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Insect Growth Regulators: Harnessing Hormones for Eco-Friendly Pest Control

*Manchikatla Saisri[1] and Kennedy Ningthoujam[2]
College of Post Graduate Studies in Agricultural Sciences, Central Agricultural University (Imphal), Umiam, Meghalaya -793 103, India
*Corresponding Author's email: saisrientomon3010@gmail.com

Insect hormones and peptides regulate essential physiological processes in insects, including homeostasis, metabolism, muscle contraction, immunity, reproduction, development, growth and behavior, offering immense potential for designing novel bioinsecticides. The discovery of natural and synthetic chemicals mimicking insect juvenile hormones (JHs) that are classified as insect growth regulators (IGRs) or third-generation insecticides, represents a major breakthrough in pest management by disrupting the insect endocrine system. This study examines the mechanisms and applications of JH analogs (JHAs), anti-JH compounds, and nonsteroidal ecdysone agonists like tebufenozide, methoxyfenozide, and halofenozide, which target specific pests such as lepidopteran and coleopteran larvae with high specificity and low toxicity to higher animals. By leveraging these hormone-based IGRs in integrated pest management, farmers and researchers can achieve effective, eco-friendly insect control while minimizing resistance and environmental harm. The findings offer practical guidance for sustainable agriculture and future bioinsecticide development.

1. Evolution and Use of Insect Growth Regulators in Pest Control

Conventional insecticides (chlorinated hydrocarbons, organophosphates, carbamates, neonicotinoids, and botanicals such as pyrethrum) act primarily on the nervous system and often pose risks of persistence, non-target toxicity, and resistance (Ramaseshadri et al., 2011; Retnakaran et al., 2003). Over the past 20–30 years, insect growth regulators (IGRs) have emerged as selective agents that target endocrine pathways controlling molting, metamorphosis, and reproduction, resulting in slower but highly stage-specific mortality and better compatibility with IPM (Ramaseshadri et al., 2011; Triseleva, 2012). Key hormone systems exploited include juvenile hormone (JH) and ecdysteroids (molting hormones), which together orchestrate successive molts and the larva–pupa–adult transition.

A pulse of 20-hydroxyecdysone (20E) initiates apolysis, new cuticle formation, and ecdysis, while the presence or absence of JH determines whether the molt is larval, pupal, or adult (Retnakaran et al., 2003). Synthetic analogs and antagonists of these hormones disrupt this balance to produce lethal outcomes such as precocious or incomplete molts, non-viable adultoids, or dwarf pupae, providing a basis for highly targeted pest control (Triseleva, 2012). Because endocrine pathways are largely insect-specific, IGRs tend to show low toxicity to vertebrates and many beneficial arthropods, supporting their use in sustainable agriculture and public health programs

2. Mechanism of IGRs

Insect growth regulators (IGRs) precisely disrupt insect endocrine pathways by acting as agonists or antagonists of juvenile hormone (JH) and ecdysone. These hormones orchestrate critical processes like molting, metamorphosis, and reproduction through receptor-mediated signaling across all life stages, with IGRs binding specific targets like the JH receptor

(Met/Tai) or ecdysone receptor (EcR/RXR) to derail normal development (Jindra et al., 2013). The stage-specific effects of IGRs are outlined below.

a. Effects on Eggs

IGRs penetrate egg chorion and disrupt embryonic development, often preventing hatch by interfering with cell division or embryonic molting; if larvae emerge, they are typically non-viable and perish soon after.

b. Effects on Larvae

Exposure halts proper ecdysis (molting), trapping larvae in prolonged juvenile phases, inducing supernumerary molts, or causing malformed cuticles that lead to desiccation and starvation; JH analogs maintain high larval JH titers to block pupation.

c. Effects on Pupae

Ecdysone agonists trigger premature or incomplete molts within the pupal case, resulting in failure to eclose as functional adults; the protective pupal cocoon cannot shield against these internal disruptions.

d. Effects on Adults

Surviving adults exhibit disrupted gonadal development, producing sterile eggs or infertile sperm, thus breaking reproductive cycles without reducing their immediate nuisance behavior.

3. Types of IGRs

3.1 Juvenile Hormone Analogs (JHAs)

JHAs mimic endogenous JH and disrupt metamorphosis and reproduction; important commercial examples include methoprene, hydroprene, pyriproxyfen, and fenoxycarb. Thousands of JH-like molecules have been synthesized, but only a limited number are used widely due to the need for high potency, stability, and safety.

3.1.1 Sensitivity and Selectivity

JHAs act almost exclusively in arthropods because vertebrates lack JH receptors and JH-regulated metamorphosis, giving these compounds high species selectivity and low vertebrate toxicity (Tunaz and Uygun, 2004; Riddiford and Truman, 1978). Sensitivity peaks at developmental windows when endogenous JH is naturally low or absent (embryogenesis, metamorphic molts, and adult reproductive maturation), so precise timing strongly influences efficacy (Hoffman and Lorenz, 1998).

