are some obstacles in the development of such insecticides due to the limited knowledge about the receptors and difficulties in delivery of drugs to pests, rapid progress in genetics and computational biology contributes to the development of safer and smarter insecticides.

Keywords: GPCRs, Neuropeptide receptors, RNA interference, CRISPR/Cas9, Physiological effects, Novel pest management, Signalling pathway

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1. INTRODUCTION

Insects are among the major pest threats to agriculture and food production worldwide. Chemical insecticides have traditionally been employed as the principal means for combating these pests. Nevertheless, intensive use of insecticides has resulted in considerable ecological and economic challenges. They possess several risks such as development of insecticide resistance, pollution of the environment with non-target effects, accumulation of chemical compounds in the food chain and potential health concerns (Liu et al., 2021a; Liu et al., 2021b).

The development of new, more precise and sustainable pest control mechanisms is a scientific necessity. Insect's physiology at the molecular level involves complex signalling networks in the body that regulate all aspects of the growth and development including morphogenesis, ecdysis, nutrition, reproduction, metabolism and behaviour. G-protein coupled receptors (GPCRs) represent one of the largest and most versatile families of membrane receptors that are involved in signalling pathways within the cells. These receptors transform the information received from various external messengers into internal signalling.

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The role played by GPCRs in signalling pathways is very significant in the physiology of insects. Hence they represent excellent candidates as pesticide targets. The blocking of GPCR signalling will disrupt necessary physiological functions in the pests without affecting other organisms since GPCR signalling is very specific. Among the various GPCR, neuropeptide receptors, hormone receptors and receptors controlling moulting and developmental processes have emerged as particularly promising targets for pest control strategies. Recent advances in genomic analysis, transcriptomic profiling, RNA interference technologies, CRISPR-based gene editing systems and computational in silico ligand screening provide unprecedented opportunities to target these receptors with high specificity. This comprehensive approach positions GPCR-mediated pathway disruption as a highly promising strategy for developing selective, efficacious insecticides with improved safety profiles compared to currently available broad-spectrum insecticides.

2. INSECT GPCRS - STRUCTURE, DIVERSITY AND SIGNALLING MECHANISMS

2.1 Structural Characteristics

GPCRs are membrane receptors consisting of seven transmembrane domains (Liu et al., 2021a). They are generally found at the plasma membrane which functions as signalling proteins. Upon binding of certain ligands, GPCRs undergo a conformational change and activate the associated heterotrimeric G proteins. The activated G-proteins serve as transducers that influence several effector enzymes, especially the adenylate cyclase (AC) enzyme responsible for generating cAMP. Moreover, the GPCR signalling pathway is involved in calcium-related cellular cascades that control biological functions in the insect body.

2.2 Classification and Functional Diversity

GPCRs of insects are classified according to the A-F system based on the structure and function. The largest and most known group is the class A - the rhodopsin-like receptors (family). This class includes neuropeptide receptors, biogenic amine receptors (e.g., dopamine, serotonin and octopamine) and peptide hormone receptors. Class A GPCRs assist in several physiological processes in the body such as metamorphosis, feeding, reproduction, metabolism and vision. The GPCRs belonging to class B GPCRs consist of diuretic hormone receptors and methuselah-type receptors involved in water balance, thermoregulation and stress response. Class C GPCRs contain metabotropic GABA receptors for regulation of neural activity, whereas Class F consists of frizzled and smoothened receptors for developmental signalling. This diversity observed in the structure of the insect GPCRs is likely to lead to the discovery of receptors that are selectively present in pests. This will allow researchers to develop new compounds for pest control.

