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MICRO-REVIEW

The juvenile hormone receptor as a target of juvenoid "insect growth regulators"

Marek Jindra | Lenka Bittova

Biology Center of the Czech Academy of Sciences, Institute of Entomology, Ceske Budejovice, Czech Republic

Correspondence
Marek Jindra, Biology Center, Czech Academy of Sciences, Branisovska 31, 370 05 Ceske Budejovice, Czech Republic.
Email: jindra@entu.cas.cz

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Abstract

Synthetic compounds that mimic the action of juvenile hormones (JHs) are founding members of a class of insecticides called insect growth regulators (IGRs). Like JHs, these juvenoids block metamorphosis of insect larvae to reproductive adults. Many biologically active juvenoids deviate in their chemical structure considerably from the sesquiterpenoid JHs, raising questions about the mode of action of such JH mimics. Despite the early deployment of juvenoid IGRs in the mid-1970s, their molecular effect could not be understood until recent discoveries of JH signaling through an intracellular JH receptor, namely the ligand-binding transcription factor Methoprene-tolerant (Met). Here, we briefly overview evidence defining three widely employed and chemically distinct juvenoid IGRs (methoprene, pyriproxyfen, and fenoxycarb), as agonist ligands of the JH receptor. We stress that knowledge of the target molecule is critical for using these compounds both as insecticides and as research tools.

KEYWORDS
agonist ligand, bHLH-PAS protein, *Drosophila*, hormone receptor, IGR, juvenile hormone

1 | INTRODUCTION

Insect juvenile hormones (JHs) are sesquiterpenoids modified by epoxidation and methyl esterification (Goodman & Cusson, 2012; Figure 1a). Although JHs have been known to exert some short-term effects initiated at the cell membrane, their low molecular weight and hydrophobic nature argue that an intracellular receptor controlling gene expression is a major site of action of these hormones. This gene regulatory mechanism has been confirmed once the intracellular JH receptor (hereafter JHR) was identified and functionally characterized (see Jindra, Bellés, & Shinoda, 2015 for a review). The JHs are exceptional among animal hormones in that their receptors are

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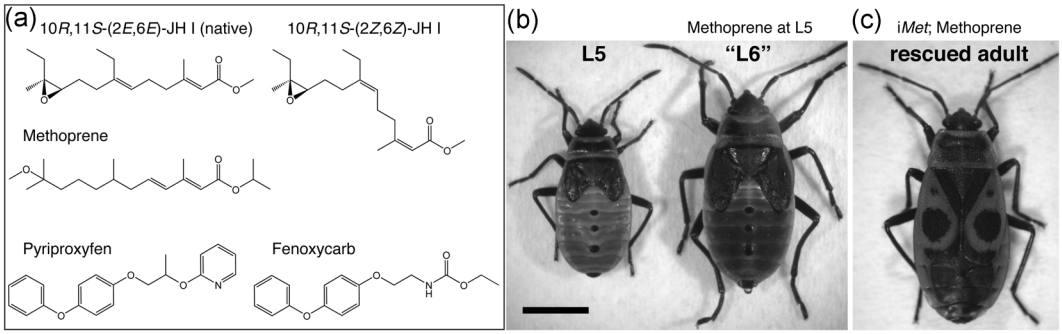

FIGURE 1 Juvenile hormone (JH) mimics and their *Met*-dependent effect. (a) Structures of JH I, its unnatural geometric isomer, and selected juvenoid insect growth regulators. (b) Treatment of final-instar larvae (L5) of *Pyrrhocoris apterus* (Heteroptera) with methoprene blocks metamorphosis and causes a supernumerary larval instar (L6). (c) Prior knockdown of the JH receptor (JHR) gene *Met* through RNAi (i*Met*) renders the animals resistant to the same methoprene treatment, thus rescuing normal development of the adults. Scale bar: 3 mm (b and c). See Konopova et al. (2011) for detailed data

basic-helix-loop-helix (bHLH) transcription factors with a tandem of Per-ARNT-Sim (PAS) domains. The JHR is activated by binding of an agonist ligand to the second, PAS-B domain (Bittova et al., 2019; Charles et al., 2011; Jindra, Uhlirova, Charles, Smykal, & Hill, 2015). An active JHR consists of two bHLH-PAS proteins, the ligand-binding Methoprene-tolerant (Met) and its partner Taiman (Tai) (Charles et al., 2011; Kayukawa et al., 2012; Li et al., 2014; Li, Mead, & Zhu, 2011; Zhang, Xu, Sheng, Sui, & Palli, 2011). Met and Tai mediate both of the major biological functions of JH by regulating metamorphosis (Daimon, Uchibori, Nakao, Sezutsu, & Shinoda, 2015; Jindra, Palli, & Riddiford, 2013; Konopova & Jindra, 2007; Konopova, Smykal, & Jindra, 2011; Lozano, Kayukawa, Shinoda, & Belles, 2014) and female reproduction (Gijbels, Lenaerts, Vanden Broeck, & Marchal, 2019; Guo et al., 2014; Liu et al., 2016; Marchal et al., 2014; Roy, Saha, Zou, & Raikhel, 2018; Smykal, Bajgar, et al., 2014).

