Agri Articles
(e-Magazine for Agricultural Articles)
Volume: 04, Issue: 03 (MAY-JUNE, 2024)
Available online at http://www.agriarticles.com
©Agri Articles, ISSN: 2582-9882

Insect Hormones as Pesticides

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Abstract
Insect hormones, particularly insect growth regulators (IGRs), have emerged as promising alternatives to conventional insecticides, offering safer and more environmentally friendly pest management solutions. These compounds, including juvenile hormone analogues, anti-JH compounds, moulting hormone analogues, anti-moulting hormone analogues, and neuropeptides, target specific physiological processes in insects, disrupting their development, reproduction, or physiological functions. Despite challenges such as limited specificity, commercialization obstacles, and bioavailability issues, ongoing research holds significant potential for harnessing the power of insect hormones in integrated pest management strategies. By further understanding and optimizing the use of IGRs and neuropeptides, more effective, sustainable, and species-specific approaches to controlling insect pests can be developed while minimizing environmental impacts.

Introduction
The discovery of insect growth regulators (IGRs) traces back to the isolation of juvenile hormone (JH) in 1956, followed by identifying plant-derived compounds like juvabione as specific juvenile hormone mimics. Industrial interest in JH as a tool for developing IGRs swiftly grew, leading to synthesizing other compounds based on a deep understanding of insect biochemistry and physiology. Unlike traditional insecticides, which interfere with various physiological processes, IGRs focus on disrupting the normal development of insects or their progeny. They induce abnormalities in insects that impair their survival rather than directly causing toxicity. This selectivity aligns well with integrated pest management (IPM) programs, which emphasize the use of environmentally friendly and species-specific control methods. The discovery and development of IGRs have revolutionized insect pest management by providing a safer and more sustainable alternative to conventional insecticides. By focusing on disrupting key regulatory processes in insect development, IGRs offer a promising solution for reducing reliance on broad-spectrum chemicals and minimizing environmental impacts.

IGRs – Types, Mode of Action, and Examples
Juvenile Hormone Analogues/Juvenoids: These compounds mimic the action of Juvenile Hormone (JH) and are promising as hormonal insecticides. JHAs disrupt insect development and reproduction by causing morphogenetic effects, sterility, and inhibition of egg viability. They can induce abnormal morphogenesis, inhibit metamorphosis, and disrupt diapause, leading to reduced pest populations. JHAs can be broadly classified into two groups: terpenoid JHAs, such as methoprene and kinoprene, and phenoxy JHAs, including fenoxycarb and pyriproxyfen. Methoprene, the first commercial JHA, has been widely used

for mosquito control and against household pests like pharaoh ants. It is also effective against agricultural pests such as sciarid flies of mushrooms and fruit and vegetable pests. Similarly, kinoprene has shown efficacy against aphids, scales, whiteflies, and mealybugs, while fenoxycarb has been used against tufted applemoth and citrus whitefly. Pyriproxyfen, another potent JHA, has demonstrated effectiveness against various insect pests. It has been used to control pests like *Myzus persicae* on cabbage, citrus whitefly, and onion thrips. Pyriproxyfen formulations have also been developed for specific applications, such as fire ant control, mosquito control, and fruit pest management.

Anti-JH/Precocenes: These compounds destroy the corpora allata and prevent JH synthesis. These compounds were hailed as "fourth-generation insecticides" due to their potential to control a wide range of insect pests. Precocenes induce various physiological and behavioural changes in insects, including precocious metamorphosis, sterilization of adult females, diapause induction, and inhibition of sex pheromone production. Despite their effectiveness, precocenes have limitations that hinder their commercialization. One limitation is their limited specificity for certain groups of insects, particularly those with hemimetabolous development. Additionally, identifying plant species that naturally produce precocenes and synthesizing these compounds in large quantities present challenges. Examples include EMD, FMev, and PB.

Moulting Hormone Analogues: Are compounds that mimic the action of ecdysone, a natural hormone involved in insect moulting and development. These compounds can be classified into two main categories: ecdysoids and ecdysteroids. Ecdysoids are non-steroidal synthetic analogues, while ecdysteroids are steroidal analogues. These compounds induce the formation of defective cuticles in insects, leading to accelerated development and eventual death. They bypass normal developmental events, resulting in abnormalities such as integument lacking scales or wax layers. The discovery of ecdysone as the first ecdysteroid in 1954 by Butenandt and Karlson paved the way for the development of synthetic MHAs. The first commercial MHA was introduced by Rohm and Hass Chemical company in 1983, followed by simpler analogues like RH-5849 and tebufenozide. Tebufenozide, proved effective against a wide range of Lepidopterous insects. Subsequent products like methoxyfenozide and halofenozide were developed to target specific insect pests like the codling moth and white grubs. These MHAs demonstrated effectiveness in reducing fertility and fecundity in various insect species. In addition to synthetic MHAs, certain plants contain phytoecdysteroids, which also exhibit moulting hormone activity. However, their complex steroidal structure, environmental instability, and limited ability to penetrate insect cuticles have posed challenges for their commercial exploitation. Moreover, elevating phytoecdysteroid levels in certain plant species may offer natural protection against phytophagous pests like insects and nematodes.