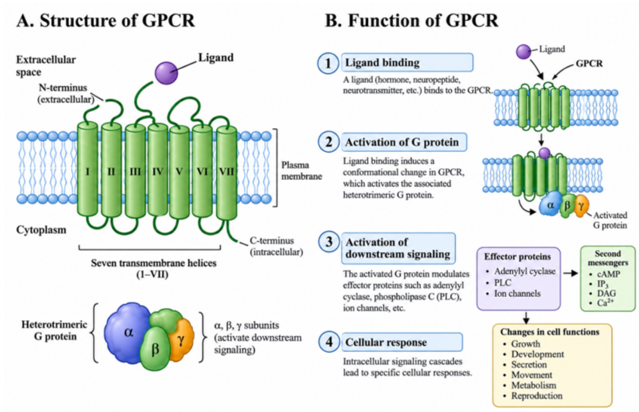

Figure 1. GPCR Structure and Function

3. PHYSIOLOGICAL FUNCTIONS OF GPCRS IN INSECT PHYSIOLOGY

The Physiological mechanisms which are controlled by GPCR signal transduction pathway play an important role in insect survival and population dynamics are:

3.1 Growth and Moulting

Neuropeptide and hormone-linked GPCRs play an important role in the regulation of moulting and development. Dysfunction of GPCR leads to disruption in the moulting process and ecdysis failure, causing reduced survival and developmental arrest in insects.

3.2 Feeding and Energy Metabolism

Numerous GPCRs have a role in appetite regulation, gastrointestinal functions and metabolism. Dysfunction of these receptors leads to reduced feeding activity, leading to inadequate nutrition, retarded growth and metabolic disorder.

3.3 Reproduction and Fecundity

Signalling via GPCR is involved in reproduction, endocrine function and oogenesis. Disrupt in the receptor activation result in decreased reproductive success and reduced population growth rate.

3.4 Behaviour and Sensory Responses

GPCR family responsible for neurotransmitter or neuropeptide signalling plays a crucial role in behaviour such as locomotion, mating and host recognition. Dysfunction in such receptors may alter behaviour which is vital for the survival and reproduction of pests (Liu *et al*., 2021b).

Table 1. Key GPCR Subtypes in Agricultural Pest Species and Their Physiological Functions

Receptor	Physiological Function	Key Species
Ecdysis-Triggering Hormone receptor	Moulting, reproduction and courtship	*Manduca sexta*, *Drosophila melanogaster*
Dopamine/Ecdysone receptor	Morphogenesis, sexual behaviour and locomotion	*Agrotis ipsilon*
Adipokinetic hormone receptor	Lipid mobilization and energy metabolism	*Bactocera dorsalis*
Astakine receptor	Juvenile hormone synthesis and feeding regulation	*Diploptera punctata*
Diuretic hormone receptor	Developmental arrest and diapause	*Bombyx mori*, *Helicoverpa zea*
Octopamine receptor	Stress response, feeding, locomotion	*D. melanogaster*
Tyramine receptor	Behavioural regulation and antiparasitic target	*Rhipicephalus microplus*
Neuropeptide F receptor	Feeding behaviour and appetite control	*Schistocerca gregaria*

4. GPCRS MEDIATING CONTROL STRATEGIES

The critical physiological functions performed by GPCRs in insect life make them excellent candidates for the development of new IPM approaches. While conventional insecticides act in a non-specific manner on the physiology of insects, the new approaches utilizing GPCRs will ensure targeted inhibition of particular receptors.

4.1 Neuropeptide-GPCR Targeting Strategy

Neuropeptides act as signalling molecule that have physiological roles via interaction with certain GPCRs. Targeting such receptors through either blocking or over activation is an effective way of interfering with certain physiological activities like moulting, feeding and reproduction. It therefore forms a key area of study in the field of molecular entomology and insect control.

4.2 RNA Interference (RNAi) Mediated Target

RNA interference is a very powerful molecular tool for studying the function of G protein-coupled receptors (GPCRs). Using dsRNA complementary to certain GPCR mRNA will result in the reduction of the GPCRs' expression levels through post-transcriptional gene silencing. RNAi techniques can be used for functional characterization of GPCRs and for studies of their possible uses in pest control (Keyes-Scott et al., 2023). High-throughput RNA interference (RNAi) screens have helped identify potential GPCR candidates regulating larval growth, moulting and metamorphosis. This highlights the applicability of the method in insect control (Bai et al., 2011).