Interestingly, several thousand synthetic compounds with JH-like effects have been described (Henrick, 2007; Ramaseshadri, Farkaš, & Palli, 2012; Slama, Romanuk, & Sorm, 1974), many of which are structurally distinct from the native hormone (Figure 1a). Starting from the mid-1970s, some of these "juvenoids" have found commercial use, constituting a new class of insecticides termed insect growth regulators (IGRs) or insect growth disruptors (Minakuchi & Riddiford, 2006; Pener & Dhadialla, 2012). Since JH does not occur in vertebrates, the juvenoid IGRs are considered safe to humans.

It is remarkable that while the insect JHR is highly selective in binding the natural stereoisomers of JH, it can be bound and activated by chemically unrelated IGR compounds with superior potency (Bittova et al., 2019). In this review, we will explain that regardless of their structural departure from native JHs, at least some juvenoid IGRs exert their effect through the JHR, that is, the same mechanism engaged by the hormone itself. Considering the chemical diversity, we will refer to juvenoid IGRs or JH mimics rather than JH analogs.

2 | THE DEVELOPMENTAL ROLE OF JUVENILE HORMONE AND THE EFFECT OF JUVENOID INSECTICIDES

The nominal function of JH is to maintain the juvenile character during the periodic larval molts (Jindra et al., 2013; Nijhout, 1994; Riddiford, 1994). When larvae attain appropriate size, JH synthesis ceases, causing a drop in expression of a gene *Krüppel-homolog 1* (*Kr-h1*), whose role is to repress metamorphosis (reviewed by Belles, 2019; this issue). This decline in JH signaling permits formation of an adult. While the temporal absence of JH is requisite for metamorphosis to occur, the JHR genes are expressed constantly (Kayukawa & Shinoda, 2015; Konopova & Jindra, 2007; Konopova et al., 2011;

Lozano et al., 2014; Minakuchi, Namiki, & Shinoda, 2009; Smykal, Daimon, et al., 2014). Therefore, treatment with JH or its mimic at the critical JH-free periods (early last-instar larva or pupa) blocks metamorphosis and causes abnormal recurrence of the larval or pupal stage, in some insects producing supernumerary giant larval instars (Figure 1b). Disrupting metamorphosis is the main insecticidal activity of juvenoid IGRs.

3 | JUVENOID INSECTICIDES PREDATE DISCOVERY OF THEIR TARGET MOLECULE

The effect of JH on blocking metamorphosis had been discovered by Wigglesworth (1934) three decades before the first chemical structures of JHs (JH I and JH II) were resolved by the late 1960s (Dahm, Röller, & Trost, 1968; Meyer, Schneiderman, Hanzmann, & Ko, 1968; Röller, Dahm, Sweeley, & Trost, 1967). At the same time, the first JH-mimicking compound, juvabione, was identified from the American balsam fir (Bowers, Fales, Thompson, & Uebel, 1966), following a serendipitous finding that paper manufactured from this tree prevented metamorphosis in European linden bugs, *Pyrrhocoris apterus* (Slama & Williams, 1965).

These discoveries together with the ability of JH-like compounds to penetrate insect cuticle inspired the idea of using juvenoids as novel means of controlling insects (Williams, 1967), and led to syntheses of a large number of biologically active compounds (Henrick, 2007; Pener & Dhadialla, 2012; Slama et al., 1974). Based on the structure of the native JH, the Zoecon Corporation developed an array of aliphatic juvenoids (Henrick, Staal, & Siddall, 1973) of which methoprene (Figure 1a), since 1975, became the first commercially registered IGR (Altosid®), originally to control mosquito larvae (Henrick, 2007; Pener & Dhadialla, 2012). Various formulations of methoprene are additionally deployed against some other dipterans, fleas, ants, and pests of stored products (Henrick, 2007; Pener & Dhadialla, 2012; Ramaseshadri et al., 2012). Zoecon was followed by the Roche/Maag and Sumitomo Chemical companies as well as by academic researchers. Their efforts led to carbamate (Dorn, Frischknecht, Martinez, Zurflüh, & Fischer, 1981; Wimmer et al., 1997) or pyridine (Hatakoshi, Agui, & Nakayama, 1986) derivatives, respectively, in which aromatic and/or heterocyclic rings replaced the isoprene units of the original JH backbone (Figure 1a). These juvenoids, including the commercially registered fenoxycarb and pyriproxyfen, are more stable than methoprene and highly active against a broader spectrum of insects.