- **Sensitivity of eggs-**

JHAs such as pyriproxyfen are most effective against very young eggs, causing hatch failure or early larval mortality; activity declines as embryogenesis progresses (Prabhaker and Toscano, 2007; Boina et al., 2010).

- **Sensitivity of immature stages** -

Late larval instars are highly susceptible during the first 2–3 days after molting, when cuticle is soft and endocrine signals are reorganizing, giving excellent control of stored-product beetles and lepidopteran pests (Parthasarathy and Palli, 2009).

- **Sensitivity of adults-**

In adults, JHAs disrupt oogenesis and vitellogenesis, delay egg maturation, and can induce sterility, making them useful for long-term suppression in vectors and soft-bodied pests (Fathpour et al., 2007; Kerna and Stewart, 2000).

3.1.2 Mode of Action

JHAs act primarily via two mechanisms: (1) competition with endogenous JH for binding proteins (JHBP) and degrading enzymes (JH esterase, epoxide hydrolase), thereby prolonging high “JH-like” titers in the hemolymph (Nijhout, 1994; Kamita et al., 2003); and (2) direct agonism at the Met/Tai receptor complex, maintaining expression of JH-dependent genes such as Kr-h1 and thereby blocking expression of metamorphic genes like Broad-Complex, even in phases when JH is normally absent (Jindra et al., 2013). By artificially maintaining a juvenile endocrine state during normally low-JH periods (e.g., pupal commitment, adult reproductive maturation), JHAs induce supernumerary larval molts, malformed pupae, or reproductive failure in adults (Jindra et al., 2013). Their greater metabolic stability compared

to natural JHs (due to resistance to P450 oxidation and slower esterase hydrolysis) enhances persistence and field efficacy, while still allowing relatively rapid environmental degradation (Nijhout, 1994; Kamita et al., 2003).

3.1.3 Environmental Persistence and metabolic fate of JHA

Most JHAs degrade relatively quickly in sunlit water, soil, and vegetation, forming polar metabolites that have low bioaccumulation potential and low acute toxicity to fish, birds, and mammals. Microencapsulated or granular formulations can extend residual activity for weeks to months in target habitats (e.g., mosquito breeding sites) while still maintaining an overall favorable environmental profile (Hustedt et al., 2020).

3.1.4 Key JHA Examples in Pest Control

Juvenile hormone analogs (JHAs) are widely used in agriculture, public health, and stored-product protection due to their stage-specific action and low non-target toxicity. Below is a concise summary on major JHAs and their key pest control applications represented in the table 1.

Table 1. Key juvenile hormone analogs (JHAs) and their major pest control applications

JHA	Target Pest	Main Use / Application	Mode of Action	Reference
Methoprene	*Aedes aegypti* (mosquito)	Larval control in water bodies; prevents adult emergence	Mimics JH, blocks metamorphosis, causes death at pupal stage	Mohandass et al. (2006); WHO (2000)
Pyriproxyfen	*Bemisia tabaci* (whitefly)	Greenhouse/field crops; reduces nymph–adult transition	Inhibits adult emergence, reduces fecundity, blocks nymphal development	Mohandass et al. (2006)
Hydroprene	*Tribolium castaneum* (flour beetle)	Stored grains and food products; reduces adult emergence	Induces supernumerary molts, causes larval–pupal intermediates and death	Arthur et al. (2009)

3.1.5 Advantages and limitations

JHAs provide long-term suppression by preventing immature stages from successfully metamorphosing and by reducing adult fertility, which lowers population growth across generations rather than giving immediate knockdown. Extensive toxicological evaluations show low acute and chronic toxicity to mammals and birds and minimal bioaccumulation, making them suitable for use in sensitive environments and IPM programs. They may prolong larval stages, allowing continued feeding damage before death, which limits their usefulness where rapid crop protection is essential. Stage-specificity and limited residual activity often require careful timing and repeated applications, especially in field crops. Adoption in row-crop agriculture has been modest compared to fast-acting neurotoxic insecticides, although they are highly valued in vector control, structural pest management, and stored products.

3.2 Anti-Juvenile Hormones (Anti-JHs)

Anti-JHs reduce JH titers or block its synthesis, promoting precocious metamorphosis or reproductive failure in target insects. Precocene I and II, originally isolated from *Ageratum* spp., are the best-known examples and act on the corpora allata, leading to “chemical allatectomy” and JH deficiency (Staal, 1986; Bede et al., 2001).

3.2.1 Mechanism and Corpora allata effects

Anti-JHs cause structural and functional degeneration of the corpora allata, suppressing JH synthesis and leading to premature metamorphosis, malformed pupae or adults, and reduced

fertility. Because JH also regulates behavior and reproduction, its disruption can reduce oviposition and egg viability and, in some cases, alter behaviors important for pest success.