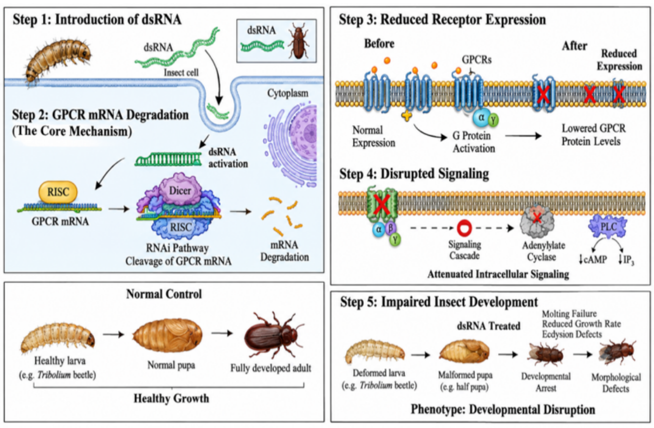

Figure 2. RNAi mediating target on GPCR

4.3 Ligand-Based Approaches

Rational design of specific GPCR agonists, antagonists, synthetic peptides (peptidomimetics) and structural analogues offers substantial promise for disrupting GPCR-mediated signalling. Modern approaches integrating molecular docking, structural biology and artificial intelligence-driven drug discovery enable identification of bioactive compounds with high specificity for insect GPCRs, potentially avoiding non-target effects.

4.4 Genome Editing Approaches

CRISPR/Cas9-based genome editing strategies enable rapid functional screening of candidate GPCR genes by systematically determining their contributions to essential insect biological processes including growth, moulting, reproduction and survival. Functional validation of candidate genes is critical prior to consideration for practical application in developing genetic approaches to pest control.

5. EMERGING STRATEGIES, CURRENT CHALLENGES AND FUTURE RESEARCH DIRECTIONS

5.1 Opportunities and Emerging Technologies

The convergence of cutting-edge technologies including omics approaches (genomics, transcriptomics and proteomics), RNA interference, CRISPR genome editing, structural biology and high-throughput computational screening will substantially expand opportunities for discovering novel GPCR targets in economically important agricultural pests. Transcriptomic and proteomic analyses enable identification of preferentially expressed receptors, while complementary functional assays elucidate their physiological relevance and pest-specific functions.

5.2 Outstanding Challenges

However, several problems have emerged in spite of much advancement made in this area with regard to using GPCR in pest management. First of all, not all the insect GPCRs have been studied completely in terms of their functions and endogenous ligands for them have not been found yet. Second of all, efficient delivery systems for RNAi molecules have to be created in order to deliver molecules into appropriate cells and tissues. Besides, specific ligands with proper pharmacokinetics have to be created. Finally, it is extremely important to find GPCR targets that would be unique for pest species only.

5.3 Future Research Priorities

Future research will need to emphasize the following: (1) systematic discovery of vital and specific GPCRs based on comparative genomics; (2) detailed study of endogenous ligands and the modes of signalling; (3) confirmation of target validity using RNAi and genome editing techniques; (4) the combination of computational tools and molecular and physiological studies to allow rapid discovery of GPCR-targeting bioactive; (5) development of improved methods for delivering RNAi and peptide molecules; and (6) comprehensive evaluation of possible off-target and ecological effects before field applications.

6. CONCLUSION

The G-protein coupled receptors make excellent potential molecular targets for designing the next line of effective, selective and sustainable pesticides. This is because they regulate key physiological functions such as moulting and growth, feeding and metabolism, reproduction and behaviours functions which were critical to the survival of insects. Emerging technologies that have been made possible by recent developments in RNA interference (RNAi), genome modification, neuropeptides and in silico ligand identification have opened up tremendous possibilities of designing innovative approaches to tackle important insect pests based on GPCR targets. However, although there are still some difficulties ahead that need to be solved related to targeting, identifying the endogenous ligands, optimizing the delivery system, and achieving species specificity, the combination of molecular biology, bioinformatics and structural biology techniques provides promising means for overcoming these issues. The implementation of GPCR-based pest control technology marks a new era of selective and ecologically friendly methods of insecticide action rather than general ones.

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