Depending on the subject species, the synthetic JH mimics often exceed, in potency, the biological effect of JH itself. This "supernatural" activity relative to the native hormone may partly be owing to chemical stability and resistance to metabolic processing within the insect, but in fact could not be explained without knowing a molecular mechanism of action. As discussed below, we have shown that JH mimics act through the same receptor as does the endogenous JH. It seems uncanny that methoprene and the other juvenoid IGRs had been in use for four decades before their target molecule was identified.

4 | METHOPRENE RESISTANCE LEADS TO THE JH RECEPTOR

A crucial step toward discovering the elusive receptor was made in the lab of Thomas G. Wilson (Wilson & Fabian, 1986) through genetic screens in the fly *Drosophila melanogaster* for mutants surviving exposure to methoprene. Several mutations (induced chemically, by irradiation or transposon insertion) uncovered a single gene named *Methoprene-tolerant* (*Met*), whose loss had a partly dominant effect allowing the mutants to complete development under doses of methoprene that killed Met^{+} flies (Wilson & Ashok, 1998; Wilson & Fabian, 1986; Wilson, Wang, Beňo, & Farkaš, 2006). Various Met^{-} mutants also tolerated ectopic treatment with a native JH III (Wilson & Fabian, 1986) as well as administration of the chemically unrelated JH mimic pyriproxyfen (Abdou et al., 2011; Jindra, Uhlirova, et al., 2015; Riddiford & Ashburner, 1991). This led Wilson and Ashok (1998) to propose that resistance to the juvenoid IGRs results from the absence of their target molecule (also see a commentary by Feyereisen, 1998) and that JH mimics are JH agonists (Wilson, 2004). Cloning of *D. melanogaster Met* revealed the bHLH-PAS identity of its product (Ashok, Turner, & Wilson, 1998). The somewhat

surprising fact that loss of *Met* caused, besides the IGR resistance, only subtle developmental defects (Wilson & Fabian, 1986; Wilson et al., 2006) was later explained by a partial functional redundancy with an ancestral paralogous gene *germ cell-expressed* (*gce*) (Abdou et al., 2011; Jindra, Uhlirova, et al., 2015) from which *Met* arose via duplication in the *Drosophila* lineage (Baumann, Fujiwara, & Wilson, 2010).

Initial evidence that *D. melanogaster* Met can bind JH III with a high (nanomolar) affinity (Miura, Oda, Makita, & Chinzei, 2005) was confirmed also for the Gce protein (Charles et al., 2011; Jindra, Uhlirova, et al., 2015) and extended to other insects possessing only one Met/Gce ortholog, primarily the beetle *Tribolium castaneum* (Charles et al., 2011) and the mosquito *Aedes aegypti* (Li et al., 2014). Molecular modeling and experimental mutagenesis within the PAS-B domain identified amino acid residues critical for binding of JH III to a hydrophobic pocket of the Met/Gce proteins from *T. castaneum*, *A. aegypti*, and *D. melanogaster* (Charles et al., 2011; Jindra, Uhlirova, et al., 2015; Li et al., 2014). Jindra, Uhlirova, et al. (2015) demonstrated that the JH-binding capacity of Gce and Met was required for either protein to sustain normal development, thus establishing the JH receptor function in vivo.

5 | DIVERSE JUVENOIDS ARE AGONIST LIGANDS OF JHR

Synthetic JH mimics not only serve as efficient biorational insecticides. They also make important research "tool compounds" that can replace the natural insect JHs in many experimental setups (Ramaseshadri et al., 2012). Relative to available commercial preparations such as the racemic JH III, the synthetic juvenoids are purer, stable, and incomparably cheaper. Methoprene, fenoxycarb, or pyriproxyfen (Figure 1a) are routinely employed for manipulating insect development or physiology and to study the impact of JH signaling in various organ-culture, cell-based, or in vitro systems. Knowing whether these compounds and the native hormone engage in the same molecular interactions to achieve a common response is therefore important. Given the chemical diversity among juvenoids, however, a common mechanism should not be taken for granted.

Evidence that methoprene requires Met to block metamorphosis was obtained in the pupae of *T. castaneum* (Konopova & Jindra, 2007; Minakuchi et al., 2009) and in final-instar larvae of *P. apterus* (Konopova et al., 2011), where systemic RNAi knockdown of *Met* before methoprene application permitted normal adult development (Figure 1c). In these settings, removal of Met prevented ectopic induction of the JH-response gene *Kr-h1* by methoprene (Konopova & Jindra, 2007; Minakuchi et al., 2009) and in *T. castaneum* also by pyriproxyfen (Charles et al., 2011). A genetic rescue test was performed in *D. melanogaster*. Functional transgenic Met or Gce proteins restored sensitivity to methoprene or pyriproxyfen in the resistant Met^{-} background, whereas mutated Met or Gce variants incapable of JH III binding did not (Jindra, Uhlirova, et al., 2015).