3.2.2 Morphological Deformities and Anti-Gonadotropic Effects

Precocene-treated *Chrysomya megacephala* larvae show severe metamorphic defects: half-pupariated larvae, malformed puparia, pupal–adult intermediates, and adultoids with defective abdomens and crumpled, non-functional wings, due to premature JH deficiency disrupting tissue differentiation and cuticle deposition. In females, anti-JH action blocks corpora allata function, inhibiting vitellogenesis and yolk uptake, thereby severely impairing ovarian maturation. In *Diploptera punctata*, *Nilaparvata lugens*, and *Velarifictorus ornatus*, ≥50 µg Precocene I suppresses ovarian development. In *Spodoptera littoralis*, precocene (5th–6th instar) causes dose-dependent reduction in oviposition by inhibiting ovarian DNA synthesis and follicular cell proliferation, resulting in fewer mature oocytes and greatly reduced egg laying.

3.2.3 Sericulture Applications and Safety to Beneficial Insects

In sericulture, anti-JHs and certain JH analogs (e.g., imidazole- and benzoate-based ETB analogs) induce trimolters in *Bombyx mori*, causing larvae to skip the 5th instar and pupate after three molts, thereby shortening larval duration and improving cocoon and silk quality (Wu et al., 2013). These compounds are selective and safe for beneficial insects: they do not induce diapause in *Nasonia vitripennis* or affect survival and parasitism in *Diaeretiella rapae*, and show no adverse effects on larval development or adult behaviour of *Apis mellifera* at field-relevant doses, confirming their compatibility with IPM (De Loof et al., 1979; Fluri, 1983).

3.2.4 Other anti-JH allelochemicals

- Polyacetylenic sulfoxide from crown daisy / garland chrysanthemum (*Chrysanthemum coronarium*, syn. *Glebionis coronaria*) causes sterility in the milkweed bug *Oncopeltus fasciatus*.
- Arborine from orangeberry / five-leafed glycosmis (*Glycosmis pentaphylla*) suppresses corpora allata activity in crickets.
- Extracts of country mallow / Indian mallow (*Abutilon indicum*) show anti-JH and larvicidal activity against vector mosquitoes (Arivoli and Tennyson, 2011).

3.3. Ecdysone Agonists

Ecdysone agonists are synthetic insecticides that mimic 20-hydroxyecdysone (20E), binding to the EcR/USP nuclear receptor complex and prematurely activating molting and metamorphosis genes. In Lepidoptera, 20E, in the absence of JH at the commitment peak, initiates metamorphosis via the Broad-Complex (Riddiford et al., 2003). Diacylhydrazines (DBHs) are non-steroidal agonists that penetrate cuticle and midgut and persist due to slow metabolism, making them effective against feeding larvae. Tebufenozide and methoxyfenozide are highly specific to Lepidoptera (open-feeding caterpillars), while halofenozide is more active against Coleoptera (e.g., scarab larvae). They bind selectively to insect EcR/USP and are considered safe for non-targets owing to their insect-specific mode of action.

3.3.1 Mode of Action

Benzoyl hydrazines (DBHs) are non-steroidal ecdysone agonists that mimic 20-hydroxyecdysone (20E), bind the EcR/USP complex, and activate molting genes, triggering apolysis, head capsule slippage, and formation of a pharate larva beneath the old cuticle (Riddiford et al., 2003). Unlike the transient natural 20E pulse, DBHs are metabolically stable and persistently occupy EcR/USP (Riddiford et al., 2003). This prolonged activation disrupts molting timing: early events (apolysis, pharate formation) occur, but later processes (proper cuticle deposition, tanning, ecdysis) are suppressed. Larvae thus undergo incomplete, precocious molts, fail to shed the old cuticle or form a functional new one, become trapped, and die from desiccation, starvation, and inability to feed or move before the next stage (Retnakaran et al., 2003).

In 6th-instar spruce budworm, 100 ng tebufenozide causes premature molting within 48 h with apolysis but failed ecdysis; SEM shows wrinkled, untanned cuticle and deep mandibular muscle invaginations, while histology reveals early cuticulin–epicuticle deposition but no sclerotization.

3.3.2 Advantages and limitations

- **High Specificity:** Target insect EcR/USP receptors only; lepidopteran-specific (tebufenozide, methoxyfenozide) and coleopteran-specific (halofenozide) with minimal non-target effects on mammals, birds, beneficial insects.
- **Environmentally Safe:** Low mammalian toxicity, rapid environmental degradation, ideal for IPM programs.
- **Effective Field Control:** 90% spruce budworm population reduction with carryover effects to next generation (aerial application 70g/ha).

Limitations

- **Stage-Specific Action:** Target actively feeding larvae only; ineffective against adults, eggs, or non-feeding immatures.
- **Ingestion Required:** Must be consumed (open-feeding larvae); poor contact toxicity limits versatility.
- **Resistance Development:** Some insects show resistance via ABC transporter efflux pumps that selectively expel agonists.
- **Precocious Molt Delay:** Slow kill via incomplete molting (desiccation/starvation); unsuitable where immediate control needed.

Conclusion

Insect Growth Regulators (IGRs) offer sustainable pest control through key advantages: highly effective at minute doses (economical), target-specific (safe for natural enemies), biodegradable/non-persistent (environmentally friendly), and non-toxic to humans, animals, and plants unlike broad-spectrum neurotoxins. Future IPM programs will increasingly incorporate endocrine-based IGRs, leveraging insect hormone specificity for precise, eco-friendly control options.

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