Anti-Moulting Hormone Analogues: Are compounds that antagonize the action of moulting hormone in insects. Unlike hormones, they are synthetic or naturally occurring compounds that interfere with the synthesis or activity of ecdysone, the moulting hormone. AMHAs can be classified into azosterols and non-steroidal compounds. Azosterols and non-steroidal compounds act by antagonizing the conversion of phytosterols to cholesterol, which is essential for the synthesis of ecdysone. By disrupting this process, AMHAs delay moulting in insects. However, despite their potential, AMHAs have not been extensively commercialized. Some naturally occurring compounds, such as ajugalactone from *Ajuga decumbens* and ajugarins from *Ajuga remota*, have been identified as possessing AMHA properties. Additionally, compounds like azadirachtin from *Azadirachta indica* and plumbagin from *Plumbago capensis* have demonstrated antagonistic effects on ecdysone production. For example, azadirachtin disrupts ecdysteroid titer in locusts, while plumbagin directly inhibits ecdysone production in the prothoracic gland. Other synthesized compounds, such as

fluorinated analogues of imidazole IGR KK-42, have shown ecdysone antagonistic effects in insects like mealworms. Despite their potential efficacy, the use of AMHAs for insect control is currently limited due to factors such as high cost and potential interference with steroid hormone regulation in higher animals.

Chitin Synthesis Inhibitors: Disrupt the synthesis of chitin, a vital component of insect exoskeletons, by targeting the enzyme chitinase. Chitin, derived from glucose monosaccharides, forms polysaccharide chains of β-1-4-acetylglucosamine units. CSIs act on chitin synthetase, the enzyme catalyzing the final step of chitin polymerization, thereby preventing chitin formation. This disruption leads to desiccation and eventual death in insects. Additionally, CSIs inhibit other enzymes and DNA biosynthesis in larval cells. The insecticidal activity of benzoylphenylurea analogs, pioneered by the Philip Duphar Company in the 1970s, led to the discovery of effective products like DU 19.111. Diflubenzuron emerged as the first commercial CSI. Buprofezin exhibits both insecticidal and acaricidal properties, affecting the reproduction of affected adults. Hexflumuron finds use in termite control, luring and eliminating termites via bait stations. Lufenuron is recommended for controlling dog fleas, inhibiting egg hatching after ingestion by fleas. Chlorfluazuron and diflubenzuron prove effective against pests like the potato Colorado beetle and mushroom pests. Diflubenzuron also combats pear psylla and citrus psylla, significantly reducing their populations. Lufenuron shows promise in controlling the Mediterranean fruit fly and codling moth. Buprofezin and novaluron target mealybugs and Spodoptera in cotton, respectively. Diflubenzuron and teflubenzuron effectively tackle rice grain moth and pulse beetle. Triflumuron reduces larval and adult mealworm stocks in broiler and turkey houses, while diflubenzuron proves efficacy against hornflies on cows.

Neuropeptides: Insect neuropeptides play diverse physiological roles in insects, including regulating processes like diuresis, ecdysis (moulting), pheromone biosynthesis, and controlling muscle activity. The first neuropeptide discovered, proctolin, was isolated in 1975, sparking subsequent research into these signalling molecules. Despite the identification of around 40 neuropeptides to date, none have been successfully commercialized as insect control agents due to challenges like poor bioavailability, short half-life, and difficulties in pharmacokinetics. However, there is significant potential in harnessing the power of neuropeptides for pest management. One promising avenue is manipulating the genes encoding these neuropeptides to be expressed in entomopathogenic microorganisms like viruses, bacteria, fungi, and nematodes. This approach could disrupt insect physiology by affecting neuropeptide levels, thereby enhancing the efficacy of these pathogens in controlling pests. Expression of a diuretic hormone gene from *Manduca sexta* in *Bombyx mori* NPV reduced the survival time of infected insects by 20 per cent.

Incorporating the PBAN (pheromone biosynthesis activating neuropeptide) gene from *Helicoverpa zea* into *Autographa californica* MNPV resulted in a 19-26 per cent reduction in survival time in the host *Trichoplusia ni*. Modification of the juvenile hormone esterase (JHE) gene from *Manduca sexta*, resulting in a mutant form of the enzyme with increased stability, led to a 66 per cent reduction in feeding damage when incorporated into AcMNPV and tested against *M. sexta*. Despite these advancements, there are limitations to the commercialization of neuropeptides. Issues like photo-instability, inability to penetrate the insect cuticle, and susceptibility to heat due to their proteinaceous nature poses significant challenges. However, researchers are exploring solutions such as developing peptidomimetics (molecules that mimic peptides) that can penetrate the insect cuticle, as well as incorporating neuropeptides and antineuropeptide genes into host plants or entomopathogenic microorganisms.

Conclusion

Insect hormones, particularly insect growth regulators (IGRs), offer a promising alternative to traditional insecticides, providing safer and more environmentally friendly pest management solutions. These compounds, such as juvenile hormone analogues, anti-JH compounds, moulting hormone analogues, anti-moulting hormone analogues, and neuropeptides, target specific physiological processes in insects, disrupting their development, reproduction, or physiological functions. Despite challenges such as limited specificity, commercialization obstacles, and bioavailability issues, ongoing research and advancements hold significant potential for harnessing the power of insect hormones in integrated pest management strategies. By further understanding and optimizing the use of IGRs and neuropeptides, we can develop more effective, sustainable, and species-specific approaches to controlling insect pests while minimizing environmental impacts.

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