Only a handful of synthetic JH mimics were tested for direct interaction with the JHR, so far positively in all cases. For instance, methoprene and pyriproxyfen competed with radiolabeled JH III for binding to the recombinant *Tribolium* Met or *Drosophila* Gce proteins in an in vitro assay (Charles et al., 2011; Jindra, Uhlirova, et al., 2015). In both cases, pyriproxyfen was a better competitor than unlabeled JH III itself, and it docked to the ligand-binding pocket of Met with a greater negative change of free energy as calculated from the model (Charles et al., 2011). The binding affinity of methoprene to either protein was lower than that of pyriproxyfen, perhaps reflecting a weaker potency of methoprene relative to pyriproxyfen in *Tribolium* (Kostyukovsky, Chen, Atsmi, & Shaaya, 2000) and *Drosophila* (Riddiford & Ashburner, 1991) bioassays. In terms of binding affinity to Met or Gce, methoprene surprisingly ranked lower than JH III, although in a cell-based reporter assay, methoprene was a stronger activator than JH III (Jindra, Uhlirova, et al., 2015). This rare discrepancy suggests that performance of different compounds may vary in different assays for unknown reasons.

We have recently combined a set of methods to systematically compare agonist activities between JH I and the IGR fenoxycarb toward *Drosophila* Gce (Bittova et al., 2019). In a direct in vitro binding assay, fenoxycarb (similar to pyriproxyfen) competed against JH III for the Gce protein with an affinity about five-fold higher than JH I (Figure 2a); the difference was 10-fold in a cell-based system (Miyakawa & Iguchi, 2017) that measured ligand-dependent interaction between Gce and Tai (Figure 2b). In the *Drosophila* S2 cell line, fenoxycarb was more than 100-fold more potent than JH I

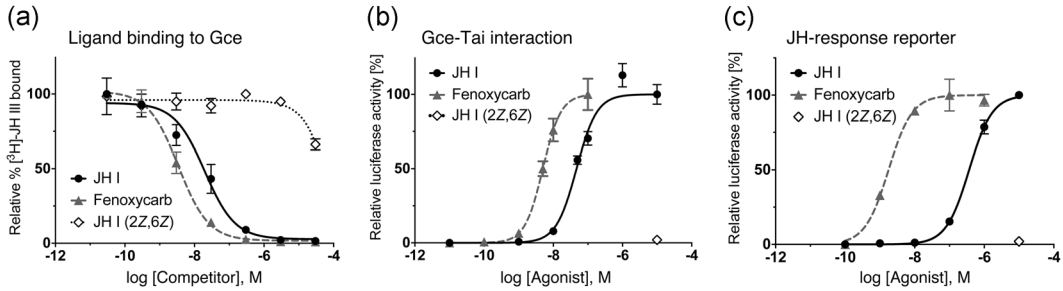

FIGURE 2 Fenoxycarb surpasses a native insect JH in a set of agonist activities. Fenoxycarb showed a higher binding affinity than JH I for the in vitro translated *Drosophila* Gce protein as inferred from competition against [^{3}H]-JH III (a) and was more effective in stimulating ligand-dependent interaction of Gce with Tai in a two-hybrid assay (b). Fenoxycarb was much more potent than JH I in transcriptional activation of a JH-responsive reporter in *Drosophila* S2 cells (c). An unnatural geometric isomer of JH I (Figure 1a) was inactive in all assays. See Bittova et al. (2019) for detailed data. JH, juvenile hormone

in activating Gce-dependent transcription of a luciferase reporter construct driven by JH-response elements (Figure 2c). Overall, fenoxycarb surpassed the natural hormone in all agonist activities tested, whereas an unnatural geometric isomer of JH I (Figure 1a) was inactive in these assays (Bittova et al., 2019).

6 | CONCLUSION

In summary, the information accrued so far strongly argues that at least some chemically diverse juvenoids are genuine agonist ligands of the intracellular JH receptors, thus providing a plausible mechanism of action for these compounds. While the exact nature of their binding to the receptor may differ from that of natural JHs, the juvenoid IGRs effectively compete with JH III for Met/Gce. Future studies should address the structural basis of JHR interactions with ligands of such diverse chemistries.

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ORCID

Marek Jindra http://orcid.org/0000-0002-2196-9924
Lenka Bittova http://orcid.org/0000-0002-3556-5234

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